LBA500 **Oral Abstract Session**

De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP): A multicentre, open-label, randomised, phase 3 trial.

Hong-Fei Gao, Wei Li, Zhiyong Wu, Jie Dong, Yin Cao, Yanxia Zhao, Qian-Jun Chen, Shihui Ma, Jie Ouyang, Jin-Hui Ye, Huawei Yang, Yuanqi Zhang, Yongcheng Zhang, Gangling Zhang, Yingyi Lin, Ying Lin, Guo-Lin Ye, Zefei Jiang, Kun Wang; Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Department of Breast Cancer, The First People's Hospital of Foshan, Foshan, China; Diagnosis & Treatment Center of Breast Diseases, Shantou Central Hospital, Shantou, China; Guilin Municipal Hospital of Traditional Chinese Medicine, Guilin, China; Department of Breast Surgery, Dongguan People's Hospital, Dongguan, China; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Traditional Chinese Medicine Hospital of Guangdong Province, Guangzhou, China; Breast Center, Zhongshan City People's Hospital, Zhongshan, China; Dongguan Tungwah Hospital, Dongguan, China; Department of Breast Oncology, The First People's Hospital of Zhaoqing, Zhaoqing, China; Guangxi Medical University Cancer Hospital & Guangxi Cancer Institute, Guangxi Cancer Hospital & Medical University Oncology School & Cancer Center, Nanning, China; Affiliated Hospital of Guangdong Medical University, Zhanjiang, China; Department of Breast Care Surgery, The First Affiliated Hospital/School of Clinical Medicine of Guangdong Pharmaceutical University, Guangzhou, China; Department of Breast Surgery, Baotou Cancer Hospital, Baotou, China; Breast Disease Center, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; The First People's Hospital of Foshan, Foshan, China; Breast Cancer Department, Fifth Medical Center of PLA General Hospital, Beijing, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

Predicting pathologic complete response (pCR) from clinicopathologic variables and HER2DX genomic test in stage II/III HER2+ breast cancer treated with taxane, trastuzumab, and pertuzumab (THP): Secondary results from the EA1181/ CompassHER2 pCR trial.

Nadine M. Tung, Fengmin Zhao, Angela DeMichele, Aleix Prat, Eric P. Winer, Jean Wright, Abram Recht, Anna Weiss, Judy A. Tjoe, Sheldon M. Feldman, Gabrielle Betty Rocque, Mary Lou Smith, Ciara Catherine O'Sullivan, Sagar D. Sardesai, Patricia Villagrasa, Sunil S. Badve, Ann H. Partridge, Kathy Miller, Lisa A. Carey, Antonio C. Wolff; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute, ECOG-ACRIN Biostatistics Center, Malden, MA; University of Pennsylvania, Philadelphia, PA; Hospital Clínic Barcelona, Barcelona, Spain; Yale Cancer Center, New Haven, CT; Lineberger Comprehensive Cancer Center, Chapel Hill, NC; Department of Surgery, University of Rochester, Rochester, NY; Green Bay Oncology, Appleton, WI; Montefiore Einstein Center for Cancer Care, Bronx, NY; O'Neal Comprehensive Cancer Center at The University of Alabama at Birmingham, Birmingham, AL; Research Advocacy Network, Naperville, IL; Mayo Clinic, Rochester, MN; The Ohio State University - James Comprehensive Cancer Center, Columbus, OH; Reveal Genomics SL, Barcelona, Spain; Emory University School of Medicine, Atlanta, GA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: EA1181 (NCT04266249) is a single-arm trial of neoadjuvant THP for patients with clinical anatomic stage II/III HER2+ breast cancer; patients with cT4 or cN3 disease were excluded . Assessing the primary endpoint, 3-year recurrence-free survival in patients with a pCR (ypT0/Tis, ypN0), requires longer follow-up. Here, we present results for the secondary objective of pCR rate and its relation to clinicopathologic factors and the HER2DX pCR likelihood score (Reveal Genomics) derived from gene expression and clinical features. **Methods:** Patients received 4 cycles of trastuzumab and pertuzumab (HP) with weekly paclitaxel (12 weeks) or docetaxel (q3w x 4), followed by surgery. Clinicopathologic features were assessed for all patients and HER2DX pCR score (stratified by ER status) was determined using the diagnostic biopsy in a representative subset of study participants. **Results:** 2175 patients were enrolled. Median age was 55 years (range 22-88 years); 58% had clinical stage IIA, 33% stage IIB, and 9% stage III. 45% had nodal involvement (mostly cN1). 781 tumors were HER2+/ER- and 1394 HER2+/ER+ (locally tested). 2141 patients started THP, for whom the pCR rate was 44% overall, 63.7% in HER2+/ER- and 32.4% in HER2+/ER+ tumors. Disease progressed during THP in 16 patients (0.7%). The pCR rate varied inversely to the proportion of cells staining for ER among patients with HER2+/ER+ breast cancer: 1-10%+, 62.5%; 11-69%, 51.6%; ≥70%, 22.5% ($p < 0.001$). The pCR rate was significantly associated with higher grade, especially in HER2+/ER+ disease. T and N stage did not significantly affect pCR rate. Among 569 patients assessed for the HER2DX pCR score, the pCR rate was significantly greater for patients with a higher vs lower score, regardless of ER status (Table). Further correlations and interactions will be presented. **Conclusions:** Neoadjuvant THP resulted in pCR in nearly two-thirds of pts with clinical stage II/III HER2+/ER- and in one-third with HER2+/ER+ breast cancer. There was no association with clinical stage. Lower ER expression and higher grade were associated with higher pCR rates. The HER2DX pCR score was a significant predictor of pCR, regardless of ER status. Clinical trial information: NCT04266249. Research Sponsor: National Cancer Institute; Breast Cancer Research Foundation; Susan G. Komen for the Cure.

	All Participants		HER2+/ER-		HER2+/ER+	
	# patients enrolled	pCR rate (95% CI)	# patients enrolled	pCR rate (95% CI)	# patients enrolled	pCR rate (95% CI)
Evaluable Cohort	2141	44% (42-46%)	774	64% (60-67%)	1367	32% (30-35%)
HER2DX Cohort	569	48% (44- 52%)	230	69% (63-75%)	339	34% (29-39%)
HER2DX pCR-high score	182 (32%)	68% (60-74%)	147 (64%)	70% (62-77%)	36 (11%)	58% (41-74%)
HER2DX pCR-medium score	161 (28%)	67% (59- 74%)	70 (30%)	74% (62- 84%)	89 (26%)	61% (50-71%)
HER2DX pCR-low score	226 (40%)	19% (14- 25%)	13 (6%)	31% (9-61%)	214 (63%)	18% (13-24%)
P-value HER2DX score		<0.001		0.010		<0.001

Prediction of survival after de-escalated neoadjuvant therapy in HER2+ early breast cancer: A pooled analysis of three WSG trials.

Monika Karla Graeser, Oleg Gluz, Christine zu Eulenburg, Sherko Kuemmel, Matthias Christgen, Rachel Wuerstlein, Hans Heinrich Kreipe, Peter Schmid, Marc Thill, Michael Wilhelm Braun, Claudia Schumacher, Joke Tio, Johannes Schumacher, Andreas D. Hartkopf, Chrisitan Schem, Kerstin Luedtke-Heckenkamp, Felix Hilpert, Ronald Kates, Ulrike Nitz, Nadia Harbeck; West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and Department of Gynecology, University Medical Center Hamburg, Hamburg, Germany; West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and University Hospital Cologne, Cologne, Germany; West German Study Group, Moenchengladbach, Germany; Breast Unit, Kliniken Essen-Mitte, Essen, and Charité-Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Essen, Germany; Hannover Medical School, Institute of Pathology, Hannover, Germany; Breast Center, Dept. OB&GYN, University of Munich (LMU) and CCCLMU, West German Study Group, Munich, Germany; Hanover Medical School, Institute of Pathology, Hannover, Germany; Barts Cancer Institute, London, United Kingdom; Agaplesion Markus Krankenhaus, Frankfurt Am Main, Germany; Red Cross Hospital, München, Germany; St. Elisabeth Hospital, Cologne, Germany; University Hospital Muenster, Münster, Germany; Palleos Healthcare GmbH, Wiesbaden, Germany; Department of Obstetrics and Gynecology, University of Tuebingen, Tuebingen, Germany; Krankenhaus Jerusalem, Mammazentrum Hamburg, Hamburg, Germany; Department of Oncology and Hematology, Niels-Stensen-Kliniken, Georgsmarienhütte, Germany; Oncologic Medical Center at the Jerusalem Hospital Hamburg, Hamburg, Germany; University Hospital Munich, Munich, Germany

Background: Current treatment de-escalation strategies in HER2+ early breast cancer (eBC) aim to mitigate acute and late toxicities by reducing or entirely omitting systemic chemotherapy (sCTx). We analyzed the outcomes and investigated predictors of survival in three randomized de-escalation trials investigating short (12-week) neoadjuvant treatments (NAT) with and without sCTx (paclitaxel, pac) in HER2+ eBC. **Methods:** In total, 713 patients (pts) were analyzed. WSG-ADAPT-HR-/HER2+ (NCT01817452) compared trastuzumab and pertuzumab (T + P, n=92) vs. T +P + pac (n=42); WSG-ADAPT-HR+/HER2+ (NCT01779206) compared trastuzumab emtansine (T-DM1, n=118) vs. T-DM1 + standard endocrine therapy (ET, n=125) vs. T + ET (n=129); WSG-TP-II (NCT03272477) compared neoadjuvant/adjuvant T + P + ET (n=100) vs. T + P + pac (n=107). Omission of further sCTx was allowed in pts with pathological complete response (pCR, ypT0/is ypN0); sCTx was mandatory for non-pCR pts. pCR was the primary endpoint of each trial; survival was a secondary endpoint. Kaplan-Meier method and Cox regression were applied for survival analysis. **Results:** Median follow-up of 60.7 months was available for 713 pts (sCTx: n=149; sCTx-free NAT: n=564). 395 tumors (55%) were cT2-4, 414 (58%) were grade 3, and 223 pts (31%) were clinically node-positive. Ten (7%) and 74 (13%) pts had iDFS events, 8 (5%) and 51 (9%) had dDFS events, and 6 (4%) and 34 (6%) pts died in the sCTx and sCTx-free NAT groups, respectively. In the sCTx and sCTx-free NAT groups, the respective 5-year survival rates were 98% (95%CI 93, 99) and 97% (95%CI 95, 98) for OS (HR 0.88; 95%CI 0.36, 2.11; p=0.775) and 96% (95%CI 91, 98) and 88% (95%CI 85, 91) for iDFS (HR 0.56; 95%CI 0.29, 1.08; p=0.083). 95 (66%) and 171 (31%) pts had a pCR after sCTx and sCTx-free NAT, respectively. iDFS events occurred in 5 (5%) pts with pCR and 5 (10%) without pCR after sCTx and in 14 (8%) with pCR and 59 (16%) pts without pCR after sCTx-free NAT. 5-year iDFS rates in pts with pCR were 98% (95%CI 91, 99) after sCTx and 94% (95%CI 89, 97) after sCTx-free NAT (HR 0.76; 95%CI 0.27, 2.14; p=0.609). In univariate analysis, iDFS was associated with pCR (HR 0.18; 95%CI 0.04, 0.77) in the sCTx group and with cT (3-4 vs 1: HR 2.54; 95%CI 1.22, 5.28) and cN stage (cN+ vs cN-: HR 2.27; 95%CI 1.44, 3.58), grade (3 vs 1-2: HR 1.79; 95%CI 0.86, 3.74) and pCR (HR 0.47; 95%CI 0.26; 0.84) in the sCTx-free NAT group. Detailed subgroup analyses including the impact of standard chemotherapy on outcome will be presented at the meeting. **Conclusions:** This pooled analysis demonstrates that de-escalation trials in HER2+ eBC are feasible and safe for patients. 12× weekly paclitaxel + HER2 blockade is an effective and well-tolerated regimen with excellent 5-year survival. The favorable survival after pCR to sCTx-free NAT lays the groundwork for further de-escalation strategies, such as the currently ongoing WSG-ADAPT-HER2-IV evaluating T-DXd as NAT. Clinical trial information: NCT01817452, NCT01779206, NCT03272477. Research Sponsor: None.

Comparison of marking techniques for target lymph nodes in 2,596 patients with node-positive breast cancer treated with neoadjuvant chemotherapy: Results from the prospective multicenter AXSANA/EUBREAST-03/AGO-B-053 study (NCT04373655).

Maggie Banys-Paluchowski, Steffi Hartmann, Nina Ditsch, Jana de Boniface, Oreste Davide Gentilini, Elmar Stickeler, Guldeniz Karadeniz Cakmak, Michael Hauptmann, Marc Thill, Rosa Di Micco, Markus Hahn, Dawid Murawa, Isabel T. Rubio, David Pinto, Michalis Kontos, Laura Niinikoski, Maria Luisa Gasparri, Helidon Nina, Lia Pamela Rebaza, Thorsten Kühn, AXSANA Study Group; Department of Obstetrics and Gynecology, University Hospital of Schleswig Holstein, Campus Lübeck, Lübeck, Germany; Department of Gynecology and Obstetrics, University Hospital Rostock, Rostock, Germany; Department of Gynecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany; Department of Medical Epidemiology and Biostatistics, Karolinska Institutet and Department of Surgery, Capio St. Göran's/Department of Surgery, Capio St. Göran's Hospital, Stockholm, Sweden; Breast Unit, IRCCS San Raffaele Scientific Institute/Università Vita-Salute San Raffaele, Milan, Italy; University Hospital Aachen, Aachen, Germany; Zonguldak BEUN The School of Medicine, Breast and Endocrine Unit, General Surgery Department, Kozlu/Zonguldak, Turkey; Brandenburg Medical School Theodor Fontane, Neuruppin, Germany; Agaplesion Markus Krankenhaus, Frankfurt Am Main, Germany; Breast Surgery Unit, IRCCS Ospedale San Raffaele, Milan, Italy; Department of Gynecology and Obstretrics, University Hospital Tübingen, Tübingen, Germany; General Surgery and Surgical Oncology Department, Collegium Medicum, University in Zielona Gora, Zielona Gora, Poland; Breast Surgical Unit, Clinica Universidad de Navarra, Madrid, Spain; Breast Unit, Champalimaud Clinical Centre, Champalimaud Foundation, Lisboa, Portugal; Department of Surgery, University of Athens Laiko Hospital, Athens, Greece; Breast Surgery Unit, Comprehensive Cancer Center, Helsinki University Hospital, University of Helsinki, Helsinki, Finland; Ospedale Regionale di Lugano EOC; Centro di Senologia della Svizzera Italiana (CSSI), Ente Ospedaliero Cantonal, Lugano, Switzerland; Department of Surgery, Oncology Hospital, Tirana, Albania; Breast Surgery, Oncosalud, Lima, Peru; Department of Gynecology and Obstetrics, University of Ulm; Breast Cancer Center, Die Filderklinik, Ulm; Filderstadt, Germany

Background: Surgical axillary staging in patients with node-positive (cN+) breast cancer scheduled for neoadjuvant chemotherapy (NACT) varies significantly, and includes axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), targeted axillary dissection (TAD), and target lymph node biopsy (TLNB). SLNB/TAD/TLNB aim at reducing surgical morbidity without loosing staging accuracy. Comparative data on marking techniques for TAD/TLNB are limited. Here, different marking techniques from the largest available international prospective cohort are critically evaluated. **Methods:** AXSANA is an ongoing cohort study investigating oncological and patient-reported outcomes after different axillary procedures in cN+ breast cancer treated with NACT. In the present analysis, the subgroup of patients receiving marking of their TLN is selected, and detection and removal rates are analyzed. The entire dataset is continuously and systematically monitored for data quality assurance. **Results:** 6,129 patients from 291 sites in 26 countries were included between June 2020 and January 6th, 2025. Of these, 2,596 had $\geq$ 1 TLN marked before NACT and had completed surgery at time of analysis. The mean number of suspicious nodes at diagnosis was 1.9 ($\geq$ 4 in 13.4%). 2,484 patients (95.7%) received a minimally invasive biopsy of $\geq$ 1 node. TLN marking was performed using a clip in 2,003 patients (77.2%), a magnetic seed in 287 (11.1%), carbon ink in 192 (7.4%), radar marker in 119 (4.6%), radioactive seed in 18 (0.7%), radiofrequency identification device (RFID) in 12 (0.5%) or other methods in 2 (0.1%). $>$ 1 type of marker was placed in 36 patients (1.4%). 1 TLN was marked in 2,427 patients (93.5%), followed by 2 TLNs in 138 (5.3%) and $\geq$ 3 in 27 patients (1%). The mean number of marked TLNs was highest if carbon ink was used (mean 1.21), followed by clip (1.07), magnetic seed (1.06) and radar marker (1.04); no patient received $>$ 1 radioactive seed/RFID. 1,895 patients (73.0%) achieved ycN0 status. Targeted removal of the TLN was planned in 2,100 patients (80.9%): 2,076 (80.0%) were scheduled for a TAD and 24 (0.9%) for a TLNB. TLN was detected and removed during TAD/TLNB in 1,915 patients (91.2%). TLN detection rate was highest in patients whose TLNs were marked with probe-guided techniques (96.6%; radioactive seed: 100%, magnetic seed: 96.9%, radar marker: 96.1%, RFID: 90%), followed by carbon (94.9%) and clip (89.6%; $p < 0.001$). TAD/TLNB removed a median number of 3 nodes (mean 4.1, SD 2.77; carbon: median 4, mean 4.29, SD 3.52, probe-guided: median 3, mean 3.82, SD 2.63, clip: median 3, mean 4.15, SD 2.75). **Conclusions:** This large prospective analysis of patients with initially cN+ breast cancer receiving NACT demonstrates that probe-guided markers provide superior TLN detection rates. Clinical trial information: NCT04373655. Research Sponsor: AGO-B; AWOgyn; Claudia von Schilling Foundation for Breast Cancer Research; Ehmann Foundation Savognin; EndoMag; Merit Medical; Mammotome.

Predicting nodal burden after neoadjuvant chemotherapy (NAC) with circulating tumor (ct)DNA for surgical planning: Results from the I-SPY2 trial.

Rita Mukhtar, Katrina Dimitroff, Christina Yau, Laura van t Veer, Jo Chien, Gillian L. Hirst, Lamorna Brown Swigart, Angela DeMichele, Douglas Yee, Hope S. Rugo, Rebecca Arielle Shatsky, Claudine Isaacs, Kamran A. Ahmed, Julia C. Tchou, Henry Mark Kuerer, Chantal Reyna, Candice A. Sauder, Laura Esserman, Judy Caroline Boughey, Mark Jesus M. Magbanua; Division of Surgical Oncology, Department of Surgery, University of California, San Francisco, San Francisco, CA; University of California, San Francisco, San Francisco, CA; Department of Laboratory Medicine, University of California, San Francisco, San Francisco, CA; UCSF Comprehensive Cancer Center, San Francisco, CA; University of Pennsylvania, Philadelphia, PA; Masonic Cancer Center, University of Minnesota, Minneapolis, MN; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of California, San Diego Medical Center, La Jolla, CA; Lombardi Cancer Center, Georgetown University, Washington, DC; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; The University of Texas MD Anderson Cancer Center, Houston, TX; Loyola University Medical Center, Maywood, IL; University of California, Davis Comprehensive Cancer Center, Sacramento, CA; Department of Surgery, University of California, San Francisco, San Francisco, CA; Mayo Clinic, Rochester, MN

Background: Axillary surgery in breast cancer is used for staging and therapeutic purposes, but axillary lymph node dissection (ALND) confers high risk of complications including lymphedema. Accordingly, trials have focused on right-sizing axillary surgery, with options ranging from complete omission of surgery, sentinel lymph node (SLN) surgery, targeted axillary dissection (TAD), or ALND. Identifying a biomarker to reliably predict nodal burden would facilitate accurate selection of surgical management. We evaluated whether the presence or absence of ctDNA in the blood pre and post NAC is associated with residual nodal burden. **Methods:** I-SPY2 is a prospective, multicenter NAC trial for patients with clinical stage II-III high-risk breast cancer. Patients are randomized to novel NAC agents, with pathologic complete response being the primary endpoint. As part of the trial, serial ctDNA is assessed with a highly sensitive tumor-informed assay using up to 16 patient-specific tumor mutations (Signatera) at baseline, 3 weeks, 12 weeks, and post-NAC. We determined whether ctDNA positivity or negativity post-NAC, and the change in ctDNA status baseline/post-NAC (-/-, -/+, +/+, +/-) are associated with ypN category (N0, N1, N2). **Results:** ctDNA status was available post-NAC in 495 patients and change in ctDNA status from baseline was available in 493. At baseline, ctDNA was detected in 160/220 (72.3%) cN0 patients and 227/273 (83.2%) cN+ patients (p=0.006). Post-NAC, ctDNA was detected in 11/220 (5%) cN0 patients and 34/273 (12.5%) cN+ patients (p=0.004). While baseline ctDNA status was not associated with ypN category, there was a significant association between post-NAC ctDNA status and ypN category. For ctDNA + patients post-NAC, 33.3% were ypN0, 31.1% were ypN1, and 35.6% were ypN2 at surgery; in contrast, for ctDNA - patients post-NAC, 67.1% were ypN0, 23.1% were ypN1, and 9.8% were ypN2 ($p<0.0001$). Dynamic ctDNA changes were also associated with ypN category, with significantly more ypN0 patients among ctDNA -/- or ctDNA +/- cases, and more ypN2 patients in those who did not clear ctDNA (+/+) (p=0.0001, Table). **Conclusions:** To our knowledge this is the first study to demonstrate a significant relationship between ctDNA and ypN category, which has important surgical implications. CtDNA negativity was associated with low likelihood of ypN2 disease, making these patients excellent candidates for SLN surgery or TAD. Ongoing analyses will incorporate receptor subtype and timing of clearance of ctDNA. CtDNA in breast cancer may help tailor surgical management of the axilla, potentially reducing patient morbidity without compromising prognostic information. Research Sponsor: None.

ctDNA baseline/post-NAC	ypN0 (n=317)	ypN1 (n=116)	ypN2 (n=60)
ctDNA -/- (n=105)	72.4%	19.1%	8.6%
ctDNA -/+ (n=1)	0.0%	100.0%	0.0%
ctDNA +/+ (n=44)	34.1%	29.6%	36.4%
ctDNA +/- (n=343)	65.9%	23.9%	10.2%

15-year outcomes for women with premenopausal hormone receptor-positive early breast cancer (BC) in the SOFT and TEXT trials assessing benefits from adjuvant exemestane (E) + ovarian function suppression (OFS) or tamoxifen (T)+OFS.

Prudence A. Francis, Gini F. Fleming, Olivia Pagani, Barbara Walley, Sherene Loi, Marco Colleoni, Meredith M. Regan, on behalf of SOFT and TEXT Investigators, IBCSG, BIG and North American BC Groups; Peter MacCallum Cancer Centre, Melbourne, Australia; University of Chicago, Chicago, IL; Geneva University Hospitals, SAKK, Lugano Viganello, Switzerland; University of Calgary, Calgary, AB, Canada; Istituto Europeo di Oncologia, IRCCS, Milan, Italy; Dana-Farber Cancer Institute and IBCSG Statistical Center, Boston, MA

Background: Long-term follow-up of the SOFT and TEXT randomized trials has shown persistent reduction of recurrence from inclusion of OFS in adjuvant endocrine therapy, and clinically meaningful improvement in overall survival (OS) among patients at higher baseline risk of recurrence. We report a final update after a median follow-up of 15y in SOFT and 16.6y in TEXT. **Methods:** SOFT and TEXT enrolled premenopausal women with HR+ early BC from November 2003 to April 2011 (2660 in TEXT, 3047 in SOFT intention-to-treat populations). TEXT randomized women within 12 weeks of surgery to 5y E+OFS vs T+OFS; chemotherapy (CT) was optional and concurrent with OFS. SOFT randomized women to 5y E+OFS vs T+OFS vs T alone, within 12 weeks of surgery if no CT planned, or within 8 months of completing (neo) adjuvant CT. Both trials were stratified by CT use. The primary endpoint was disease free survival (DFS) which included invasive local, regional, distant and contralateral breast events, second non-breast malignancies and deaths. Secondary endpoints included invasive breast cancer-free interval (BCFI), distant recurrence free interval (DRFI) and OS. 20y data collection was completed in Q4'2024: 80% of surviving patients had final follow-up during or subsequent to 2020, for 70% it was during 2023-2024. 15y Kaplan-Meier estimates and hazard ratios (HR) with 95% CIs are reported. **Results:** There were 815 DFS events and 388 deaths reported in SOFT; and 669 DFS events and 325 deaths in TEXT. In SOFT, a moderate DFS benefit of T+OFS vs T (HR 0.85; 0.72-1.00) persisted, however 1/6 DFS events were not BC related; BCFI benefit was HR 0.82 (0.69-0.98). E+OFS vs T further reduced DFS events (HR 0.73; 0.61-0.86). The 15y DFS in SOFT was 67.0% for T, 70.5% for T+OFS and 73.5% for E+OFS. There were consistent but non-significant decreased hazards of death for T+OFS vs T (HR 0.87; 0.68-1.10) and E+OFS vs T (HR 0.85; 0.67-1.08). 15y OS was 85.3%, 86.7%, 86.9% respectively. For the TEXT+SOFT combined analysis of E+OFS vs T+OFS (n=2346 vs 2344) DFS, BCFI and DRFI continued as significantly improved for E+OFS over T+OFS. 15y DFS was 74.9% vs 71.3% (HR 0.82; 0.73-0.92). 15y OS was 87.8% vs 87.0% (HR 0.94; 0.80-1.11) respectively. 15y estimates by CT use are tabulated. **Conclusions:** The high level 15y final results of the SOFT and TEXT confirm a role for OFS- and aromatase inhibitor-containing adjuvant endocrine therapy for premenopausal women. Analysis is ongoing. Clinical trial information: NCT00066690 (SOFT) and NCT00066703 (TEXT). Research Sponsor: ETOP IBCSG Partners Foundation, BCRF, US NCI, Pfizer, Ipsen, et al have supported long-termfollow-up of the trials.

15y (%)	Events	SOFT Prior CT (n=1628)	SOFT no CT (n=1419)
	CT+noCT	T / T+OFS / E+OFS	T / T+OFS / E+OFS
DFS	536+279	60.9 / 63.0 / 66.3	73.9 / 79.1 / 82.1
DRFI	367+56	73.5 / 73.8 / 77.6	94.7 / 94.7 / 96.8
OS	318+70	77.4 / 79.4 / 79.8	94.4 / 95.1 / 95.2
		TEXT CT (n=1607)	**TEXT no CT (n=1053)**
		T+OFS / E+OFS	T+OFS / E+OFS
DFS	456+213	68.5 / 72.1	76.8 / 81.8
DRFI	286+69	79.0 / 81.3	91.6 / 94.6
OS	266+59	82.7 / 84.3	94.1 / 94.8

Updated survival outcomes and predictors of benefit from ovarian function suppression in premenopausal women with hormone-receptor–positive breast cancer: Results from the ASTRRA trial.

Jai Min Ryu, Soong June Bae, Woo Chul Noh, Hyun-Ah Kim, Soo Yeon Baek, Seock-Ah Im, Seho Park, Eun-Gyeong Lee, Min-Ho Park, KyongHwa Park, Su Hwan Kang, Eunhwa Park, Jong Eun Lee, Min Hyuk Lee, Woosung Lim, Eun Young Kim, Tae Hyun Kim, Seonok Kim, Jung Ho Park, Hee Jeong Kim; Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Seoul, South Korea; Department of Surgery, Konkuk Universitiy Medical Center, Seoul, South Korea; Department of Surgery, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, South Korea; Department of Surgery, Ajou University School of Medicine, Suwon, South Korea; Seoul National University College of Medicine, Cancer Research Institute, Seoul National University, Seoul, South Korea; Division of Breast Surgery, Department of Surgery, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; Center for Breast Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Korea, Republic of; Chonnam National University Medical School, Gwangju, Korea, Republic of (South); Division of Oncology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea; Department of Surgery, Yeungnam University Medical Center, Yeungnam University College of Medicine, Daegu, South Korea; Dong-A University Hospital, Dong-A University College of Medicine, Busan, South Korea; Department of Surgery, Soonchunhyang University Cheonan Hospital, Cheonan, South Korea; Soonchunhyang University Hospital, Seoul, South Korea; Ewha Womens University Medical Center, Seoul, South Korea; Department of General Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea; Inje University Busan Paik Hospital, Busan, South Korea; Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, South Korea; Hallym University Sacred Heart Hospital, Anyang, South Korea; Department of Surgery, Division of breast surgery, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, Songpa-gu, South Korea

Background: The ASTRRA trial previously demonstrated that adding ovarian function suppression (OFS) to tamoxifen (TAM) showed consistent disease free survival (DFS) benefit at 8-yr follow-up analysis in premenopausal women with hormone-receptor (HR)–positive breast cancer who remain premenopausal or resume menstruation after chemotherapy. Here, we aimed to update the survival outcomes and identify patients most likely to benefit from OFS to tailor clinical decision-making. **Methods:** A total of 1,282 premenopausal women were randomized 1:1 to receive either 5 years of TAM alone (TAM-only) or 5 years of TAM with OFS for 2 years (TAM + OFS). The primary endpoint was DFS, and the secondary endpoint was overall survival (OS). For the HER2-negative cohort, a composite risk score (range: 0–5) for breast cancer-free interval (BCFI) was calculated based on tumor size, nodal status, and tumor grade using a Cox regression model. The impact of OFS was analyzed by composite risk score and stratified by age. The events for BCFI were defined as local, regional, or distant recurrence; invasive contralateral breast cancer; or death resulting from breast cancer as the first event. **Results:** With a median follow-up of 117.6 months, the 10-year DFS rate was 83.7% in the TAM + OFS group compared to 75.9% in the TAM-only group (hazard ratio [HR], 0.68; 95% CI, 0.53-0.87). Meanwhile, there were no significant differences in 10-year OS: 94.6% in the TAM + OFS vs. 93.2% in the TAM-only group (HR, 0.79; 95% CI, 0.50-1.27). In the 776 patients with HER2-negative breast cancer, there were no significant differences in the distribution of age group (P = .320), tumor size (P = .572), lymph node status (P = .577), or histologic grade (P = .249) between TAM + OFS and TAM-only groups. Worse 10-year BCFI was significantly associated with younger age ($<$ 40 vs. 40-45 years, P = .026), larger tumor size ($\geq$ 2cm vs. $<$ 2cm, $P <$ .001), lymph node positivity (positive vs. negative, $P <$ .001), and aggressive histologic grade (III vs. II vs. I, P = .006), respectively. Among patients with a high composite risk score (4–5, n = 282, 36.3% of the HER2-negative cohort), the 10-year BCFI was significantly improved with OFS: 76.6% in the TAM + OFS group vs. 65.7% in the TAM-only group (HR, 0.62; 95% CI, 0.40–0.98). This benefit was particularly pronounced in patients aged 40–45 years. **Conclusions:** We demonstrated the consistent benefit of adding OFS for 2 years to TAM in improving 10-year DFS. In patients with HR-positive/HER2-negative breast cancer and a high composite risk score, the addition of TAM plus OFS resulted in a 10.9% improvement in the 10-year BCFI, suggesting this approach may be beneficial, especially for those aged 40-45 years. Clinical trial information: NCT00912548. Research Sponsor: National Research & Development Program for Cancer Control through the National Cancer Center funded by the Ministry of Health & Welfare, Republic of Korea; No. HA23C014400.

The impact of ovarian function suppression with adjuvant endocrine therapy on survival outcomes in young germline *BRCA* mutation carriers with breast cancer: Secondary analysis of an international cohort study.

Paola Zagami, Yara Abdou, Virginia Delucchi, Hee Jeong Kim, Florence Coussy, Ava Kwong, Antonio Di Meglio, Giuseppe Curigliano, Judith Balmaña, Katarzyna Pogoda, Luisina Ines Bruno, Ann H. Partridge, Jeong Eon Lee, Sabine C. Linn, Hans Wildiers, Roberto Borea, Elisa Agostinetto, Lisa A. Carey, Eva Blondeaux, Matteo Lambertini; UNC Lineberger Comprehensive Cancer Center/University of Milan/ European institute of Oncology IRCSS (IEO), Chapel Hill, NC; Division of Oncology, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; Department of Surgery, Division of breast surgery, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, Songpa-gu, South Korea; Universite Paris Cité, Institut Curie, Paris, France; Hong Kong Hereditary Breast Cancer Family Registry,Surgery Centre & Cancer Genetics Centre, Hong Kong Sanatorium & Hospital,The University of Hong Kong, Hong Kong, Hong Kong; Cancer Survivorship Program, INSERM 981, Gustave Roussy, Villejuif, France; European Institute of Oncology, IRCCS and University of Milano, Milano, Italy; Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; SUMA (Grupo Cooperativo Argentino para el Estudio y la Investigación del Cáncer de Mama), Argentina, Argentina; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea; Department of Molecular Pathology, Netherlands Cancer Institute (NKI), Amsterdam, Netherlands; Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium; Università degli Studi di Genova, Genova, Italy; Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Brussels, Belgium; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; U.O. Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, University of Genova, Genova, Italy; U.O. Clinical Oncology, IRCCS Ospedale Policlinico San Martino, University of Genova, Genova, Italy

Background: In young women with hormone receptor-positive (HR+) breast cancer (BC), ovarian function suppression (OFS) has been shown to improve outcomes when combined with adjuvant endocrine therapy (ET). However, limited evidence exists on its efficacy in germline *BRCA (gBRCA)* carriers. Here we investigated the association between OFS plus ET and outcomes in the largest global cohort of young g*BRCA* carriers with BC. **Methods:** The BRCA BCY Collaboration (NCT03673306) is an international, multicenter, hospital-based, retrospective cohort study of women harboring germline *BRCA1/2* pathogenic/likely pathogenic variants, diagnosed between 2000 and 2020 with stage I-III invasive BC at age of ≤ 40 years. The analysis included patients with HR+ BC and available data on ET and OFS. The OFS group included patients treated with luteinizing hormone-releasing hormone agonists (LHRHa) and/or bilateral risk-reducing salpingo-oophorectomy (RRSO) within 1 year of BC diagnosis. Outcome analyses included disease-free survival (DFS), BC-free interval (BCFI) and overall survival (OS). Cox proportional hazard models, stratified for country, year of diagnosis, nodal status, and surgery type and adjusted for RRSO and bilateral risk-reducing mastectomy (time-dependent), were used to explore the association between OFS use (vs non-use) and outcomes. Sensitivity analysis explored OFS as time-dependent covariate. To address immortal time bias, an additional Cox model accounted for left truncation, considering differences in time to *BRCA* testing. **Results:** Among 5,660 patients from 109 centers, 1,865 patients with HR+ BC were included, of whom 1,071 (57%) received OFS plus ET (35% with an aromatase inhibitor [AI], 65% with tamoxifen [tam])and 794 (43%) received tam alone. Patients receiving OFS were more likely to have node-positive disease (56% vs 47%), receive treatment in recent years (36% vs 17%), undergo mastectomy (70% vs 57%) and be tested for g*BRCA* at diagnosis (46% vs 30%). With a median follow-up of 7.8 years (IQR 4.6-12.1), OFS combined with ET was associated with significantly improved DFS (adjusted HR [aHR] 0.79, 95% CI 0.66-0.94), BCFI (aHR 0.74, 95% CI 0.61-0.89) and OS (aHR 0.66, 95% CI 0.50-0.88) over tam alone. Sensitivity analysis using OFS as a time-dependent factor yielded consistent results. No significant interactions were observed between OFS use and specific g*BRCA* mutations or HER2 status. Sub-analyses by type of ET (OFS + AI vs. OFS + tam vs. tam alone) will be presented at the conference. **Conclusions:** In this global cohort of young *BRCA* mutation carriers, OFS combined with ET was associated with improved DFS, BCFI and OS versus tam without OFS. These findings support the consideration of OFS as a key component of adjuvant therapy in this population. Research Sponsor: None.

Efficacy and safety of elinzanetant for vasomotor symptoms associated with adjuvant endocrine therapy: Phase 3 OASIS 4 trial.

Fatima Cardoso, Donal J. Brennan, Paula Briggs, Gilbert Donders, Nick Panay, Nazanin Haseli Mashhadi, Cecilia Caetano, Maja Franscuski, Claudia Haberland, Kaisa Laapas, Christian Seitz, Lineke Zuurman; ABC Global Alliance, Lisbon, Portugal; UCD School of Medicine, Dublin, Ireland; Liverpool Women's Hospital, Liverpool, United Kingdom; Department of Clinical Research for Women, Tienen, Belgium; Queen Charlotte's & Chelsea Hospital, London, United Kingdom; Bayer plc, Reading, United Kingdom; Bayer CC AG, Basel, Switzerland; Bayer AG, Berlin, Germany; Bayer Oy, Espoo, Finland

Background: Vasomotor symptoms (VMS) associated with adjuvant endocrine therapy (AET) impact quality of life and decrease treatment adherence, worsening breast cancer outcomes. There are few effective treatment options and none approved for this indication. **Methods:** The 52-week randomized phase 3 trial OASIS 4 (NCT05587296) evaluated the safety and efficacy of elinzanetant (EZN), a dual neurokinin-1 and -3 receptor antagonist, in women aged 18–70 years being treated for, or at high risk of developing, hormone receptor-positive (HR+) breast cancer and experiencing ≥35 moderate-to-severe VMS/week associated with AET. Women were randomized 2:1 to receive once-daily EZN 120 mg for 52 weeks or placebo (P) for 12 weeks followed by EZN for 40 weeks. Primary endpoints were mean change in moderate-to-severe VMS frequency from baseline to weeks 4 and 12 analyzed using mixed model with repeated measures (one-sided p-values). Secondary endpoints were mean changes from baseline in moderate-to-severe VMS frequency to week 1 and moderate-to-severe VMS severity to weeks 4 and 12. Treatment-emergent adverse events (TEAEs) were reported throughout the study. **Results:** Mean (standard deviation [SD]) baseline daily VMS frequency was 11.4 (6.9) in the EZN group (n=316) and 11.5 (6.4) in the P group (n=157). Reductions from baseline in VMS frequency were observed from week 1 (EZN: -4.0 [5.1]; P: -1.8 [3.8]). At week 4, mean (SD) VMS frequency reduced by -6.5 (6.1) with EZN and -3.0 (5.0) with P, with statistical significance between EZN and P (least squares [LS] mean difference [95% confidence interval (CI)]: -3.5 [-4.4, -2.6]; $p<0.0001$). At week 12, reductions in VMS frequency were -7.8 (6.2) with EZN and -4.2 (6.1) with P, with statistical significance between EZN and P (LS mean difference [95% CI]: -3.4 [-4.2, -2.5]; $p<0.0001$). Reductions in VMS severity were greater with EZN vs. P (week 4: -0.7 [0.6]; -0.4 [0.4], week 12: -1.0 [0.7]; -0.5 [0.6]). During the placebo-controlled period, 220 (69.8%) and 98 (62.0%) patients reported TEAEs in the EZN and P groups, respectively. Somnolence, fatigue, and diarrhea were more frequently reported with EZN (Table). Fewer TEAEs were reported in both groups during weeks 13–52. **Conclusions:** EZN was efficacious with a fast onset and well tolerated for the treatment of VMS associated with AET. TEAE frequency was as expected for this type of trial. Adequate VMS management can improve adherence to AET and, therefore, improve cancer outcomes and quality of life. Clinical trial information: NCT05587296. Research Sponsor: Bayer.

n (%)	EZN Week 1–12 n=315	P Week 1–12 n=158	Total EZN Week 1–52 N=465
Any TEAE	220 (69.8%)	98 (62.0%)	368 (79.1%)
Headache	30 (9.5%)	20 (12.7%)	56 (12.0%)
Arthralgia	20 (6.3%)	10 (6.3%)	52 (11.2%)
Fatigue	30 (9.5%)	8 (5.1%)	43 (9.2%)
Somnolence	34 (10.8%)	6 (3.8%)	42 (9.0%)
Diarrhea	16 (5.1%)	3 (1.9%)	32 (6.9%)
Back pain	10 (3.2%)	7 (4.4%)	29 (6.2%)
Nausea	19 (6.0%)	10 (6.3%)	29 (6.2%)
Any serious TEAE	8 (2.5%)	1 (0.6%)	33 (7.1%)

LBA509 **Rapid Oral Abstract Session**

NRG-BR003: A randomized phase III trial comparing doxorubicin plus cyclophosphamide followed by weekly paclitaxel with or without carboplatin for node-positive or high-risk node-negative TNBC.

Vicente Valero, Gong Tang, Priya Rastogi, Charles E. Geyer Jr., Linda H. Colangelo, Alice Tam Kengla, William Johnson Irvin Jr., Matei P. Socoteanu, Jame Abraham, Benjamin T. Esparaz, Kathryn B. Alguire, Lawrence E. Flaherty, Ismail Jatoi, Melinda L. Telli, Issam Makhoul, Tanner Freeman, Greg Yothers, Sandra M. Swain, Eleftherios P. Mamounas, Norman Wolmark; The University of Texas MD Anderson Cancer Center, Houston, TX; NRG Oncology SDMC; Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA; NSABP Foundation, Inc.; UPMC Hillman Cancer Center; and University of Pittsburgh School of Medicine, Pittsburgh, PA; NRG Oncology Statistical and Data Management Center; Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA; Kaiser Permanente Walnut Creek Medical Center, Walnut Creek, CA; Bon Secours Saint Francis Medical Center Cancer Institute/Southeast Clinical Oncology Research (SCOR), Midlothian, VA; Texas Oncology-Longview Cancer Center, US Oncology, Longview, TX; Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; Heartland Cancer Research NCORP/Cancer Care Specialists of Illinois, Decatur, IL; Cancer Research Consortium of West Michigan, Grand Haven, MI; Department of Hematology and Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI; Division of Surgical Oncology, UT Health Science Center, San Antonio, TX; Stanford University School of Medicine, Stanford, CA; CARTI Cancer Center, Little Rock, AR; NSABP Foundation, Inc.; University of Pittsburg School of Medicine, Pittsburgh, PA; Georgetown Lombardi Comprehensive Cancer Center; Georgetown University Medical Center; and MedStar Health, Washington, DC; NSABP and AdventHealth Cancer Institute, Orlando, FL; NSABP Foundation, Inc.; UPMC Hillman Cancer Center; University of Pittsburgh School of Medicine, Pittsburgh, PA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2025, issue of the *Journal of Clinical Oncology*.

Prospective randomized phase II trial to assess the efficacy and safety of neo-adjuvant olaparib/carboplatin (OC) in comparison to docetaxel/epirubicin/cyclophosphamide (TAC) in patients with early triple-negative breast cancer (TNBC) with homologous recombination deficiency (HRD): Primary results from the ABCSG 45 trial.

Christian F. Singer, Dominik Hlauschek, Daniel Egle, Zsuzsanna Bago-Horvath, Georg Pfeiler, Christine Brunner, Christian Peters-Engl, Edgar Petru, Daniel Uwe Reimer, Renate Pusch, Michael Seifert, Petra Pichler, Christoph Suppan, Annette Reiner, Richard Greil, Yen Yen Tan, Rupert Bartsch, Katharina Knoll, Anna Sophia Kermanidis, Michael Gnant; Department of Obstetrics and Gynecology and Center for Breast Health, Comprehensive Cancer Center, Medical University of Vienna and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria; Austrian Breast and Colorectal Cancer Study Group, Wien, Austria; Department of Gynecology, Breast Cancer Center Tirol, Medical University of Innsbruck and Austrian Breast and Colorectal Cancer Study Group, Innsbruck, Austria; Department of Pathology and Comprehensive Cancer Center, Medical University of Vienna, and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria; Department of Gynecology, Breast Cancer Center Tirol, Medical University of Innsbruck, Innsbruck, Austria; Institute for Gynecological Oncology and Senology, Karl Landsteiner Society, Hietzing Hospital, Vienna, Austria; Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria; Ordensklinikum Linz, Barmherzige Schwestern, Abteilung Interne I, Medizinische Onkologie und Hämatologie, Linz, Austria; Clinical Department for Internal Medicine 1, University Hospital St Poelten, Karl Landsteiner University of Health Sciences, St. Poelten, Austria; Division of Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria; IIIrd Medical Department, Paracelsus Medical University, Salzburg Cancer Research Institute-Center for Clinical Cancer and Immunology Trials, Cancer Cluster Salzburg, and Austrian Breast and Colorectcal Cancer Study Group, Salzburg, Austria; Department of Obstetrics and Gynecology and Center for Breast Health, Comprehensive Cancer Center, Medical University of Vienna, Wien, Austria; Department of Medicine I, Division of Oncology, Medical University of Vienna and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria; Austrian Breast and Colorectal Cancer Study Group, Viena, Austria; Comprehensive Cancer Center, Medical University of Vienna and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria

Background: Carboplatin-based regimen are effective in patients (pts) with eTNBC, and olaparib improves the outcome of pts with *BRCA1/2* pathogenic variants (PV), but the safety / efficacy of OC co-treatment in HRD-positive TNBC is unknown. ABCSG 45 (EU CT 2024-512821-10) is a prospective multicenter phase II study investigating the efficacy and tolerability of OC compared to conventional chemotherapy in HRD-positive eTNBC. **Methods:** Pts with HRD (Myriad genetics)-positive eTNBC were randomized to 6 cycles of olaparib (100 mg bid, days 4-16) / carboplatin (AUC 5) q3w, or 6 cycles of docetaxel/epirubicin/cyclophosphamide (75/50/500) q3w (TAC). In an initial dose-finding phase, 100 mg bid was identified as olaparib combination dose. Stratification factors were tumoral *BRCA1/2* and menopausal status. Primary endpoint was centrally assessed residual cancer burden (RCB), pCR and QoL were secondary endpoints. Planned sample size was 90 pts, randomized 1:1 to achieve 80% power (two-sided alpha=0.05) to detect a RCB 0/I difference of 31%. Differences between treatment arms were assessed with a two-sided Cochran Mantel-Haenszel test using stratification factors. Pre-defined subgroup analysis was performed with logistic regression. **Results:** A total of 90 pts (OC: n=46; TAC: n=44), of whom 42 (47%) were *BRCA1/2* PV carriers, were randomized between November 2019 and December 2023. Median age was 50.5 years (range 27.0-80.0). 40% had cT1, 55.6% cT2, and 4.4% cT3/4 tumors, and 60% of pts were clinically N0. 94.4% of tumors were G3, and Ki67 was >60% in 71.1%. Overall, the RCB0/I rate with OC was 52.2% vs. 70.5% with TAC (stratified risk difference = -18.8% (95%CI: -39.6% to 2.0%); p=0.068). In pts with *BRCA1/2* PV, RCB0/I rates were comparable: 77.3% (OC) vs. 65.0% (TAC), while in 47 pts with *BRCA1/2* wild type (WT), OC was significantly less effective: RCB0/I of 29.2% vs 73.9% in TAC (interaction p=0.008). pCR was achieved in 47.8% (OC) vs 59.1% (TAC; p=0.231). In pts with a *BRCA1/2* PV, OC resulted in 77.3% pCR rate, vs. TAC 65.0%, in *BRCA1/2 WT* pts pCR was achieved by 20.8% (OC) vs. 56.5% (TAC) (interaction p=0.021). OC treatment resulted in more ≥ grade 3 hematologic toxicities with 30% vs 3% thrombocytopenia and 43% vs 18% neutropenia but caused fewer non-hematological toxicities. **Conclusions:** In this prospective randomized study in HRD-positive TNBC, 6 cycles of TAC resulted in strikingly high RCB0/I and pCR rates, independent of *BRCA1/2* status. 6 cycles of OC achieved a pCR rate of >77% in BRCA1/2 PV but were less effective in pts with *BRCA1/2* WT disease. These results may help to optimize neoadjuvant treatment strategies in TNBC. This research was conducted with support from AstraZeneca Austria GmbH. Clinical trial information: 2024-512821-10. Research Sponsor: None.

A phase 2 study of response-guided neoadjuvant sacituzumab govitecan and pembrolizumab (SG/P) in patients with early-stage triple-negative breast cancer: Results from the NeoSTAR trial.

Rachel Occhiogrosso Abelman, Shannon McLaughlin, Geoffrey G. Fell, Ana Christina Garrido-Castro, Filipa Lynce, Lorenzo Trippa, Philip Daniel Poorvu, Aron S. Rosenstock, Arielle J. Medford, Seth Andrew Wander, Amy H. Comander, Steven J. Isakoff, Beverly Moy, Nadine M. Tung, Elizabeth A. Mittendorf, Leif Ellisen, Sara M. Tolaney, Aditya Bardia, Laura Spring; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute/Mass General Brigham, Boston, MA; Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Massachusetts General Cancer Center, Harvard Medical School, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute/ Brigham and Women's Hospital, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; University of California Los Angeles Jonsson Comprehensive Cancer Center, Los Angeles, CA; Mass General Cancer Center, Harvard Medical School, Boston, MA

Background: Sacituzumab govitecan (SG) is a TROP-2 directed antibody-drug conjugate (ADC) approved for metastatic triple negative breast cancer (TNBC). Pembrolizumab (P), an anti-programmed death 1 monoclonal antibody, is approved for early-stage TNBC and metastatic PD-L1 positive TNBC. However, safety and efficacy of SG+P in early TNBC is not known. We published results of Arm A1 investigating neoadjuvant SG monotherapy in early TNBC (Spring et al. Annals of Onc 2024). Here we present results from Arm A2 of the NeoSTAR study investigating the combination of neoadjuvant SG + P in early-stage TNBC (NCT04230109). **Methods:** Patients (pts) with early TNBC (tumor size ≥2 cm or node positive) with no prior treatment were eligible. Pts received SG at starting dose of 10mg/kg on days 1,8 of a 21-day cycle for 4 cycles with P 200 mg given on day 1 of each cycle. After trial regimen, pts underwent imaging to determine residual radiographic disease per RECIST v1.1. A biopsy was performed if residual disease (RD) was suspected. Additional neoadjuvant chemotherapy (ANACT) was at discretion of the treating physician prior to definitive surgery. The primary objective was rate of pathologic complete response (pCR) with neoadjuvant SG/P. Secondary objectives included need for ANACT, radiographic response (RR), safety and tolerability (adverse events [AEs] per CTCAE v5.0) and event-free survival. A Simon two-stage design and standard descriptive statistics were utilized, including 95% binomial confidence intervals for all rates estimated. **Results:** From 5/19/23-8/13/24, 50 pts were enrolled (median age: 57 years, range 23-77). Clinical anatomic stage was II in 48 pts (96%) and III in 2 pts (4%). 64% of pts were node negative at diagnosis. 44 pts (88%) completed the trial regimen (5 pts had toxicity, 1 pt progressed on treatment). In interim analysis, 5/15 had pCR and so the remaining 35 were enrolled. The pCR rate per protocol (pts with pCR at surgery directly after SG/P without ANCT) was 16/50 (34%, 95% CI 19.5-46.7). The RR rate (complete CR or partial response PR) was 66% (95% CI 50-78%), 30% CR and 36% PR. Of 26 pts who received ANACT, 9 experienced pCR (2 biopsy-confirmed RD, 6 negative or non-diagnostic RD biopsy, 1 no biopsy). Overall, 25 (50%, 95% CI 35.5-64.5) pts had pCR at surgery. Of 5 pts with pathogenic BRCA mutations, 3 (60%) had pCR after SG/P, and 1 pt had pCR after ANACT. 20 pts (40%) had grade 3 or higher AEs. The most common AEs were nausea (28, 56%), alopecia (26, 52%), fatigue (23, 46%), and diarrhea (22, 44%). Dose reductions of SG occurred in 4 pts (8%). Updated survival and biomarker data will be presented at the meeting. **Conclusions:** In the first trial to investigate the SG/P combination in early TNBC, 34% of pts had pCR. Additional research is needed to determine the optimal duration and sequence of neoadjuvant SG/P and chemotherapy for pts with TNBC. Clinical trial information: NCT04230109. Research Sponsor: None.

The Promise study: A presurgical randomized clinical trial of CE/BZA vs placebo in postmenopausal women with ductal carcinoma in situ.

Swati Kulkarni, Geoffrey Greene, Luis Blanco, Thea Tlsty, Philippe Gascard, Danielle Kline, Masha Kocherginsky, Yangruijue Ma, Rebecca Aft, Mary Ahn, Judy Ellen Garber, Kirstyn Brownson, Emilia Diego, David Euhus, Julia Tchou, Melissa Lazar, Michael Avram, Lauren Schulte, Denisha Brown, Natalie H. Friedman; Northwestern University Feinberg School of Medicine, Chicago, IL; University of Chicago, Chicago, IL; Northwestern University, Chicago, IL; University of California, San Francisco, San Francisco, CA; Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; Division of Biostatistics, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; Washington University in St. Louis School of Medicine, St. Louis, MO; Northwestern Medicine Regional Medical Group , Winfield, IL; Dana-Farber Cancer Institute, Boston, MA; Huntsman Cancer Hospital, Salt Lake City, UT; Division of Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA; Johns Hopkins Medicine, Baltimore, MD; University of Pennsylvania, Philadelphia, PA; Thomas Jefferson University, Philadelphia, PA; Northwestern Medicine, Chicago, IL

Background: Conjugated estrogen/bazedoxifene (CE/BZA), the first tissue selective estrogen complex, was developed as an alternative to combination estrogen and progesterone therapy to treat hot flashes and osteoporosis. Preclinical studies found that CE/BZA reduced mammary ductal proliferation and increased expression of anti-tumorigenic markers in breast stroma. Our study aimed to determine if a pre-surgical window-of-opportunity intervention with CE/BZA in women with ductal carcinoma in situ (DCIS) had a protective effect on the duct epithelium and stroma of DCIS lesions without impacting quality of life. Differences between CE/BZA and placebo arms for the primary endpoint, change in Ki-67 protein expression, and quality-of-life endpoints are reported here. **Methods:** This multicenter, randomized, double-blind placebo-controlled Phase 2 trial was conducted between 9/19/17 and 8/21/24. Post-menopausal women with estrogen receptor positive (ER+) DCIS undergoing surgery were randomized to CE 0.45 mg /BZA 20 mg or placebo for 28 +/-7 days. Percentage of nuclei staining for Ki-67 was evaluated on slides from the baseline core biopsy and surgical specimen. Changes were compared between arms using the two-sample t-test, while changes within arms were analyzed using paired t-test. Analyses were done on log2 scale to satisfy the normality assumption. The Breast Cancer Prevention Trial Eight Symptom Scale (BESS) and Menopause-Specific Quality of Life (MENQOL) surveys were self-administered by patients before and after the intervention. Wilcoxon's signed-rank and rank-sum tests were used to perform within- and between-arm comparisons, respectively. **Results:** Of the 171 patients consented,141 enrolled, and 117 completed the study. Ninety-four patients (46= CE/BZA, 48=placebo) took >80% of the medication and had Ki-67 evaluated at baseline and post-intervention. The BESS and MENQOL surveys were completed by 100 and 108 patients, and 125 patients were evaluated for toxicity. The mean absolute change in Ki-67 was -5.62 (SD=10.2; p=0.003) in the CE/BZA arm and -1.07 (SD=10.8; p=0.6) in the placebo arm, with a greater reduction in CE/BZA arm (p=0.016). There was no difference between arms in the BESS score across all 8 domains or in the MENQOL score. However, within each arm, vasomotor symptoms decreased in the CE/BZA arm (p=0.002) but not in the placebo arm (p=0.4). No grade > 3 treatment related adverse events were reported. **Conclusions:** In this prospective randomized clinical trial, CE/BZA significantly reduced epithelial proliferation in ER+ DCIS with no impact on quality of life compared to placebo. These results support consideration that CE/BZA is a safe option to manage menopausal symptoms for women concerned about their risk of developing breast cancer, and provide supportive evidence that CE/BZA may reduce the risk of developing invasive breast cancer. Clinical trial information: NCT02694809. Research Sponsor: U.S. National Institutes of Health; 1R01CA218436-01.

The WinPro trial: A window of opportunity study of endocrine therapy with and without prometrium in postmenopausal women with early stage hormone receptor-positive breast cancer.

Lucy Haggstrom, Kate Middleton, Davendra Segara, Andrew Ong, Janne Bingham, Emma-Kate Carson, Belinda Emma Kiely, Dhanusha Sabanathan, Kate Saw, Man Ting Siu, Aura Serrano, Leila Eshraghi, Sandra O'Toole, Bruce Mann, Geoffrey J. Lindeman, Alexander Swarbrick, Wayne Tilley, Alan S. Coates, Andrew Parker, Elgene Lim; St Vincent's Hospital Sydney and University of New South Wales, Sydney, NSW, Australia; St Vincent's Hospital Sydney, Sydney, NSW, Australia; St Vincent's Private Hospital Sydney, Sydney, NSW, Australia; Campbelltown Hospital, Sydney, NSW, Australia; Royal Adelaide Hospital, Adelaide, NSW, Australia; Macarthur Cancer Therapy Center, Sydney, Australia; Nepean Cancer Care Centre, Kingswood, Australia; Garvan Institute of Medical Research, Darlinghurst, NSW, Australia; The Royal Melbourne Hospital, Melbourne, VIC, Australia; Peter MacCallum Cancer Centre/Walter and Eliza Hall Institute, Melbourne, Australia; Garvan Institute of Medical Research, Sydney, NSW, Australia; University of Adelaide, Adelaide, Australia; St Vincent's Hospital and Garvan Institute of Medical Research, Sydney, NSW, Australia

Background: Preclinical evidence has shown that progesterone is a tumour suppressor in estrogen receptor positive (ER+) breast cancer. Prometrium is bioidentical to human progesterone, currently used for treating menopausal symptoms. **Methods:** The WinPro trial is a randomised, multi-centre, phase 2, window of opportunity trial of preoperative endocrine therapy in post-menopausal women with early-stage, ER+, progesterone receptor (PR) +, HER2- breast cancer. Patients (pts) were randomised 1:1:1 to letrozole (let) 2.5mg daily, letrozole 2.5mg daily + prometrium (pro) 300mg daily, or tamoxifen (tam) 20mg daily + prometrium 300mg daily for 11-17 days before surgery. The primary endpoint was the percent proportional reduction in Ki67 between biopsy and surgery ('Ki67 suppression') in let vs let + pro in the per protocol population. Other endpoints were safety, changes in ER, PR and androgen receptor (AR) via immunohistochemistry (IHC) and H-scores, spatial transcriptomics and RNA sequencing. **Results:** From Feb 2018 to June 2024,244 pts were enrolled across 6 Australian sites. 239 pts were randomised to let (n=78, 32.6%), let + pro (n=79, 33.1%), and tam + pro (n=82, 34.3%). 189 pts completed per protocol: let (n=66, 34.9%, let + pro (n=64, 33.9%), and tam + pro (n=59, 31.2%). Baseline characteristics were well balanced across arms. There was no significant difference in Ki67 suppression between let (88.2%) vs let + pro (89.2%) (p = 0.4). Ki67 suppression appeared inferior with tam + pro (61.5%). Treatments were well tolerated, with hot flushes less frequent in let + pro (13.3%) vs let (22.4%) or tam + pro (20.5%). IHC analyses showed no change in ER% after treatment, a decrease in PR% after treatment with let and let + pro, and a decrease in AR% after treatment in all groups. H-score, spatial transcriptomics, RNA sequencing and PAM50 analyses are underway. **Conclusions:** The WinPro trial showed that the addition of pro to let in post-menopausal women with ER+, PR+, HER2- breast cancer was safe, reduced hot flushes and led to similar reduction in Ki67 as let alone. Ongoing translational analyses are underway which will examine the changes in gene expression in malignant, immune and stromal cells at sub-cellular resolution and provide further insight into the mechanisms of response and resistance to endocrine therapy. Clinical trial information: ACTRN12618000928213. Research Sponsor: Cancer Council New South Wales; National Health and Medical Research Council, Australian Government; Besins Healthcare.

	Baseline			Surgery		
	Let N = 67	Let + pro N = 64	Tam + pro N = 60	Let N = 67	Let + pro N = 64	Tam + pro N = 60
Ki67% suppression, median (Q1, Q3)	-	-	-	88.2 (74.6, 93.0)	89.2 (78.3, 93.9)	61.5 (32.3, 75.9)
Ki67%, median (Q1, Q3)	8.5 (4.5, 16.0)	10.5 (5.0, 16.3)	10.8 (6.0, 17.0)	1.0 (0.5, 2.5)	1.0 (0.5, 2.0)	3.5 (2.0, 7.5)
ER%, median (Q1, Q3)	95 (95, 95)	95 (95, 95)	95 (95, 95)	95 (95, 95)	95 (95, 95)	95 (95, 95)
PR%, median (Q1, Q3)	90 (50, 95)	90 (35, 95)	90 (50, 95)	20 (4, 70)	20 (2, 70)	90 (33, 95)
AR%, median (Q1, Q3)	40 (10, 90)	28 (8, 80)	70 (20, 90)	15 (2, 60)	10 (2, 75)	10 (1.3, 45)

Early results of the French multicenter, randomized SHARE trial comparing whole breast irradiation versus accelerated partial breast irradiation in postmenopausal women with early-stage low risk breast cancer: Analysis of toxicity and cosmetic outcomes.

Yazid Belkacemi, Isabelle Gabelle Flandin, Marie-Cecile Le Deley, Clemence Leguillette, Kamel Debbi, Adeline Petit, Philippe Guilbert, Julien Geffrelot, Christian Carrie, Eleonor Rivin Del Campo, Chantal Hanzen, Claire Brunaud, Isabelle Lecouillard, Nicolas Magné, Emilie Bogart, Guillaume Auzac, Thomas Lacornerie, Jerome Lemonnier, Celine Bourgier, Eric Lartigau; AP-HP, Department of Radiation Oncology and Henri Mondor Breast Center, Henri Mondor University Hospital, University of Paris Est Creteil (UPEC), Paris, France; Hôpital Michallon - Centre hospitalier universitaire de Grenoble, Grenoble, France; Centre Oscar Lambret, Lille, France; AP-HP. Service d'Oncologie Radiothérapie, Groupe Hospitalo-Universitaire Henri Mondor, IMRB INSERM 955 (i-Biot), Université Paris Est Créteil (UPEC), Créteil, France; Institut Bergonié, Bordeaux, France; Institut Godinot, Reims, France; Centre François Baclesse, Radiation Oncology Department, Caen, France; Centre Léon Bérard, Lyon, France; APHP, Service d'Oncologie Radiothérapie, Hôpital Tenon, Sorbonne Université, Paris, France; Henri Becquerel Center, Rouen, France; Institut de Cancérologie de Lorraine, Vandoeuvre-lés-Nancy, France; Centre Eugène Marquis, Rennes, France; Institut de Cancerologie de la Loire, Saint-Priest-En-Jarez, France; Institut Gustave Roussy, Villejuif, France; R&D Unicancer, Paris, France; ICM / PARC EUROMEDICINE, Montpellier, France

Background: Locoregional management of early stage breast cancer (BC) has evolved from maximal tolerable to minimal effective therapies. Significant advancements in radiation therapy (RT), such as limited target volumes and hypofractionation, have led to accelerated partial breast irradiation (APBI). This study reports on toxicity and cosmetic outcomes of APBI in post-menopausal women with unifocal pT1-N0-M0 invasive BC. **Methods:** The SHARE trial (NCT01247233) is a non-inferiority, multicenter, randomized trial comparing local control of APBI versus Whole Breast Irradiation (WBI). Eligible patients were postmenopausal women over 50 years who had lumpectomy with surgical margins > 2mm. Only patients who had at least 4-5 clips placed in the tumor bed during surgery were eligible. Patients were randomized to receive either WBI (50Gy in 25 fractions (fr) with optional 16Gy-boost or 40Gy in 15 fr, or 42.5Gy in 16fr) or APBI (38.5Gy or 40Gy in 10fr twice daily). Primary endpoint was local recurrence. Secondary endpoints included grade >2 toxicity (NCI-CTCAE-v4) and cosmetic outcomes (good/excellent versus intermediate/poor) evaluated by both patients and doctors, over the follow-up time. We estimated the cumulative incidences (CI) using the Kalbfleisch-Prentice method due to competing events, and cause-specific Hazard Ratios (cs-$HR_{APBI/WBI}$) from Cox models adjusted on stratification factors. **Results:** Among 1006 patients (503 per arm) enrolled between December-2010 and July-2015, with a median follow-up of 5.8 years, 28 deaths and 11 local recurrences were reported. The risk of severe toxicity appeared significantly reduced in the APBI-arm when considering all type of toxicity (cs-$HR_{APBI/WBI}$=0.74, [95%-CI: 0.61-0.89], p=0.001; 3-year CI=45% [41-49] in WBI vs 36% [32-40] in APBI), or only breast skin toxicity (cs-HR=0.55 [0.44-0.70], p<0.001; 3-year CI=36% [32-40] vs 21% [18-25], respectively). Conversely, for non skin breast toxicities, WBI was less toxic: cs-$HR_{APBI/WBI}$=2.06 (1.49-2.86), p<0.001). We observed no significant difference of patient-reported cosmetic results: cs-$HR_{APBI/WBI}$=1.08 (0.85-1.37), p=0.54. Findings were similar for doctor-evaluated results. Rib fractures incidence was nearly double in APBI compared to WBI. **Conclusions:** The SHARE trial showed that APBI is associated with reduced severe and skin-related toxicities compared to WBI, with no significant difference in cosmetic outcomes. Conversely, WBI was less toxic concerning non-skin breast toxicity, mainly breast fibrosis. The question that currently remains open on a practical level is how to consider APBI in the context of the widespread adoption of the "Fast Forward" regimen for patients at low risk of recurrence. Clinical trial information: 2010-A00243-36. Research Sponsor: French Ministry of Health PHRC-2010 Cancérologie; La Ligue contre le cancer.

Dalpiciclib (Dalp) plus endocrine therapy (ET) as adjuvant treatment for HR+/HER2− early breast cancer (BC): The randomized, phase 3, DAWNA-A trial.

Zhi-Ming Shao, Jihui Hao, Shui Wang, Qingyuan Zhang, Yuanting Gu, Fuguo Tian, Shouman Wang, Quchang Ouyang, Longzhen Zhang, Yunjiang Liu, Jing Cheng, Shundong Cang, Zhenzhen Liu, Chunsen Xu, Jianyun Nie, Ye Lv, Jun Qian, Ting Wang, Mengzhu Yu, Fei Wu; Fudan University Shanghai Cancer Center, Shanghai, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Jiangsu Province Hospital/The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; Harbin Medical University Cancer Hospital, Harbin, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Shanxi Provincial Cancer Hospital, Taiyuan, China; Xiangya Hospital of Central South University, Changsha, Hunan, China; Hunan Cancer Hospital, Changsha, China; The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China; Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Changchun, China; Henan Provincial People's Hospital, Zhengzhou, China; Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; Fujian Medical University Union Hospital, Fuzhou, China; Yunnan Cancer Hospital, Kunming, China; General Hospital of Ningxia Medical University, Yinchuan, China; The First Affiliated Hospital of Bengbu Medical University, Bengbu, China; The First Affiliated Hospital, Air Force Medical University, Xian, China; Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: Dalp, a potent CDK4/6 inhibitor, has demonstrated significant improvements in PFS when combined with ET in both first-line and later-line settings for HR+/HER2− advanced BC. We conducted a randomized, double-blind, phase 3 trial (DAWNA-A) to further evaluate Dalp with ET as adjuvant therapy for high-risk, early HR+/HER2− BC and here present findings from the pre-specified first interim analysis (IA1). **Methods:** Women aged 18-75 y, with stage II-III, HR+/HER2− BC, who had completed definitive local therapy (surgery and/or radiotherapy) and had pathologically confirmed ipsilateral axillary lymph node involvement, were enrolled. Patients (pts) were randomized (1:1) to receive oral Dalp (125 mg QD; 3-wk on/1-wk off, for 2 y) + ET (letrozole 2.5 mg/anastrozole 1 mg/tamoxifen 10 mg/toremifene 60 mg QD, for 5 y) or placebo + ET. Pre/peri-menopausal pts received LHRH agonists (perimenopausal use at investigator's discretion). Stratification factors were menopausal status (pre/peri vs post), clinical stage (II vs III), number of involved nodes (<4 vs ≥ 4), and adjuvant chemo (y vs n). The primary endpoint was invasive disease-free survival (iDFS). IA1 was pre-planned at ~254 iDFS events (~50% of total expected). As of Oct 25, 2024, 268 iDFS events occurred and IA1 was performed; the actual superiority boundary was a 1-sided $p < 0.00205$ (Lan-DeMets [O'Brien-Fleming] boundary). **Results:** Between Apr. 30, 2021 and Jul. 19, 2024, 5274 pts were randomized (Dalp, n=2640; placebo, n=2634). As of data cutoff, median follow-up was 20.3 mo (range 0.0–41.9). Dalp + ET significantly prolonged iDFS vs placebo + ET (HR 0.56, 95% CI 0.43–0.71; 1-sided $p < 0.0001$); iDFS benefits with Dalp were generally consistent across stratification factors and other baseline subgroups. DFS and distant DFS (DDFS) also favored Dalp + ET over placebo + ET (Table). TRAEs led to discontinuation of Dalp in 2.1% of treated pts in Dalp arm and of placebo in 0.8% in placebo arm. Tr-SAE occurred in 3.7% and 1.5%, respectively. There was no death due to TRAEs. **Conclusions:** Addition of Dalp to ET as adjuvant treatment significantly improved iDFS, with a tolerable safety profile. These data support the use of Dalp for treating HR+/HER2- early BC. Clinical trial information: NCT04842617. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy outcomes.

		Dalp + ET (n=2640)	Placebo + ET (n=2634)
iDFS	Event, n (%)	98 (3.7)	170 (6.5)
	3-y rate*, % (95% CI)	89.1 (85.8–91.7)	86.2 (83.3–88.6)
	HR† (95% CI); p value‡	0.56 (0.43–0.71); p <0.0001	
DFS	Event, n (%)	108 (4.1)	195 (7.4)
	3-y rate*, % (95% CI)	88.0 (84.5–90.7)	83.8 (80.5–86.6)
	HR† (95% CI); p value‡	0.53 (0.42–0.67); p <0.0001	
DDFS	Event, n (%)	93 (3.5)	149 (5.7)
	3-y rate*, % (95% CI)	90.2 (87.2–92.6)	88.7 (86.2–90.8)
	HR† (95% CI); p value‡	0.60 (0.46–0.78); p<0.0001	

*Kaplan–Meier method. †Stratified Cox proportional hazards model. ‡Stratified Log-rank test (1-sided).

Efficacy and safety of ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in NATALEE: Analysis across menopausal status and age.

Kevin Kalinsky, Mattea Reinisch, Yen-Shen Lu, Marc Debled, Binghe Xu, Lowell Hart, Stephanie L. Graff, Qiang Liu, Michael Untch, Sherene Loi, Priyanka Sharma, Viktoriya Sakalosh, Melissa Gao, Elizabeth Chertow Santarsiero, Sorcha Waters, Shaheen Islam, Seock-Ah Im; Winship Cancer Institute at Emory University, Atlanta, GA; Interdisziplinäres Brustzentrum Kliniken Essen Mitte and Interdisciplinary Breast Center, University Hospital Mannheim, Essen and Mannheim, Germany; National Taiwan University Hospital, Taipei, Taiwan; Institut Bergonié, Bordeaux, France; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Florida Cancer Specialists, Sarah Cannon Research Institute and Wake Forest University School of Medicine, Fort Myers and Winston-Salem, NC, FL; Brown University Health Cancer Institute, The Warren Alpert Medical School of Brown University, Providence, RI; Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; Multidisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; Peter MacCallum Cancer Centre, Melbourne, Australia; University of Kansas Medical Center, Westwood, KS; Translational Research in Oncology (TRIO), Tuscany, Italy; Novartis Pharma AG, Basel, Switzerland; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Ireland, Dublin, Ireland; Novartis Healthcare Private Limited, Hyderabad, Telangana, India; Seoul National University College of Medicine, Cancer Research Institute, Seoul National University, Seoul, South Korea

Background: The NATALEE trial demonstrated significant invasive disease–free survival benefit with RIB + NSAI vs NSAI alone in patients (pts) with stage II/III HR+/HER2− early breast cancer (EBC) at high risk of recurrence. Here, we report outcomes by menopausal status and age. **Methods:** Pts were treated with RIB + NSAI or NSAI alone in NATALEE; premenopausal (PreM) women also received goserelin. Men were excluded from this analysis. Efficacy, safety, and quality of life were analyzed by menopausal status (assessed at randomization or start of adjuvant endocrine therapy, whichever was first) and age (PreM [<40 y, ≥40 y]; postmenopausal [PostM; <60 y, ≥60 y]). Data cutoff was April 29, 2024. **Results:** A greater portion of PreM vs PostM pts had ECOG performance status 0 (86.8% vs 80.1%), Ki-67 >20% (39.9% vs 34.4%), N1-N3 nodal stage (63.4% vs 56.9%), and T3/T4 tumors (28.7% vs 24.0%) at diagnosis. There was consistent treatment benefit with RIB + NSAI vs NSAI alone across groups and ages (median follow-up, 44.2 months) (Table). Fewer PreM pts discontinued RIB due to AEs vs PostM (16.1% vs 22.9%); reductions due to AEs were similar (22.4% vs 23.6%). Of pts who discontinued due to AEs, more PreM pts did so without a dose reduction vs PostM (75.4% vs 67.5%). Within menopausal groups, fewer pts in the younger cohorts discontinued RIB due to AEs (Table). Alanine aminotransferase elevation was the most common AE leading to discontinuation in the PreM (6.2%) and PostM groups (8.0%). Time to deterioration in global and physical functioning scales of the EORTC QLQ-C30 was similar between treatment arms for all subgroups. **Conclusions:** RIB + NSAIprovides treatment benefit to a broad range of pts with stage II/III HR+/HER2− EBC across menopausal status and age. In younger PreM pts, who typically have more aggressive disease characteristics, treatment favored RIB + NSAI, and these pts were least likely to discontinue RIB due to AEs. Clinical trial information: NCT03701334. Research Sponsor: None.

	PreM (n = 2238)			PostM (n = 2844)		
Hazard ratio[a] (95% CI)	All RIB = 1115 NSAI = 1123	<40 y RIB = 237 NSAI = 276	≥40 y RIB = 878 NSAI = 847	All RIB = 1424 NSAI = 1420	<60 y RIB = 703 NSAI = 735	≥60 y RIB = 721 NSAI = 685
Invasive disease–free survival	0.671 (0.518-0.870)	0.690 (0.419-1.137)	0.662 (0.488-0.897)	0.746 (0.607-0.917)	0.835 (0.619-1.128)	0.673 (0.506-0.896)
Distant disease–free survival	0.655 (0.498-0.861)	0.647 (0.383-1.091)	0.659 (0.478-0.908)	0.759 (0.612-0.941)	0.854 (0.625-1.168)	0.681 (0.506-0.916)
Recurrence–free survival	0.641 (0.486-0.845)	0.723 (0.429-1.220)	0.610 (0.439-0.846)	0.735 (0.588-0.919)	0.811 (0.590-1.114)	0.668 (0.487-0.915)
Disposition in RIB arm, n (%)						
RIB discontinuation due to AE	179 (16.1)	25 (10.5)	154 (17.5)	326 (22.9)	125 (17.8)	201 (27.9)
RIB reduction due to AE	248 (22.4)	64 (27.0)	184 (21.1)	332 (23.6)	169 (24.2)	163 (22.9)

[a]Hazard ratios between treatment arms (RIB + NSAI; NSAI alone), stratified by stage, prior chemotherapy, and geographic region.

The TRADE study: A phase 2 trial to assess the tolerability of abemaciclib dose escalation in early-stage HR+/HER2- breast cancer.

Erica L. Mayer, Dario Trapani, Se Eun Kim, Meredith Gail Faggen, Natalie Sinclair, Pedro Manuel Sanz-Altamira, Chiara Battelli, Shana Berwick, K.M. Steve Lo, Jose Acevedo, Sarah J. Sinclair, Alys Malcolm, Leticia Varella, Sarah L. Sammons, Susan T. Schumer, Philip Daniel Poorvu, Erin Wallace, Esther Pasternak, Nabihah Tayob, Sara M. Tolaney; Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; European Institute of Oncology, IRCCS, Milan, Italy; Dana-Farber Cancer Institute, Boston, MA; New England Cancer Specialists, Scarborough, ME; Beth Israel Deaconess Medical Center, Boston, MA; Stamford Hospital, Stamford, CT; Boston University Medical Center, Boston, MA; Northern Light Cancer Institute, Brewer, ME; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: The CDK4/6 inhibitor abemaciclib (abema) is approved with adjuvant endocrine therapy (ET) for high-risk node positive hormone receptor positive (HR+) HER2- breast cancer. This regimen reduces cancer recurrence, yet therapy may be complicated by toxicity, limiting patient (pts) ability to maintain dose or continue medication. In the phase III monarchE study, 25.8% of pts discontinued abema early for reasons other than recurrence, 18.5% for adverse events (AEs), and 43.6% required dose reduction. Experiences with other targeted therapies suggest initial dose escalation may reduce toxicity and discontinuation. TRADE is a prospective, single-arm, phase 2 study evaluating whether a dose-escalation strategy of adjuvant abema improves drug tolerability. **Methods:** Eligible pts had node-positive HR+/HER2- breast cancer and were candidates for adjuvant abema with ET. All pts started abema at 50 mg BID for 2 weeks (wks), escalated to 100 mg BID for 2 wks, then escalated to final dose of 150 mg BID onwards. Escalation required absence of ongoing grade 3/4 or persistent grade 2 toxicity; anti-diarrheal medication was used as needed. The primary endpoint, measured at 12 wks, was a composite rate of discontinuation of abema for any reason or inability to reach or maintain the 150 mg dose. Based on assumptions from monarchE, the experimental hypothesis was that a dose-escalation schedule of abema would significantly reduce rate of the composite primary endpoint at 12 wks from 40%. **Results:** 90 pts enrolled, 89 evaluable for the primary endpoint (1 progression before 12 wks). Median age was 58 [range 24-78], 4% were Black, 3% were Hispanic. 48% had stage II disease, 52% had stage III, all received AI, 14% concurrent OFS. The study achieved the predefined primary endpoint with 26 pts (29.2%; 90% CI [21.3-38.2]; p=0.046) meeting the composite endpoint at 12 wks: 6 (6.7%) for early discontinuation (3 [3.4%] for toxicity), 8 (9.0%) for inability to reach 150 mg, and 12 (13.5%) for dose reduction from 150 mg. The most frequent >grade 2 treatment related AEs by 12 wks were neutropenia (23.3%), diarrhea (22.2%), and fatigue (20%). Rates of clinically significant diarrhea (> grade 2) within 0-4, 4-8, and 8-12 wks were 5.6%, 14.6%, 15.3%, in contrast to rates from monarchE of 20.5%, 12.1%, 7.3% in the same periods. **Conclusions:** The TRADE study is a positive trial meeting its primary endpoint. Use of an adjuvant abema dose escalation strategy allowed a greater number of pts (70.8%) to reach and maintain the 150 mg dose at 12 wks than in monarchE. Early discontinuation was infrequent, and 93.3% were continuing therapy at 12 wks. Reduced incidence and severity of clinically important toxicity such as diarrhea was observed. This dosing strategy could be considered when initiating adjuvant abemaciclib. Further follow-up will assess long-term tolerability, dosing maintenance beyond 12 wks, and correlative analyses. Clinical trial information: NCT06001762. Research Sponsor: Lilly.

Impact of chemotherapy on financial toxicity in African-American breast cancer patients: Early findings from the navigator-assisted hypofractionation (NAVAH) phase I clinical trial.

Maya J. Stephens, Nimisha Kasliwal, Ursula Burnette, Louisa Onyewadume, Chesley Cheatham, Tamika Smith, Corey Wayne Speers, Janice A. Lyons, Shearwood McClelland III; Medical College of Georgia, Augusta, GA; University Hospitals, Cleveland, OH; University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; University Hospital Seidman Cancer Center, Case Western Reserve University, Cleveland, OH; University Hospitals Seidman Cancer Center, Cleveland, OH; University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH; University Hospitals Seidman Cancer Center and Case Western Reserve University, Chagrin Falls, OH; The University of Oklahoma Health, Oklahoma City, OK

Background: With the rising cost of chemotherapy, the financial toxicity (FT) of systemic therapy can substantially impair patient quality of life. FT is also associated with various socioeconomic factors, one being race. Patients of African American race often bear the worst burden of cancer treatment-related FT, with a 40% increased mortality from breast cancer. The degree to which chemotherapy prior to radiation therapy (RT) impacts FT has yet to be formally quantified. We report early FT findings among African American breast cancer patients prior to receipt of adjuvant RT on the ongoing Navigator-Assisted Hypofractionation (NAVAH) Phase I clinical trial (ClinicalTrials.gov ID: NCT05978232) to assess the impact of chemotherapy on FT. **Methods:** African-American breast cancer patients undergoing RT were eligible if age 18+ with pathologically confirmed breast cancer following resection. As part of the trial, patients were assisted by a patient navigator during and after treatment. FT was measured using the validated 12-item COmprehensive Score for financial Toxicity-Functional Assessment of Chronic Illness Therapy (COST-FACIT) survey instrument. COST-FACIT scoring was used to find FT in patients before receipt of RT. Values from 26-44 represent Grade 0 FT (none), values from 14-25 represent mild Grade 1 FT (mild), values from 1-13 represent Grade 2 FT (moderate), and values of 0 represent Grade 3 FT (severe). The chi-square test was used to identify statistically significant differences ($p < 0.05$) between patients who received chemotherapy versus no chemotherapy prior to receipt of RT. **Results:** The first 32 enrolled patients completing the pre-RT COST-FACIT survey were evaluated. 53% of patients underwent chemotherapy before RT. Mild to moderate FT was apparent in 56% of patients. The mean and median COST-FACIT score (range 4.4-39) was 25 (+/- 10.4). 78% of patients who experienced some level of FT underwent chemotherapy and 22% of patients experiencing FT did not receive chemotherapy ($p = 0.0015$). Of patients who did not experience FT, 21% received chemotherapy and 79% of patients did not. In total, 82% of patients who underwent chemotherapy before RT reported mild to moderate FT. Grade 3 FT was not observed. **Conclusions:** The NAVAH study is the first to objectively compare FT among patients receiving chemotherapy before RT for early-stage breast cancer. Our findings indicate that more than 80% of patients who underwent chemotherapy experienced FT. Approximately 1 in 5 patients not experiencing FT received chemotherapy. The findings indicate that chemotherapy plays a significant role in patient quality of life, highlighting a subsection of patients who may benefit from proactive financial assistance to reduce the detrimental effect of FT on their livelihood. Clinical trial information: NCT05978232. Research Sponsor: Susan Komen Foundation; National Medical Fellowships.

Out-of-pocket cost modeling of EUROPA trial arms for adjuvant breast cancer therapy: Five days of radiation versus five years of antiestrogen therapy.

Ena Chinedum Oboh, Victoria Shiqi Wu, Martha Khlopin, Shearwood McClelland III; The George Washington University School of Medicine and Health Sciences, Washington, DC; Case Western Reserve University School of Medicine, Cleveland, OH; Stephenson Cancer Center at The University of Oklahoma Health Sciences Center, Oklahoma City, OK; Stephenson Cancer Center, Departments of Radiation Oncology and Neurological Surgery, The University of Oklahoma College of Medicine, Oklahoma City, OK

Background: Optimal adjuvant therapy following breast-conserving surgery in adults with low-risk, early-stage breast cancer remains uncertain. Cost and financial toxicity remain significant concerns for breast cancer patients. There is limited granular analysis of the role of insurance in the aggregate cost of five fractions of adjuvant radiotherapy (RT) versus adjuvant endocrine therapy (ET), as is being explored in the EUROPA Phase III trial. This study aims to disaggregate costs, estimate out-of-pocket (OOP) expenses by insurance plan, and increase transparency to better inform treatment decisions. **Methods:** Treatment protocols were aligned with the EUROPA trial arms. For our financial model, we used five-fraction RT and ET prescribed over 5 years, with follow-up after two years (consistent with EUROPA trial results) and five years (full duration of prescribed antiestrogen therapy). OOP costs, deductibles, and copays/coinsurance were calculated using Medicaid, Original Medicare, Medigap Plan G, and Medicare Part D plans. Data sources included medicare.gov, medicaid.oh.gov, aarpmedicareplans.com, and the CMS physician fee schedule. Price estimates reflect actual insurance plan costs rather than claims data. The model assumes a Medicare- and/or Medicaid-eligible patient aged ≥ 70 years with early-stage estrogen-receptor positive breast cancer after breast-conserving surgery. **Results:** Original Medicare beneficiaries face estimated OOP treatment costs of $1,049.06 for adjuvant ET at 24 months and $2,130.25 at five years. For five-fraction RT, the estimated OOP costs are $1,490.93 at 24 months and $2,320.12 at five years. Medigap Plan G beneficiaries incur lower OOP expenses: $682 for adjuvant ET at 24 months and $1,705 at five years, and $514 at 24 months and $1,285 at five years for five-fraction RT. In contrast, Medicaid beneficiaries have no OOP expenses for either treatment option, as Medicaid fully covers all treatments. **Conclusions:** The EUROPA trial highlights HRQOL outcomes at 24 months for endocrine therapy versus radiotherapy in women aged 70+ with luminal A-like early breast cancer. This cost analysis, based on actual cost estimates, provides a clear comparison of OOP expenses across Medicaid and Medicare plans. While RT has higher upfront OOP costs at 24 months under Original Medicare, the cost difference narrows over five years, with RT incurring slightly higher cumulative costs. This reflects RT's one-time nature versus the ongoing costs of ET, which more than doubles over the same period. Medigap Plan G beneficiaries experience significantly reduced OOP costs, favoring RT further at five years, while Medicaid eliminates OOP costs entirely for either treatment, ensuring equitable access to both options. These findings support the initial EUROPA trial results favoring RT over ET for HRQOL and treatment-related toxicity. Research Sponsor: None.

Impact of body mass index (BMI) on efficacy and safety of abemaciclib in breast cancer patients (pts) treated in the monarchE trial.

Christine Desmedt, Signe Borgquist, Laura Garcia-Estevez, Miguel Martin, Stephen R. D. Johnston, Fatima Cardoso, Adam Brufsky, Hakan Harputluoglu, Hung T. Khong, Belén San Antonio, Maria Munoz, Ran Wei, Javier Cortes; Laboratory for Translational Breast Cancer Research, KU Leuven, Leuven, Belgium; Department of Oncology, Aarhus University Hospital and Aarhus University, Aarhus, Denmark; MD Anderson Cancer Center Madrid, Madrid, Spain; Hospital General Universitario Gregorio Marañón, Madrid, Spain; Royal Marsden NHS Foundation Trust, London, United Kingdom; ABC Global Alliance, Lisbon, Portugal; UPMC Hillman Cancer Center, University of Pittsburgh Cancer Institute, Pittsburgh, PA; İnönü University, Malatya, Turkey; Banner MD Anderson Cancer Center at Banner Gateway Medical Center, Gilbert, AZ; Eli Lilly and Company, Indianapolis, IN; IOB Institute of Oncology, Quiron Group and Vall d'Hebron Institute of Oncology, Madrid, Spain

Background: Two years (yrs) of adjuvant abemaciclib + endocrine therapy (ET) resulted in sustained improvement in invasive disease-free survival (IDFS HR=0.68, 5 yrs rates: 84% abemaciclib + ET vs 76% ET, 8% absolute benefit) in pts with hormone receptor positive, human epidermal growth factor receptor 2 negative, node-positive, high-risk early breast cancer (EBC). Obesity is an established factor influencing the biology and prognosis of breast cancer; however, the specific impact on treatment (tx) outcomes remains uncertain. Here we report efficacy and safety by BMI in monarchE. **Methods:** Pts were randomized 1:1 to receive ET for at least 5 yrs +/- abemaciclib for 2 yrs. Groups were defined by baseline BMI (kg/m^2): as obese (≥30), overweight (25<30), and non-overweight (<25). IDFS/DRFS in each group was assessed using Kaplan-Meier method and unstratified Cox model. Safety was summarized by subgroup. **Results:** 1507 pts (27%) were obese, 1762 (32%) were overweight, and 2227 (41%) were non-overweight. Most obese pts were postmenopausal (67%), received aromatase inhibitor as first ET (75%) and a substantial proportion (47%) had ≥4 comorbidities, vs 60%, 69%, 34% among overweight pts and 47%, 63%, 30% among non-overweight, respectively. Pts ≥65 yrs constituted 18%, 17% and 12% of these groups. Disease characteristics were balanced across BMI groups. A consistent tx benefit in IDFS was observed with the addition of abemaciclib to ET across all 3 BMI groups: obese (HR = 0.67, 95% CI: 0.53, 0.85), overweight (HR = 0.73, 95% CI: 0.58, 0.91), and non-overweight (HR = 0.68, 95% CI: 0.55, 0.83), with an interaction p-value of 0.858. 5yr IDFS rates in the ET arm were lowest in obese pts (74%) and similar for overweight and non-overweight pts (77% in each). In the abemaciclib + ET arm, absolute improvements in IDFS were 8.8%, 5.8% and 7.9% across each respective BMI group. Similar findings were observed for DRFS. Obese pts had fewer grade≥3 (G≥3) neutropenia, and related dose hold/reductions. Despite higher G≥3 diarrhea in obese pts, related dose reductions and discontinuations were similar in all 3 groups. G≥3 ALT elevations were low in all groups. Serious AEs (SAEs) were more common in obese pts, across tx arms (Table). **Conclusions:** In pts with high-risk EBC, adjuvant abemaciclib + ET showed consistent and clinically meaningful tx benefit across BMI subgroups, along with a manageable safety profile. Additional analyses are planned to adjust for the impact of confounding factors such as comorbidities. Clinical trial information: NCT03155997. Research Sponsor: Eli Lilly and Company.

	Abemaciclib + ET			ET		
%	Obese n=723	Overweight n=886	Non-overweight n=1118	Obese n=784	Overweight n=876	Non-overweight n=1109
≥1AE Any grade	98	99	98	91	89	88
G ≥3	50	48	52	21	15	15
Neutropenia	14	19	24	0.1	0.5	2
Diarrhea	10	8	6	0.3	0.2	0.2
ALT	2	3	3	1	0.7	0.5
All tx discontinuation due to AE	7	6	5	2	0.3	0.5
Dose reductions related to any AE/diarrhea/ neutropenia	41/18/ 6	43/18/6	45/17/11	-	-	-
≥1 SAE	20	16	13	11	8	9
Fatal	3	2	1	2	1	1

The effect of endocrine therapy omission on survival in ER-negative PR-low (1–10%) early-stage breast cancer treated with chemotherapy.

Shawn Michael Doss, Priyanka Raval; Medical College of Georgia, Augusta, GA

Background: The effect of endocrine therapy omission on outcomes in breast cancer (BC) with low progesterone receptor (PR) expression (1–10%) is unknown. Previously, omitting adjuvant endocrine therapy in estrogen receptor (ER)-low (1–10%) BC was associated with worse survival (1), but whether this is also true for PR 1–10% (PR-low) BC has not been studied. We analyzed outcomes for omission of endocrine therapy in patients with ER-negative PR-low stage I–III BC who received chemotherapy. **Methods:** We identified 46,704 patients from the National Cancer Database (diagnosed 2018–2020) with PR 1–10% stage I–III BC, of whom 3651 (7.8%) were ER-negative. Of these, 2,915 (79.8%) received chemotherapy. After excluding incomplete data for covariates, 2,796 remained for analysis. Cox proportional hazards models were used to analyze overall survival (OS). Multivariate Cox regression and propensity score matching were performed to account for confounding by age, stage, comorbidity score, HER2 status, year of diagnosis, and grade. This study protocol was developed and reviewed by oncology faculty prior to implementation. **Results:** Of the final cohort of 2,796 ER-negative PR-low BC patients, 73.6% were HER2-negative and 85.0% were high grade. Stage distribution was 34.8% stage I, 43.6% stage II, and 21.6% stage III. Endocrine therapy was omitted in 2,051 (73.4%). OS was 93.9% (95% CI 93.0–94.9%) at 2 years and 86.1% (95% CI 84.3–87.9%) at 4 years, with 267 total deaths. In the univariate (unadjusted) analysis, omission of endocrine therapy was associated with worse 4-year OS (hazard ratio [HR] 1.84, 95% CI 1.34–2.53, $p<0.001$). In the multivariate (adjusted) analysis, the HR was 1.72 (95% CI 1.25–2.37, $p<0.001$). Interaction testing for endocrine therapy and HER2 status was not significant. To account for possible pandemic impacts on OS, a sensitivity analysis of 2,639 patients (after excluding those who did not survive six months beyond definitive surgery) was performed and yielded a HR of 1.50 (95% CI 1.08–2.10, p=0.016). After propensity score matching of 1,490 ER-negative PR-low BC patients (matched by age, stage, comorbidity score, HER2 status, year of diagnosis, and grade), omission of endocrine therapy was still associated with worse 4-year OS (HR 1.63, 95% CI: 1.12–2.36, p=0.010). In contrast, omission of endocrine therapy in matched ER-negative PR-negative (instead of PR-low) BC patients was not associated with worse OS (HR 1.12, 95% CI: 0.92–1.37, p=0.27). **Conclusions:** In ER-negative PR-low (1–10%) early-stage BC treated with chemotherapy, omission of endocrine therapy may be associated with worse overall survival, suggesting that endocrine therapy could improve survival in ER-negative BC patients even with only low (1–10%) PR expression. Further investigation is recommended as this retrospective study design cannot establish causality. 1. Choong, 2024, *JCO*. Research Sponsor: None.

Practice patterns related to ovarian function suppression in the SWOG S2010 clinical trial of young women with breast cancer.

Norah Lynn Henry, Joseph M. Unger, Amy Darke, Anne F. Schott, Pankaj Kumar, Marcela Mazo- Canola, Claire M. Sathe, Paula Anel Cabrera-Galeana, Alice Tam Kengla, Michael Jordan Fisch, Dawn L. Hershman; University of Michigan Medical School, Ann Arbor, MI; Fred Hutchinson Cancer Center, Seattle, WA; SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Center, Seattle, WA; University of Michigan Rogel Cancer Center, Ann Arbor, MI; Illinois CancerCare, P.C., Peoria, IL; University of Texas Health Science Center at San Antonio, San Antonio, TX; NewYork Presbyterian Hospital, Columbia University Irving Medical Center, New York, NY; Instituto Nacional de Cancerología, Mexico City, DF, Mexico; Kaiser Permanente Walnut Creek Medical Center, Walnut Creek, CA; The University of Texas MD Anderson Cancer Center; Carelon Medical Benefits Management, Houston, TX; Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY

Background: Addition of ovarian function suppression (OFS) to adjuvant endocrine therapy (ET) improves disease free survival for young patients at high risk of breast cancer recurrence. SWOG S2010, an ongoing clinical trial that has completed enrollment, is examining the benefit of active symptom monitoring for improving 18-month persistence with ET plus OFS. Because data are currently limited on the use of OFS and endocrine therapy in routine practice, this report of S2010 enrollees describes practice patterns related to the prescription of ET for young patients starting OFS plus ET for treatment of stage 1-3 hormone receptor-positive breast cancer. **Methods:** We characterized the baseline demographic, clinical, and pathologic data from the pre- and perimenopausal patients starting OFS plus ET for treatment of breast cancer enrolled in S2010 using descriptive statistics. **Results:** Of the 557 participants enrolled on S2010, median age was 44.5 years (range 23.5-57.1), 25% were Hispanic, 6% Black, 6% Asian, and 76% White. In addition, 39% were not college graduates, 9% were uninsured, and 58% worked full time. Most patients were overweight (34%) or obese (39%). Planned ET was aromatase inhibitor (AI) therapy for 423 (76%) and tamoxifen for 134 (26%). For OFS, 425 (80%) received GnRHa injections, 33 (6%) underwent bilateral salpingo-oophorectomy, and 74 (14%) had chemotherapy-induced ovarian failure (CIOF). Of the 32 (43%) participants with CIOF who were under the age of 45, 12 (38%) were planning to receive AI therapy without concomitant GnRHa therapy. There were 294 participants (55%) with anatomic stage 1 ER-positive breast cancer, of whom 127 (43%) did not receive chemotherapy. Of the 174 participants (33%) with anatomic stage 2 disease, 32 (18%) did not receive chemotherapy. **Conclusions:** Most participants on this clinical trial received GnRHa therapy as their method for OFS, and an AI for their endocrine therapy. We found that a small number of patients under the age of 45 with CIOF did not receive GnRHa therapy and planned to start AI therapy, even though such patients are at high risk of recovery of ovarian function. Additionally, approximately one-quarter of trial participants appeared to have low risk disease based on non-receipt of chemotherapy and anatomic Stage 1, despite NCCN guidance recommending that OFS be reserved for patients with higher risk features. These findings suggest that additional education about the optimal use of OFS in young women with hormone receptor-positive breast cancer may be warranted. Clinical trial information: NCT05568472. Research Sponsor: National Cancer Institute; R01CA266012; National Cancer Institute; UG1CA189974; Hope Foundation for Cancer Research.

Beyond the 5-year mark: Adherence to and continuation of extended adjuvant endocrine therapy in non-metastatic breast cancer patients.

Jenny Wei, Ashley Aller, Laurel A. Habel, Shiyun Zhu, Ninah Achacoso, Aida Shirazi, Marc A. Emerson, Raymond Liu; Department of Hematology-Oncology, Kaiser Permanente San Francisco, San Francisco, CA; Department of Hematology/Oncology, The Permanente Medical Group, Seattle, WA; Kaiser Permanente Division of Research, Oakland, CA; Kaiser Permanente, San Francisco, CA; University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Hematology Oncology, Kaiser Permanente, San Francisco, CA

Background: Extending adjuvant endocrine therapy (AET) beyond five years has been shown to be beneficial for women with non-metastatic, hormone-responsive breast cancer. While many studies have examined adherence to (taking medication according to prescribed regimen) and continuation of (taking medication for prescribed duration) AET, most have focused on the first five years of use and data beyond that period are lacking. To address this knowledge gap, we conducted a large retrospective cohort study to determine adherence to and continuation of AET beyond the first 5 years among a cohort of non-metastatic breast cancer patients treated in a community setting. **Methods:** We estimated adherence to and continuation of extended AET (tamoxifen or aromatase inhibitor) among 13,675 women at Kaiser Permanente Northern California (KPNC), an integrated healthcare system caring for approximately 4.5 million members. The cohort consisted of women diagnosed with Stage I-III, estrogen receptor positive (ER+) breast cancer and were treated at KPNC from 2008 to 2017. Adherence was defined as medication possession ratio >80% for each 12-month period during follow-up. Continuation was defined as time to last pill possession date before a 180-day gap of AET and was based on the Kaplan-Meier estimator. Both adherence and continuation were examined for the 10-year period after initiation. **Results:** Of the 13,675 eligible women who initiated AET, 81% were 50 years or older, 61% were white and 76% had an Elixhauser Comorbidity Score of 2 or less. Most women had Stage I or II breast cancer (90.9%) that was progesterone receptor positive (79%) and HER2 negative (84%). We observed a gradual decline in adherence to AET each year from 79% in year 1 to 60% in year 5, followed by a dramatic drop to 23% in year 6. After year 6, annual adherence again dropped gradually and was 10% in year 10. Median AET continuation time was 5.1 years. Similarly, there was also a striking decline in AET continuation between year 5 and 6, with 52% continuing AET to the end of year 5 and 20% continuing to the end of year 6. Only 4.5% of the cohort continued to the end of year 10. **Conclusions:** We observed a substantial drop in both adherence to and continuation of AET following year 5 into year 6 with only 4.5% of the cohort continuing to the end of year 10. This period may represent an opportunity for intervention to improve use of extended AET. Future studies are needed to identify factors affecting adherence to and continuation with extended AET. Research Sponsor: None.

Impact of initial chemotherapy dosing on subsequent dosing patterns and treatment completion in early-stage breast cancer.

Maria Jose Monroy Iglesias, Kelli O'Connell, Jenna Bhimani, Victoria S. Blinder, Rachael P. Doud, Grace B. Gallagher, Jennifer J. Griggs, Tatjana Kolevska, Candyce Kroenke, Cecile Laurent, Raymond Liu, Kanichi G. Nakata, Janise M. Roh, Yashasvini Sampathkumar, Emily Valice, Peng Wang, Erin Aiello Bowles, Elisa Victoria Bandera, Lawrence H. Kushi, Elizabeth Kantor; Memorial Sloan Kettering Cancer Center, New York, NY; Kaiser Permanente Washington Health Research Institute, Seattle, WA; Rogel Cancer Center, University of Michigan, Ann Arbor, MI; Kaiser Permanente Northern California, Vallejo, CA; Division of Research, Kaiser Permanente Northern California, Pleasanton, CA; Kaiser Permanente Northern California, Pleasanton, CA; Department of Hematology/Oncology, The Permanente Medical Group, San Francisco, CA; Division of Research, Kaiser Permanente Northern California, Oakland, CA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: While breast cancer treatment guidelines provide dosing recommendations, some patients do not receive the full expected dose at outset. Preemptive dose reduction, often due to toxicity concerns, may influence subsequent reductions or early discontinuation. The impact of initial dose reductions on subsequent care delivery remains unclear. **Methods:** The Optimal Breast Cancer Chemotherapy Dosing (OBCD) study is a cohort of 34,109 women diagnosed with stage I-IIIA breast cancer at two U.S. integrated healthcare systems between 2004-2019. We examined associations between first-cycle dose proportion (FCDP), categorized as ≥95%, 90-95%, 85-90%, <85%, with average relative dose intensity (ARDI) categories and early discontinuation. Adjusted prevalence ratios (aPRs) were estimated using generalized linear models of the Poisson family to evaluate associations between FCDP (≥95% vs. <95%) and the likelihood of further dose reductions (based on ARDI) and early discontinuation. Analyses were performed overall and stratified by age, body mass index (BMI), and Charlson comorbidity index (CCI), as older age and comorbidities, including obesity, are linked to higher risk of dose reductions. **Results:** Among 9,724 women receiving adjuvant chemotherapy, 66% of those with FCDP ≥95% remained fully dosed throughout treatment. In contrast, 46% of patients in both the 90–95% and 85–90% FCDP groups stayed in the same category. The highest likelihood of early discontinuation was seen in patients with FCDP <85% (19%) compared to 13% in the FCDP ≥95% group (p <0.01). Multivariable analyses showed that women with FCDP <95% were more likely to experience further dose reductions (aPR 1.34; 95%CI 1.21-1.49), than those with FCDP ≥95%; but interactions with BMI, CCI, or age were not statistically significant. However, the associations between FCDP and early discontinuation (aPR 1.29; 95%CI 1.11-1.50) varied by BMI (p-interaction 0.02) and age (p-interaction 0.03). A lower FCDP was positively associated with early discontinuation in women with BMI 25-30kg/m^2 (aPR 1.62; 95%CI 1.27-2.07) and BMI 30-35kg/m^2 (aPR 1.50; 95%CI 1.16-1.94), but no association was observed for BMI <25 or >35 kg/m^2. Patients aged ≤49 years (aPR 1.84; 95% CI 1.39–2.45) and 50–64 years (aPR 1.25; 95% CI 1.07–1.46) with FCDP <95% were more likely to discontinue early, with no association observed in older adults. **Conclusions:** Women with breast cancer who have FCDP <95% are more likely to experience further dose reductions, regardless of age, BMI, or CCI, suggesting that initiating treatment with reduced doses may not prevent subsequent reductions. Early discontinuation was more likely among patients with FCDP <95%, particularly those with BMI 25–30 or 30–35 kg/m^2 or younger age. These findings may reflect frailty, treatment intolerance, or patient preferences. Understanding the drivers of these decisions is key to guide strategies that balance toxicity concerns with maintaining adequate dosing to reduce treatment cessation in at-risk groups. Research Sponsor: National Cancer Institute; R37CA222793, U24CA171524, U01CA195565, P30CA008748, and P01CA154292; Geoffrey Beene Cancer Research Center at Memorial Sloan Kettering Cancer Center; National Cancer Institute; R50CA211115.

Chemotherapy (CT) declination among patients with early-stage hormone receptor positive breast cancer (BC) and high Oncotype DX recurrence scores (RS).

Inimfon Jackson, Xiudong Lei, Sharon H. Giordano, Mariana Chavez Mac Gregor; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Among patients with hormone receptor positive, HER2-negative (HR+/HER2-) BC, the 21-gene Oncotype DX assay is both prognostic of recurrence risk and predictive of CT benefit. However, some patients decline CT despite their physician's recommendations. We investigated the factors associated with CT declination and its impact on overall survival (OS) among patients with early-stage HR+/HER2- BC and high RS. **Methods:** Patients (≥18 years) diagnosed with HR+/HER2- BC from 2018-2021, with pathologic (p) T1-T3, pN0-N1 disease and RS >25, were identified in the National Cancer Database. Multivariable logistic regression was used to examine the factors associated with CT declination. Furthermore, multivariable Cox proportional hazards regression was used to evaluate the association between CT declination and OS based on a propensity score matched 1:5 cohort using year of diagnosis, age, race/ethnicity, pT and pN. **Results:** Among 23,416 patients with early-stage HR+/HER2- BC and RS >25, 74.3% were non-Hispanic White (NHW) and 12.1% were Black. Overall, 2601 (11.1%) patients declined CT despite physician recommendation (median RS of 30). Among those declining CT, 15.8% also declined endocrine therapy. On univariate analysis, CT declination was associated with older age, Black race and lobular histology. After adjustment, each unit increase in RS was associated with lower odds of CT declination (aOR=0.97; 95%CI 0.96–0.97). A more recent year of diagnosis was associated with lower odds of CT declination while older age and Black race (aOR=1.33; 95%CI 1.17–1.51) were associated with higher odds. Additionally, patients on Medicaid (aOR=1.66; 95%CI 1.40–1.97) and Medicare (aOR=1.29; 95%CI 1.12–1.48) had higher odds of declination compared to those on private insurance. Having pN1 disease was associated with lower odds of declination than pN0 disease (aOR=0.74; 95% 0.66–0.83). There was no association between comorbidity and declination. Notably, CT declination was associated with an increased risk of death after a median follow-up of 3 years (aHR=1.28; 95%CI 1.02–1.61) among 10,909 matched patients. Sensitivity analyses among patients with RS >30 showed similar results. **Conclusions:** Though prospective studies have demonstrated the benefit of CT among patients with high RS, 11% of patients declined CT. We observed a decrease in CT declination over time, as well as with increasing RS. Of note, Black patients, and those on Medicaid or Medicare were more likely to decline chemotherapy. CT declination was associated with worse OS. While the reasons for treatment declination are multifactorial, research is needed to understand the underlying disparities and work toward improving cancer care delivery. Research Sponsor: Susan G. Komen Foundation; SAC220221; The Breast Cancer Research Foundation; 23-190.

Treatment-related neutropenia as a predictor of response to adjuvant palbociclib in the PALLAS trial (ABCSG-42/AFT-05/BIG-14-13/PrE0109).

Kristina Fanucci, Amylou C. Dueck, Erica L. Mayer, Miguel Martin, Tufia C. Haddad, Nicholas Zdenkowski, Guenther G. Steger, Yelena Novik, Jennifer Marie Suga, Julie Lemieux, Tiffany A. Traina, Sibylle Loibl, Meritxell Bellet, Antonio C. Wolff, Jana Machacek-Link, Eric Roland Gauthier, Sara Scovil, Dominik Hlauschek, Michael Gnant, Angela DeMichele; Dana-Farber Cancer Institute, Boston, MA; Alliance Statistics and Data Management Center and Mayo Clinic Rochester, Rochester, MN; Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Hospital General Universitario Gregorio Marañón, Madrid, Spain; Mayo Clinic, Rochester, MN; Hunter Valley Oncology, Gateshead, Australia; Medical University of Vienna, Vienna, Austria; New York University, New York, NY; Kaiser Permanente, Vallejo, CA; CHU de Québec Université Laval, Quebec, QC, Canada; Memorial Sloan Kettering Cancer Center, New York, NY; GBG Forschungs GmbH, Neu-Isenburg, Germany; Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; ABCSG, Wien, Austria; Pfizer Inc., San Francisco, CA; Alliance Trials Foundation, Boston, MA; ABCSG, Vienna, Austria; University of Pennsylvania, Philadelphia, PA

Background: The PALLAS trial (NCT02513394) investigated the efficacy of the addition of palbociclib (palbo) to standard adjuvant endocrine therapy (ET) to reduce breast cancer recurrence. Previous analyses of this trial have not shown significant benefit of combination palbo+ET over ET alone. Given prior data showing that extent of neutropenia is associated with response to palbo and other cell cycle-specific therapies, we evaluated whether extent of neutropenia could identify responders to palbo in the adjuvant setting. **Methods:** PALLAS is a global, open-label, phase III trial that randomized patients (pts) with stage II-III hormone-receptor positive, HER2-negative breast cancer to receive ET for ≥5 years with or without standard-dose palbo for 2 years in 28-day cycles. The primary endpoint is invasive disease-free survival (iDFS). For this exploratory analysis, the palbo population was classified into pts with treatment-emergent high-grade neutropenia (HGN) with maximum grade ≥3 (absolute neutrophil count <1000), or low-grade/no neutropenia (LGN) with maximum grade <2; these groups were compared to each other and to the ET alone group for 5-year iDFS outcomes. Logistic regression examined individual baseline characteristics associated with HGN during the first 3 cycles within the palbo group. Impact of HGN during the first 3, 6, and 12 cycles on iDFS was tested using univariate and multivariable landmark Cox regression. **Results:** The safety population included 5736 pts, 2840 allocated to palbo+ET, 2896 to ET alone. Prior publications reported no new safety signals, low rates of serious infection, and no grade 5 treatment-related events. The palbo+ET group consisted of 1006 (35.4%) LGN and 1834 (64.6%) HGN. 5-year iDFS results are shown in the table. Pts who received palbo+ET and developed HGN by the end of cycle 6 had significantly improved 5-year iDFS compared to those who received ET alone (p=0.04), which remained statistically significant when adjusting for body mass index (BMI), prior chemotherapy, and race. Multivariable logistic regression showed lower BMI, prior chemotherapy, Asian race, and prior mastectomy were significantly associated with HGN (all p<0.05). **Conclusions:** In this exploratory analysis of the phase III PALLAS adjuvant trial, addition of palbo to ET appeared to be superior to ET alone in pts who developed HGN in the first 6 cycles of treatment but not in those who had LGN. These findings are consistent with observations in the metastatic setting suggesting that neutropenia could be a useful biomarker for palbo concentration and efficacy. Clinical trial information: NCT02513394. Research Sponsor: Pfizer.

Maximum grade neutropenia measured at end of cycle:	5-year iDFS				
	Palbo+ET HGN (%)	Palbo+ET LGN (%)	ET alone (%)	Hazard Ratio	p-value
3	84.9	84.4		1.06	0.54
	84.9		82.9	1.17	0.06
6	85.6	84.9		1.08	0.44
	85.6		83.4	1.19	0.04
12	86.3	85.9		1.06	0.57
	86.3		85.0	1.12	0.20

Real-world (RW) analysis of characteristics and risk of recurrence (ROR) in Black patients (pts) with HR+/HER2− early breast cancer (EBC) eligible for NATALEE.

Yara Abdou, Sonya A. Reid, Komal L. Jhaveri, Mark D. Pegram, Ilana Schlam, Joseph A. Sparano, Brooklyn T. Olumba, Elizabeth Chertow Santarsiero, Vaidyanathan Ganapathy, Murat Akdere, Fen Ye, Julia Kim, Michael A. Danso; Division of Oncology, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN; Memorial Sloan Kettering Cancer Center, New York, NY; Stanford University School of Medicine, Stanford, CA; Dana-Farber Cancer Institute, Boston, MA; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; Memorial Hermann Southwest Hospital, Houston, TX; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Pharma AG, Basel, Switzerland; Genesis Research, Hoboken, NJ; Brock Cancer Center, Virginia Oncology Associates and Sarah Cannon Research Institute, Norfolk, VA

Background: The NATALEE trial showed statistically significant and clinically meaningful invasive disease–free survival benefit with ribociclib + nonsteroidal aromatase inhibitor (NSAI) vs NSAI alone in pts with stage II/III HR+/HER2− EBC at high ROR that deepened even after all pts were off ribociclib. Prior RW analyses have shown clinically meaningful ROR at 5 y despite endocrine therapy (ET) among NATALEE-eligible pts. TAILORx and RxPONDER reported racial disparities in recurrence and outcomes; however, further understanding of characteristics and unmet needs in Black pts is needed. This RW analysis describes pt characteristics and outcomes among Black pts eligible for NATALEE and receiving ET. **Methods:** Data from the US Flatiron Health EHR-derived deidentified database (2011-2023) were used. Selection criteria included pts aged ≥18 y with anatomical stage I-III (AJCC) HR+/HER2− EBC who had primary tumor surgical resection and started adjuvant ET. Pt characteristics and treatment patterns were analyzed in Black vs White pts eligible for NATALEE. ET (any) adherence was defined as proportion of days covered ≥80%. Recurrence-free survival (RFS), distant recurrence–free survival (DRFS), and overall survival (OS) were assessed descriptively and using multivariate Cox regression analysis. **Results:** A total of7481 pts met selection criteria. Overall, 41.2% (242/588) of Black and 33.0% (1697/5142) of White pts met NATALEE eligibility criteria. Compared with White pts, Black pts were younger (median age, 59 y vs 62 y) and more likely to be premenopausal (29.3% vs 23.8%), have anatomical stage III disease (35.1% vs 25.7%), more extensive nodal involvement (19.8% N0, 54.1% N1, 14.0% N2, and 7.0% N3 vs 24.0% N0, 53.3% N1, 11.3% N2, and 6.2% N3), higher use of Medicaid (13.2% vs 3.6%), lower socioeconomic status (lowest socioeconomic status quintile, 33.9% vs 11.4%), higher obesity (body mass index ≥30, 52.9% vs 38.4%), and lower ET adherence (3 y ET adherence: 57.0% vs 65.2%; 5 y ET adherence: 48.3% vs 56.2%). Five-y RFS, DRFS, and OS rates were 74.3%, 77.6%, and 85.0%, respectively, in Black pts and 83.2%, 84.5%, and 90.9% in White pts. Compared to White pts, Black pts had worse RFS (hazard ratio, 1.5; P=0.0045), DRFS (hazard ratio, 1.4; P=0.0272), and OS (hazard ratio, 1.7; P=0.0023) after adjusting for age, menopausal status, body mass index, tumor size and grade, nodal status, chemotherapy use, and socioeconomic status index. **Conclusions:** In a RW dataset of pts eligible for adjuvant ribociclib based on NATALEE inclusion criteria, Black pts had a higher recurrence risk and worse survival compared with White pts, underscoring the opportunity to improve outcomes and address racial disparities in Black pts with HR+/HER2− EBC. Research Sponsor: None.

Real-world patterns of Oncotype DX (O-Dx) testing and chemotherapy (CT) use among patients with early-stage, hormone receptor–positive (HR+) breast cancer (BC).

Marija Sullivan, Xiudong Lei, Inimfon Jackson, Sharon H. Giordano, Mariana Chavez Mac Gregor; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: O-Dx, a 21-gene assay, has transformed the management of patients with early-stage, HR+, HER2-negative (HER2-) BC by guiding personalized treatment decisions regarding adjuvant CT. However, real-world patterns of CT use based on recurrence score (RS) remain a topic of interest. Using a large, hospital-based database, we evaluated testing patterns, factors associated with O-Dx testing, and examined predictors of CT use among patients by RS. **Methods:** Patients ≥18 years with early-stage, HR+/HER2- BC diagnosed from 2018-2021 who underwent surgery and had pT1-T3, pN0-N1 disease were identified in the National Cancer Database. Descriptive analyses were used to compare baseline sociodemographic, clinical and treatment characteristics by receipt of O-Dx testing. Multivariable logistic regression was used to examine factors associated with receipt of O-Dx testing and predictors of CT use, stratified by RS into 0-10 (low risk), 11-25 (intermediate risk) and > 25 (high risk). **Results:** Of 319,771 patients with early-stage, HR+/HER2- BC, 54% (172,491) received O-Dx testing. Median age was 61 among those who received testing and 65 among those who did not. Black (aOR = 0.93; 95%CI 0.90–0.95) and Hispanic patients (aOR = 0.89; 95%CI 0.86–0.92) were less likely to receive testing than White patients. Compared to private insurance, those on Medicare (aOR = 0.93; 95%CI 0.91–0.95), Medicaid (aOR = 0.89; 95%CI 0.86–0.92), or no insurance (aOR = 0.91; 95%CI 0.85–0.98) had lower odds of O-Dx testing. While older age, higher comorbidity scores and pN1 disease were associated with lower odds of testing, recent year of diagnosis, pT2 disease, lobular histology, higher grade and treatment in academic facilities were linked to higher odds of testing. Overall, 16% (51,213) of patients received CT. Of those, 17.3% did not have an O-Dx test, while 76% of those who received CT and testing had RS > 25. 4.2% of patients aged 18-49 years received CT despite RS 0-10. Among patients without a test, being Black (aOR = 1.19; 95%CI 1.12–1.26) or Hispanic (aOR = 1.08; 95%CI 1.01–1.16) was associated with higher odds of receiving CT. Black patients with RS > 25 (aOR = 0.84; 95%CI 0.76–0.93) were less likely to receive CT than White patients. Larger tumors, pN1 disease and higher-grade tumors were associated with greater odds of CT receipt while older age at diagnosis and lobular histology were associated with lower odds regardless of RS. **Conclusions:** O-Dx testing has been increasingly incorporated into clinical practice. Our findings highlight disparities in the receipt of O-Dx testing and CT use, particularly according to RS. Black patients who did not undergo O-Dx testing were more likely to receive CT, while those with RS > 25 were less likely to receive CT. Further research is needed to explore physician and patient decision-making regarding O-Dx testing and adjuvant CT. Research Sponsor: Susan G. Komen; SAC220221; Breast Cancer Research Foundation (BCRF); 23-190.

Estrogen receptor expression in residual breast cancer following neoadjuvant chemotherapy.

Sarah K. Premji, Tanya L. Hoskin, Michael Gary Keeney, Grace Mei Yee Choong, Amye Juliet Tevaarwerk, Karthik Giridhar, Roberto Antonio Leon-Ferre, Tufia C. Haddad, Ciara Catherine O'Sullivan, Elizabeth Jane Cathcart-Rake, Timothy J. Hobday, Kathryn Jean Ruddy, Siddhartha Yadav, Prema P. Peethambaram, James N. Ingle, Judy Caroline Boughey, Matthew P. Goetz; Mayo Clinic, Rochester, MN

Background: Neoadjuvant chemotherapy (NAC) is commonly administered to patients (pts) with estrogen receptor alpha (ER) negative (immunohistochemistry [IHC] 0%) and ER-low (IHC 1-10%) breast cancer (BC). For pts without pathological complete response (pCR), ER expression may differ between baseline and residual BC following NAC. We previously demonstrated adjuvant endocrine therapy (ET) omission in ER-low early-stage BC was associated with significantly worse overall survival (OS); however, this effect was restricted to pts with residual BC following NAC and those with higher baseline ER levels (IHC 6-10%) (Choong et al., ASCO 2024). Here, we assessed how often ER was expressed in residual invasive BC for pts treated with NAC for ER-negative and ER-low BC. **Methods:** Weidentified pts with pre-treatment (tx) ER-negative and ER-low (regardless of HER2 expression) stage I-III BC treated with NAC who underwent BC surgery at Mayo Clinic Rochester between 2009 and 2023. ER IHC was performed in a CAP/CLIA laboratory. We evaluated ER expression in residual invasive BC for pts without pCR. The percent of pts with a post-tx change in ER status was estimated and reported with 95% Wilson confidence intervals. **Results:** 955 pts (838 [88%] pre-tx ER-negative; 117 [12%] pre-tx ER-low) met inclusion criteria, of whom 69% had HER2-negative and 31% HER2-positive BC. The median age at diagnosis was 52 (range: 24-86). 496 (52%) had residual BC. Residual BC was more common in HER2-negative versus (vs) positive tumors (56% vs 42%, $p < 0.001$) but did not differ significantly by ER status (ER-negative 51% vs ER-low 57%, $p = 0.22$). Of those with residual BC, 277/496 (56%) had ER re-testing. Rates of ER re-testing did not vary for pre-tx ER-negative vs -low (57% vs 51%, $p = 0.37$) but were significantly lower for HER2-positive vs HER2-negative tumors (39% vs 62%, $p < 0.001$). Among those with post-tx testing, 31/277 (11%, 95% CI: 8-15%) had an increase in ER expression from pretreatment levels (defined as ER IHC $< 1\%$ to either 1-10% or $> 10\%$; or ER IHC 1-10% to $> 10\%$). In these 31 pts, the original NAC was for either TNBC (21/31; 68%) or HER2+ BC (10/31; 32%). In pts with pre-tx ER-negative BC, 27/243 (11%, 95% CI: 8-16%) had ER expression in the residual BC including 14/243 (6%, 95% CI: 3-9%) with ER $> 10\%$ and 13/243 (5%, 95% CI: 3-9%) with ER 1-10%. For pts with baseline ER-low BC, 4/34 (12%, 95% CI: 5-27%) had ER $> 10\%$ in the residual BC. Among the 31 pts where ER increased following NAC, 21/31 (68%) received adjuvant ET, including 17/18 if ER was $> 10\%$ in the residual disease and 4/13 in those with ER 1-10%. **Conclusions:** In pts treated with NAC for ER-negative or ER-low BC not achieving pCR, we identified higher ER expression in the residual breast cancer in $> 10\%$ of pts. Given that omission of ET in ER-low BC with residual cancer following NAC is associated with worse survival, repeat biomarker testing should be considered in those without pCR, and ET individualized according to ER expression. Research Sponsor: None.

Molecular and immune profiling of breast cancer from pregnancy to postpartum: Insights into the tumour-immune landscape during breastfeeding from GEICAM EMBARCAM study.

Regina Peña-Enriquez, Begona Bermejo, Silvia Guil Luna, Yolanda Jerez Gilarranz, Jose Juan Ponce-Lorenzo, Alejandra Díaz, Juan Miguel Cejalvo, Ana Santaballa, Antonio Fernandez, Elena Galve Calvo, Álvaro Jiménez-Arranz, Blanca Cantos Sanchez de Ibarguren, Maria Helena Lopez de Ceballos, Antonio Anton, Fernando Moreno Antón, Raul Rincon, Rosalia Caballero, Marina Pollan, Angel Guerrero, Juan De La Haba; Instituto Maimónides de Investigación Biomédica de Cordoba (IMIBIC)-Hospital Universitario Reina Sofia, Universidad de Cordoba, Córdoba, Spain; Clinic University Hospital Valencia, Valencia, Spain; Instituto Maimonides de Investigación Biomédica de Cordoba (IMIBIC)-Hospital Universitario Reina Sofia, Universidad de Cordoba, Cordoba, Spain; Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC. GEICAM Spanish Breast Cancer Group, Madrid, Spain; Oncology Department, Dr. Balmis General University Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain; Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria (INCLIVA), Universidad de Valencia. GEICAM Spanish Breast Cancer Group, Valencia, Spain; Medical Oncology Department, La Fe Health Research Institute (IISLaFe), La Fe University Hospital. GEICAM SpanishBreast Cancer Group, Valencia, Spain; Hospital General Universitario de Albacete. GEICAM Spanish Breast Cancer Group, Albacete, Spain; Medical Oncology Service, Hospital Universitario Basurto (OSI Bilbao-Basurto). GEICAM Spanish Breast Cancer Group, Bilbao, Spain; Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)-Hospital Universitario Reina Sofía, Universidad de Córdoba, Córdoba, Spain; Hospital Puerta de Hierro, GEICAM Spanish Breast Cancer Group, Madrid, Majadahonda, Spain; Hospital San Pedro de Alcántara. GEICAM Spanish Breast Cancer Group, Cáceres, Spain; Universidad de Zaragoza, Instituto Investigación Sanitaria Aragón, Hospital Universitario Miguel Servet. GEICAM Spanish Breast Cancer Group, Zaragoza, Spain; Hospital Clínico Universitario San Carlos; GEICAM Spanish Breast Cancer Group, Madrid, Spain; GEICAM Spanish Breast Cancer Group, Madrid, Spain; Institute of Salud Carlos III. Consortium for Biomedical Research in Epidemiology & Public Health (CIBERESP-ISCIII). GEICAM Spanish Breast Cancer Group, Madrid, Spain; Instituto Valenciano de Oncología (IVO). GEICAM Spanish Breast Cancer Group, Valencia, Spain; Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC); University Reina Sofia Hospital, Universidad de Córdoba; GEICAM Spanish Breast Cancer Group, Córdoba, Spain

Background: Breast cancer (BC) is the most common malignancy among young women of childbearing age, with a rising incidence in this population. Pregnancy-associated breast cancer (PABC) is an aggressive entity linked to poor prognosis and elevated metastatic risk. Despite advances in BC research, the impact of pregnancy, breastfeeding, and postpartum mammary gland remodeling on tumor biology remains unclear, highlighting the need to explore their interaction with the tumor microenvironment for novel therapies. **Methods:** A gene expression and immune cell profiling analysis was conducted using the nCounter Breast Cancer 360 panel (NanoString) and CIBERSORTx (Newman 2019, Nat Biotechnol) on FFPE tumor samples from GEICAM/2017-07 EMBARCAM study (NCT04603820) PABC patients during the gestation (PABC_GS, n=21), breastfeeding (PABC_BF, n=21), and first-year post-partum (not during lactation period, PABC_FY, n=15) vs non-PABC tumours (n=49). Differential expression analysis per gene and biological signature was performed using the *limma* package. P-values were adjusted with the Benjamini-Yekutieli false discovery rate (FDR) method. Additionally, the LM22 matrix from CIBERSORTx was employed to quantify 22 immune cell types from normalized NanoString data. Statistical significance was set at 5%. **Results:** PABC clinical subtypes were 46% HR-positive/HER2-negative, 21% HER2-positive, and 33% triple-negative. Differential gene expression analysis identified similar significant enrichment pathways across all PABC groups compared to non-PABC: DNA repair-related signatures (HRD, BRCAness, BC p53) and BC proliferation (adj $p<0.05$), along with higher CDK4 expression and genomic risk ($p<0.05$). Conversely, key regulatory pathways such as apoptosis, TGF-Beta, and PD-L1 were downregulated (adj $p<0.05$). Nonetheless, it is noteworthy that the PABC_BF group showed a unique profile marked by increased immune activity and cell abundance (cytotoxic cells, CD8 T cells, T-reg, cytotoxicity), elevated SOX2 expression (adj $p<0.05$) and inflammatory chemokines levels ($p<0.01$) compared to non-PABC. The CIBERSORTx analysis supported these findings, demonstrating a significantly higher abundance of several immune cells in PABC_BF, remarkably CD8+ T-cells and T-regs, compared to all other groups ($p<0.05$). **Conclusions:** This GEICAM EMBARCAM sub-study reveals that PABC tumors display aggressive molecular features across all subtypes, contributing to poor prognosis. Notably, the breastfeeding-associated subset (PABC_BF) exhibits a highly active tumor-immune microenvironment with robust immune cell infiltration and inflammatory signalling, highlighting potential for targeted immunotherapy. These findings underscore the need for further clinical research to optimize immune-based strategies in PABC patients' management. Clinical trial information: NCT04603820. Research Sponsor: Instituto de Salud Carlos III (PI18/00817 and PI22/00969).; Fundacion Le Cado.

Prospective decision impact study of the Breast Cancer Index: Results from the BCI Registry study.

Tara B. Sanft, Natalia Siuliukina, Brandon O'Neal, Amanda Kristine Laust Anderson, Rachel Catherine Jankowitz, Mark D. Pegram, Sami George Diab, Yi Zhang, Kai Treuner, Joyce O'Shaughnessy; Yale University, New Haven, CT; Biotheranostics, A Hologic Company, San Diego, CA; Biotheranostics, Inc., San Diego, CA; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Stanford University School of Medicine, Stanford, CA; St. Joseph Cancer Center, Intermountain Health, Aurora, CO; Baylor University Medical Center, Texas Oncology, Dallas, TX and Sarah Cannon Research Institute, Dallas, TX

Background: The Breast Cancer Index (BCI) is a validated gene expression assay that provides an individualized risk of late distant recurrence and predicts the likelihood of benefit from extended endocrine therapy (EET) in HR+ early-stage breast cancer. The objective of this analysis was to assess the influence of BCI on clinical decision-making regarding EET. **Methods:** The BCI Registry study is a prospective, multi-institutional study investigating the long-term clinical outcome, decision impact, and quality of life in HR+ breast cancer patients receiving BCI testing as part of routine clinical care. Physicians and patients completed pre- and post-BCI test questionnaires to assess physician decision-making; physician confidence; and patient preferences and concerns for EET. Pre- and post-BCI responses were compared using McNemar's test and the Wilcoxon signed rank test. The BCI Registry Study is registered on ClinicalTrials.gov under NCT04875351. **Results:** In the current analysis,pre- and post-BCI testing questionnaires were completed for 2850 physicians and 2832 patients. 88.6% of patients were postmenopausal, 76.5% N0, 73.0% T1, 53.5% G2, and 13.0% HER2-positive. Following BCI testing, physicians changed treatment recommendations for EET in 41.2% (1175/2850) of patients ($p<0.001$). In cases where physicians recommended EET prior to BCI testing, 49.8% (775/1555) changed their recommendation to not treat with EET, while 31.2% (400/1280) of those who did not recommend EET prior to BCI testing changed their recommendation in favor of EET. Following BCI testing, 43.9% (1250/2850) of physicians felt more confident in their recommendation ($p<0.001$) and 43.2% (1223/2832) of patients felt more comfortable with their EET decision ($p<0.001$). The percentage of physicians having high confidence levels (confident or strongly confident) increased from 63.6% (N=1813) pre-BCI testing to 88.2% (N=2515) post-BCI testing. The percentage of physicians having low confidence levels (not at all confident, not confident, or ambivalent) decreased from 33.1% (N=943) pre-BCI testing to 11.0%(N=313) post-BCI testing. In BCI (H/I)-Low patients, 48.9% (868/1776) showed a decreased preference for EET ($p<0.001$). In BCI (H/I)-High patients, 34.6% (365/1056) showed an increased EET preference ($p<0.001$). After BCI testing, significantly more patients were less concerned about cost (23.9%, $p<0.001$), drug safety (25.7%, $p<0.001$), and EET benefit (30.9%, $p<0.001$). No significant change in concern regarding side-effects was observed ($p=0.58$). **Conclusions:** Incorporating BCI into clinical practice resulted in significant changes in physician recommendations for EET, while at the same time increasing physician confidence. Knowledge of the BCI result improved patient preference, satisfaction and reduced patient concerns regarding cost, drug safety and benefit of EET. Research Sponsor: None.

HER2DX prognostic value in older patients with HER2-positive early breast cancer: A correlative analysis from the RESPECT phase III trial.

Kazuki Nozawa, Masataka Sawaki, Yukari Uemura, Michiko Tsuneizumi, Toshimi Takano, Naomi Gondo, Fumikata Hara, Michiko Harao, Mercedes Marín-Aguilera, Patricia Villagrasa, Aleix Prat, Hiroji Iwata; Department of Advanced Clinical Research and Development, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan; Department of Breast Oncology, Nagoya Medical Center, Nagoya, Japan; Center for Clinical Science, National Center for Global Health and Medicine, Tokyo, Japan; Department of Breast Surgery, Shizuoka General Hospital, Shizuoka, Japan; Breast Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Breast and Thyroid Surgical Oncology, Sagara Hospital, Kagoshima-Shi, Japan; Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; Department of Breast Oncology, Jichi Medical University Hospital, Shimotsuke-Shi, Japan; Reveal Genomics, Barcelona, Spain; Hospital Clínic Barcelona, Barcelona, Spain

Background: HER2DX, the first multigene assay specifically designed for HER2+ breast cancer, has demonstrated potential to guide treatment decisions. However, its validation in the context of de-escalated chemotherapy regimens, including trastuzumab monotherapy, in older patients remains limited. In the RESPECT trial (NCT01104935, JCO 2020), 1-year of trastuzumab monotherapy was shown to be a clinically meaningful adjuvant option compared to de-escalated chemotherapy and trastuzumab in older patients with HER2+ early breast cancer. This exploratory analysis of HER2DX within the RESPECT trial (Trans-RESPECT study) aimed to evaluate the assay's prognostic value. **Methods:** The RESPECT Phase III trial enrolled patients aged 70–80 years with stage I–IIIA HER2+ early breast cancer. Participants were randomized to receive trastuzumab monotherapy (H group) or trastuzumab plus chemotherapy (H+CT group). Chemotherapy regimens included paclitaxel monotherapy (35.1%), anthracycline/cyclophosphamide alone (22.9%), CMF (19.8%), docetaxel monotherapy (14.5%), or docetaxel-carboplatin (3.1%). Risk stratification into HER2DX low- or high-risk groups used both the standard 50 cutoff (scale 1-99) and an exploratory 32 cutoff, previously reported in the APT trial (Tolaney et al., Lancet Oncol, 2023). The primary endpoint was relapse-free survival (RFS), with secondary endpoints including overall survival (OS). **Results:** Among 275 patients in the RESPECT trial, 154 tumors (56.0%) were profiled using HER2DX (H group: 74; H+CT group: 80). Baseline characteristics of the profiled cohort mirrored those of the overall trial population. Most patients (92.9%) had a performance status of 0, 28.6% were older than 75 years, 53.2% were HR-negative, 80.5% had node-negative disease, and the majority had pT1c (41.6%) or pT2 (44.8%) tumors. Using the HER2DX 50 cutoff, 40 patients (26.0%) were classified as high risk, and 114 (74.0%) as low risk. RFS was higher in the HER2DX low-risk group compared to the high-risk group (hazard ratio [HR] = 2.02, 95% CI: 0.97–4.19), with 5-year RFS rates of 92% and 77%, respectively. OS was also superior in the HER2DX low-risk group (HR = 2.74, 95% CI: 1.18–6.36), with 5-year OS rates of 97% and 84%. Using the HER2DX 32 cutoff, 81 patients (52.6%) were classified as high risk, and 73 (47.4%) as low risk. In the H group, 3- and 5-year RFS were 97% and 94% in the low-risk group, compared to 87% and 81% in the high-risk group. In the H+CT group, 3- and 5-year RFS were 95% and 95% in the low-risk group, compared to 93% and 83% in the high-risk group. **Conclusions:** The HER2DX genomic risk score demonstrates prognostic value in older patients with HER2+ early breast cancer, including those treated with trastuzumab monotherapy. This assay may aid in identifying patients suitable for treatment de-escalation strategies. Additional analyses will be presented at the conference. Clinical trial information: NCT01104935. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

The difference of clinical and molecular characteristics between HR-positive/HER2-positive and HR-negative/HER2-positive early breast cancer: A secondary analysis of 11 clinical trials.

Hongmei Zheng, Yalong Yang, Jianhua Liu, Rui Tian, Xinhong Wu; Department of Breast Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology; Hubei Provincial Clinical Research Center for Breast Cancer, and Wuhan Clinical Research Center for Breast Cancer, Wuhan, China; Department of Breast Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Hubei Provincial Clinical Research Center for Breast Cancer, and Wuhan Clinical Research Center for Breast Cancer, Wuhan, China; Breast cancer center, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology,Hubei Provincial Clinical Research Center for Breast Cancer, and Wuhan Clinical Research Center for Breast Cancer, Wuhan, China; Department of Breast Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology and Hubei Provincial Clinical Research Center for Breast Cancer, Wuhan, China

Background: HER2+ early breast cancer (EBC) are treated as an identical cluster of patients in clinical practice. However, the various status of hormone receptor (HR) leads to different outcomes. We aimed to clarify the difference of clinical and molecular characteristics between HR+/HER2+ and HR-/HER2+ EBC. **Methods:** This secondary analysis assessed pathologically complete response (PCR) and disease free survial (DFS) among HR+/HER2+ and HR-/HER2+ EBC patients enrolled in the 11 clinical trials. These studies included 16866 HER2+ EBC patients, with available immunohistochemistry and/or in situ hybridization results. There are five neoadjuvant trials (TRYPHAENA, Kristine, Neosphere, BERENICE and Peony) and six adjuvant trials (HERA, HannaH, Aphinity, Katherine, PrefHer and SafeHer). The primary endpoints of the trials were PCR, DFS, overall preference proportions and adverse event rates. Kaplan–Meier approach and Cox proportional hazards model were applied to estimate the association of treatment strategies with PCR and DFS among HR+ and HR- populations. The 11 trials were all registered with ClinicalTrials.gov, number NCT00976989, NCT02131064, NCT00545688, NCT02132949, NCT02586025, NCT00045032, NCT00950300, NCT01358877, NCT01772472, NCT01401166 and NCT01566721. **Results:** In the16866 HER2+ EBC patients, except for PrefHer and SafeHer trials, which has no information about HR status, there are 13801 patients with HR details, of which, HR+ 8004 (58.0%) and HR- 5713 (41.4%). In HER2+ EBC, the various status of HR leads to different outcomes. Our study revealed an interesting phenomenon that compared to HR-/HER2+ EBC, HR+/HER2+ EBC has a lower pCR rate. However, trials from adjuvant therapy studies suggested HR+/HER2+ EBC has a longer DFS, which is not consistent with other subtype patterns. The pCR rate is a near-term indicator that visualizes the response rate to a particular treatment, and the DFS is a distant indicator that reflects the overall biological behavior of the individual. The HR+/HER2+ EBC, despite its low pCR rate, potentially improves its long-term DFS due to the addition of adjuvant endocrine therapy postoperatively. **Conclusions:** Compared to HR-/HER2+ EBC, HR+/HER2+ patients has a lower pCR rate, but has a longer DFS, which deserve further exploration. Research Sponsor: None.

The stratification of the HER2+ early breast cancer patients according to HR status in the 11 clinical trials.

Trial	Total, n	HR+, n(%)	HR-, n(%)	Unknown, n
TRYPHAENA	225	114(50.6)	111(49.4)	0
Kristine	444	276(62.2)	168(37.8)	0
Neosphere	417	197(47.2)	219(52.5)	1
BERENICE	401	252(62.8)	140(34.9)	9
Peony	329	173(52.6)	156(47.4)	0
HERA	5099	2571(50.4)	2528(49.6)	0
HannaH	596	265(44.5)	257(43.1)	74
Aphinity	4804	3082(64.2)	1722(35.8)	0
Katherine	1486	1074(72.3)	412(27.7)	0
PrefHer	488	NA	NA	NA
SafeHer	2577	NA	NA	NA

HR, hormone receptor.

Patterns of early and late recurrence across breast cancer subtypes in the CCTGMA.32 trial.

Ana Elisa Lohmann, Bingshu E. Chen, Wendy R. Parulekar, Katarzyna Joanna Jerzak, Pamela Jean Goodwin; University of Western Ontario, London, ON, Canada; Canadian Cancer Trials Group, Kingston, ON, Canada; Sunnybrook Odette Cancer Centre, Toronto, ON, Canada; Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital, Toronto, ON, Canada

Background: An ongoing constant risk of recurrence out to 20 years is well established in hormone receptor positive breast cancer (BC) less so in other BC subtypes. This study aims to describe patters of early (≤ 5 years of BC diagnosis) and late recurrence (> 5 years of BC diagnosis) across immunohistochemically defined BC subtypes - luminal (ER/PgR+HER2-), triple negative (TN: ER/PgR/HER2-) and HER2+ (any ER/PgR) in CCTGMA.32 (NCT01101438) which investigated metformin vs placebo in patients enrolled 2010-2013. **Methods:** 3649 patients with high-risk non-metastatic BC were enrolled and followed for first locoregional and distant recurrence, new primary cancers and death. Annual rates of these events were calculated in each BC subtype and averaged for early (years 0-5) and late (after 5 years) post randomization. **Results:** In luminal (n = 2104), TN (n = 925), HER2+ (n = 620) BC the median follow-ups were 96.2 (range 0.2 to 120.7), 94.5 (0.03 to 120.5), 95.2 months (0.03 to 119.8), respectively. Patterns of events varied across subtypes and early vs late. In luminal BC, the early vs late annual invasive cancer event rates (ICERs) was 3.04 vs. 2.31 % (late rate 0.76 of early rate). The annual early vs late rates of distant recurrence (DR) were 2.33 vs 1.72% (late rate 0.74 of early rate). Bone was the most common site of DR both early and late. In the TN BC, the early vs late annual ICERs were 4.6 and 1.21% (late rate 0.35 of early rate). Annual early vs late DR rates were 3.09 vs. 0.20 % (late rate 0.28 of early rate). Visceral metastases (lung, liver, CNS) were most common early. In HER2+, early vs late annual ICERs were 2.93 vs 1.47% (late rate 0.50 of early rate). Annual early vs late DR rates were 2.25 vs 0.71% (late rate 0.32 of early rate). Bone and visceral metastases were common early. CNS was rare after 5 years in all BC subtypes. Second primary cancers (new BC and non-primary BC) were frequent across BC subtypes, with no fall-off over time; they were responsible for the majority of late events in TN and HER2+ BC. **Conclusions:** In luminal BC, risk of late ICER remains high (annual rate about three-quarters of early rate), while risk of late events was lower in TN and HER2+BC (late rates one quarter to one-third of early rates). Risk of second primary cancers did not decrease over time, and second primaries were the most frequent late events in TN and HER2+BC. Clinical trial information: NCT01101438. Research Sponsor: London Health Sciences Foundation - Ontario, Canada; Canadian Cancer Society Research Institute; National Cancer Institute; The Breast Cancer Foundation - New York; Canadian Breast Cancer Foundation - Ontario, Canada; Ontario Institute for Cancer Research; Apotex Canada; Hold'em for Life Charity.

	Luminal		TN		HER2+	
	Annual event rate (%)		Annual event rate (%)		Annual event rate (%)	
	Year 0-5	Year 5+	Year 0-5	Year 5+	Year 0-5	Year 5+
Any Invasive Cancer Event	3.04	2.31	4.60	1.21	2.93	1.47
Locoregional Event	0.50	0.29	1.15	0.26	0.64	0.15
Distant Recurrence*	2.08	1.29	3.09	0.20	2.03	0.57
Sites of First Metastasis:						
Bone	1.40	0.88	1.13	0.10	0.65	0.42
Lung	0.59	0.56	1.73	0.20	0.83	0.07
Liver	0.71	0.56	0.73	0.00	0.50	0.21
CNS	0.18	0.06	0.65	0.00	0.61	0.00
Second Primary Cancer**	0.66	0.92	0.96	0.90	0.60	0.74

*Including distant recurrence after a local regional events.
**Non-breast cancer and new breast cancer events.

Real-world evidence of PARPi-related MDS/AML risk in breast cancer patients: An international collaborative network analysis.

Michela Palleschi, Caterina Gianni, Filippo Merloni, Alberto Farolfi, Gema Hernández, Francesca Rusconi, Nicola Gentili, Martina Cavallucci, Giulia Miserocchi, Daniela Montanari, Chiara Casadei, Giandomenico Di Menna, Marita Mariotti, Martina Tegas, Olga Serra, Marianna Sirico, Roberta Maltoni, Samanta Sarti, Lorenzo Cecconetto, Antonino Musolino; IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; TriNetX Europe, Madrid, Spain; TriNetX Europe, Milan, Italy; Data Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) “Dino Amadori”, Meldola, Italy

Background: Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as a significant therapeutic advance in breast cancer treatment. However, concerns about therapy-related myeloid neoplasms, specifically myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), necessitate thorough investigation of their safety profile in real-world settings. **Methods:** Using the TriNetX Global Collaborative Network, we conducted a retrospective analysis comparing breast cancer patients treated with PARP inhibitors (PARPi) versus conventional chemotherapy only (anthracyclines and taxanes). Our primary analysis utilized propensity score matching (1,702 patients per group) accounting for age and race, to evaluate the risk of developing MDS/AML. Hazard ratio (HR) was used to compare the incidence of MDS/AML between the matched cohorts. Secondary analyses included an unmatched Cox proportional hazards model in a larger cohort (1,826 vs 36,257 patients), comparison between different PARP inhibitors, and assessment of mortality risk factors. **Results:** In the propensity score-matched analysis, PARPi treated patients demonstrated a statistically significant higher risk of developing MDS/AML versus chemotherapy only cohort (16 cases versus 10, HR=5.25; 95% CI: 1.96-13.92; $p<0.0001$). Treatment patterns differed notably, with PARPi-treated patients receiving more carboplatin (HR=1.73; 95% CI: 1.42-2.10) but less anthracycline therapy (HR=0.25; 95% CI: 0.20-0.31). The unmatched Cox regression analysis confirmed these findings with a higher risk of developing AML/MSD in the PARPi cohort (HR=3.47; 95% CI: 1.87-6.27) and identified age (HR=1.03; 95% CI: 1.02-1.05) and platinum therapy (HR=2.12; 95% CI: 1.26-3.59) as independent risk factors. Within the triple negative group, the data remains statistically significant (HR=3.14; 95% CI: 1.459- 6.757). No significant differences in MDS/AML risk were observed between olaparib and talazoparib. While mortality was comparable between groups, prior platinum exposure emerged as a significant mortality risk factor (HR=2.39; 95% CI: 1.09-5.09). **Conclusions:** Our findings indicate a significantly increased risk of therapy-related myeloid neoplasms with PARP inhibitor treatment compared to conventional chemotherapy, particularly in the context of previous platinum exposure in breast cancer patients. These results underscore the importance of careful patient selection and monitoring during PARP inhibitor therapy, while highlighting the need for extended follow-up studies to fully characterize long-term safety profiles. Research Sponsor: None.

Extended endocrine therapy after 5 years of adjuvant LHRH-agonist in premenopausal patients with node-positive hormone receptor (HR)-positive early breast cancer.

Carmine Valenza, Yue Zheng, Monica Milano, Elisa Giordano, Lorenzo Guidi, Pier Paolo Maria Berton Giachetti, Laura Boldrini, Grazia Castellano, Jalissa Katrini, Bianca Malagutti, Gabriele Antonarelli, Fabio Conforti, Eleonora Pagan, Vincenzo Bagnardi, Gregory John Kirkner, Dario Trapani, Kate Dibble, Elisabetta Munzone, Giuseppe Curigliano, Ann H. Partridge; Division of Early Drug Development, European Institute of Oncology IRCCS, University of Milan, Milan, Italy; Department of Data Science, Dana-Farber Cancer Institute, Boston, MA; Division of Medical Senology, European Institute of Oncology IRCCS, Milan, Italy; Division of Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS, University of Milan, Milan, Italy; Istituto Europeo di Oncologia, IRCCS, Milan, Italy; European Institute of Oncology IRCCS, Milan, Milan, Italy; European Institute of Oncology, Milano, Italy; Division of Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS, University of Milan, Milan, NA, Italy; European Institute Of Oncology, IRCCS, University of Milan, Milan, Italy; Division of New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, IRCCS, Milan, Italy. Department of Oncology and Hemato-Oncology (DIPO), University of Milan, Milano, Italy; Medical Oncology Division, Cliniche Humanitas Gavazzeni, Bergamo, NA, Italy; University of Milan-Bicocca, Milano, Italy; Istituto Europeo Oncologico, Milano, Italy; Dana-Farber Cancer Institute, Boston, MA; Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; European Institute of Oncology IRCCS, University of Milan, Milan, Italy; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: There is no evidence regarding the benefit of extended endocrine therapy (eET) beyond 5 years of adjuvant treatment with LHRH agonists (LHRHa) in premenopausal women with node-positive, HR-positive early breast cancer (eBC). **Methods:** We conducted a retrospective study on two prospectively maintained datasets (Young Women Study and IEO Breast Cancer Dataset) to evaluate the clinical benefit of eET in women who had completed 5 years of adjuvant LHRHa, remained premenopausal, and had no evidence of distant or locoregional recurrence. This study included <40y women at diagnosis (between 2006 and 2016) with node-positive HR+ eBC, with ductal, lobular, or mixed histological subtypes, receiving or not eET (tamoxifen monotherapy or LHRHa+tamoxifen/aromatase inhibitor [AI]). The primary endpoint was the invasive breast cancer-free survival (IBCFS), calculated from the 5th year of endocrine therapy (ET) and adjusted for dataset, age at diagnosis, histotype, stage, disease subtype, type of adjuvant chemotherapy and ET received. **Results:** 503 patients were included (see Table): 287 received eET for a median duration of 3.6 years (Interquartile Range: 2.1–5.0). At a median follow-up of 7.05 years (calculated from the 5th year of ET), 50 and 72 IBCFS events occurred in the eET and non-eET groups, respectively. The adjusted Hazard Ratio (HR) for IBCFS comparing the eET to the non-eET group was 0.60 (95% CI,0.41-0.88; p<0.001). For distant recurrence or death, 28 and 46 events occurred, respectively, and the adjusted HR for distant disease free-survival was 0.43 (95% CI, 0.27-0.71). Among patients receiving eET, the adjusted HR for IBCFS comparing tamoxifen monotherapy (n=137) with LHRHa+tamoxifen/AI (n=150) was 0.75 (95% CI, 0.41-1.38). **Conclusions:** Extending endocrine therapy beyond five years of LHRHa treatment resulted in significantly higher IBCFS and distant metastasis free-survival. Larger prospective studies are required to confirm this finding and determine the most effective eET strategy. Research Sponsor: None.

Patients' characteristics.

Characteristic	Extended endocrine therapy (N=287)	No extended endocrine therapy (N=216)
Age at diagnosis, median (IQR)	37 (35-39)	37 (33-39)
Dataset: IEO | YWS, n	273 | 14	212 | 4
Histotype: ductal | lobular | mixed, %	91 | 5 | 4	95 | 3 | 2
pT: pT1 | pT2 | pT3-4, %	37 | 48 | 15	41 | 52 | 7
pN: pN1 | pN2 | pN3, %	64 | 22 | 14	73 | 17 | 10
Luminal A-like | B-like (G3 or HER2+), %	47 | 53	49 | 51
LHRHa combination during years 1-5: tamoxifen | aromatase inhibitor, %	66 | 34	76 | 22
Previous chemotherapy, %	77	70
Previous radiotherapy, %	64	62

G3, grade 3; IEO, European Institute of Oncology; IQR, interquartile range; YWS, Young Women Study.

Patterns in male and female breast cancer care: A comparative analysis of stage at presentation, treatment, and survival in the Veterans Health Administration.

Ariana Naaseh, Rebecca Aft, Kara N. Maxwell, Martin W. Schoen; Washington University in St. Louis School of Medicine, St. Louis, MO; University of Pennsylvania, Philadelphia, PA; Division of Hematology and Medical Oncology, Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, MO

Background: Male breast cancer (MBC) is a rare disease that is often managed using treatment protocols derived from female breast cancer (FBC). Given its rarity, limited large-scale national cohort data exists to inform clinical treatment decisions for MBC. This study aims to compare contemporary treatment trends and survival outcomes for MBC and FBC within the Veterans Health Administration (VHA). **Methods:** We conducted a retrospective cohort study of patients diagnosed with MBC and FBC between 2000 and 2022 using national data from the VHA Cancer Cube registry. Demographics, tumor characteristics, treatment (surgery, chemotherapy, hormone therapy, and radiation), and survival were compared between MBC and FBC patients. Descriptive statistics and chi-square tests compared the cohorts. Kaplan-Meier methods and Cox proportional hazards regression model were utilized to examine overall survival (OS). **Results:** Of the 14,018 total patients who met inclusion criteria, only 13.9% (n=1952) were males. MBC patients were significantly more likely to get diagnosed at an older age (MBC 68.8 vs. FBC 60.0 years; $p \leq 0.001$) and present with stage III or IV disease (25.8% vs. 12.9%; $p < 0.001$). Compared to FBC patients, MBC patients had significantly higher rates of receiving hormone therapy (56.8% vs. 51.6%; $p < 0.001$) and lower rates of chemotherapy (34.3% vs. 37.4%; $p = 0.007$), radiation (21.2% vs. 47.3%; $p < 0.001$), and surgery (92.1% vs 93.0%; $p = 0.01$). MBC patients were significantly less likely to undergo breast-conserving surgery (BCS) (11.2% vs. 52.0%; $p < 0.001$) than FBC patients. In a Cox proportional hazard model including age and stratified by stage, MBC patients had reduced OS (6.9 vs. 19.0 years; $p < 0.001$) and higher risk-adjusted hazard of all-cause mortality (adjusted hazard ratio 1.40, 95% CI 1.30-1.49). OS for MBC was lower than FBC across all stages (Table). **Conclusions:** Our national cohort study is the largest series of patients with MBC and FBC in the VHA population to date. We demonstrate that MBC patients present with advanced-stage cancer, are less likely to receive aggressive treatments, are less likely to undergo BCS, and have reduced OS across all stages, compared to FBC patients. Our findings highlight the need for further research to optimize outcomes of MBC patients. Research Sponsor: National Cancer Institute; T32CA009621.

Stage and survival of the cohort.

Clinical Stage	All Patients (n=12066)	Males (n =1952)	Median Survival for Males (years)	Females (n=12066)	Median Survival for Females (years)	P-value
0	2518	141 (7.2%)	12.3	2377 (19.7%)	Not reached	<0.001
I	5877	601 (30.8%)	9.8	5276 (43.7%)	20.2	
II	3589	709 (36.3%)	7.1	2880 (23.9%)	17.5	
III	1324	314 (16.1%)	5.4	1010 (8.4%)	10.6	
IV	730	189 (9.7%)	1.9	541 (4.4%)	2.8	

Racial differences in the prognostic value of Oncotype (RS) and MammaPrint (MP) in postmenopausal, estrogen receptor (ER)–positive, node-negative (N0) breast cancer (BC) patients with low genomic risk: A National Cancer Database (NCDB) study.

Prashanth Ashok Kumar, Calvin Widholm, Elizabeth Goodwin Hill, Sarah L. Sammons, Abirami Sivapiragasam; George Washington University Medical Faculty Associates, Washington, DC; Medical University of South Carolina, Charleston, SC; Dana-Farber Cancer Institute, Boston, MA

Background: Postmenopausal patients with ER+, HER2 negative, N0 BC often rely on genomic testing, such as RS or MP, to determine the benefit of chemotherapy. However, the prognostic value of RS, particularly among ethnic minority patients, remains uncertain. **Methods:** We utilized the 2021 NCDB to include postmenopausal female BC patients aged >50 years. Inclusion criteria were ER+, HER2-negative patients with, stage T1-4, N0, RS <26, or MP low risk. Patients were stratified by race, Caucasian (W) and African American (AA). Univariate analysis was performed to evaluate patient and tumor characteristics. Five-year overall survival (OS) rates were constructed using Kaplan-Meier (KM) product limit estimation. Unadjusted and covariate adjusted associations between race and OS were evaluated using Cox proportional hazard (PH) regression. Associations between race and OS among subgroups were similarly evaluated to highlight disparities and trends within the population. Hazard ratios (HRs; AA: W), 95% confidence intervals (CIs) and p-values are reported. **Results:** 96,411 patients had an RS<26 [W- 89,105 (92.42%) AA-7,306(7.58%)] and 3,146 had MP low [W-2,929(93.1%) AA-217(6.9%)]. Over 93% of patients in both groups received endocrine therapy, ~75% underwent partial mastectomy and radiation, and 7% received chemotherapy. Significant racial differences in tumor size and grade were observed in the RS group: T1 tumors (AA: 75% vs. W: 78%), T2 tumors (AA: 23% vs. W: 20%, p<0.001), G1 (AA: 29% vs. W: 34%), and G3 (AA: 13% vs. W: 9.3%, p<0.001), but these differences were not seen in the MP group. At 5 years, survival for RS <26 was 95.5% (AA) vs. 97.1% (W), and for MP low, 96% (AA) vs. 96.7% (W). The adjusted HR for RS <26 showed worse outcomes for AA (HR: 1.2, 95% CI 1.1–1.31, p<0.001), especially in younger patients, grades 1–2 tumors, T1 stage, partial mastectomy and low income. For MP low, the HR was not significant (HR: 1.08, 95% CI 0.59–1.97, p=0.8). **Conclusions:** Our analysis shows that among ER+, HER2- N0 cohort with RS <26, AA patients have a 20% increase in the risk of death compared to W patients, after adjusting for patient- and tumor-related factors. In contrast, no survival disparities were observed in the MP low-risk group. These findings suggest that RS may not be fully prognostic for AA patients even when accounting for clinic-pathologic risk factors. Study limitations include its retrospective design, potential biases, and incomplete consideration of biological and socioeconomic factors. Research Sponsor: None.

The impact of racial and socioeconomic disparities on radiation therapy delays in breast cancer patients: A National Cancer Database analysis.

Mehmet Murat Zerey, Joseph Panoff, Mukesh Roy, Reshma L. Mahtani, Ana Cristina Sandoval-Leon; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Miami Cancer Insititute, Baptist Health South Florida, Miami, FL

Background: Despite advancements in breast cancer (BC) treatment, significant disparities in outcomes persist in the United States. Timely initiation of adjuvant radiation therapy (RT) is crucial, as delays are associated with increased recurrence. Using the National Cancer Database (NCDB), this study provides a larger-scale analysis of racial and ethnic (R/E) disparities, examining the role of socioeconomic (SE) factors, including education and income, on RT delays and overall survival (OS) differences. **Methods:** A retrospective analysis was conducted using data from the NCDB. The study included female patients (pts) ≥18 years with stage I-III BC diagnosed between 2004 and 2020. Pts who received chemotherapy were excluded. Pts were categorized by R/E into four groups: White (W), Black (B), Hispanic (H), and Other (O). SE variables, including income and education, were stratified into quartiles (Q1–Q4) as defined by the NCDB. A delay in RT initiation was defined as starting treatment more than 3 months (mos) after surgery. Kaplan-Meier (KM) analysis with the log-rank test was used to compare OS across groups. Cox proportional hazards regression was performed to estimate hazard ratios (HR) and assess the impact of income and education on delays in RT and survival outcomes. **Results:** A total of 395,328 female BC pts were included in the analysis. The median age of the cohort was 65. Most were W (85.2%), followed by B (7.4%), H (4.0%), and O (3.5%). Almost all pts had stage I (81.6%) BC. The majority of patients were in the highest (Q4) income and education quartiles (40.2% and 45.6% respectively). Higher RT delays (>3 mos) were observed in B (11.07%) and H (11.38%) compared to W (5.31%), ($p < 0.001$). Pts in the lowest income and education quartiles (Q1) experienced delays more frequently (8.02% and 9.29%, respectively) compared to those in Q4 (5.72% and 5.27%, respectively $p < 0.001$). KM survival analysis revealed significant differences in OS for delayed RT, with median survival of 218 mos for 0–3 mos, 211 mos for 3–6 mos, and 209 mos for >6 mos ($p < 0.001$). KM survival analysis also demonstrated worse survival for pts in Q1 income and education compared to Q4 ($p < 0.001$). Cox proportional hazards model, when adjusted for clinical, R/E and SE factors revealed that pts in Q1 for income (HR = 1.411, $p < 0.001$) and education (HR: 1.036, $p < 0.001$) had a significantly higher risk of mortality compared to Q4. **Conclusions:** This study highlights significant R/E and SE disparities in timely RT initiation and survival outcomes among BC pts. B, H, and pts with lower S/E status experienced greater RT delays, emphasizing the critical need for targeted interventions to address delays in care and improve equity in cancer treatment. Research Sponsor: None.

Association between chemotherapy use and clinical outcomes in young BRCA carriers with T1N0 breast cancer: Results from an international cohort study.

Filipa Lynce, Eva Blondeaux, Virginia Delucchi, Hee Jeong Kim, Rinat Bernstein-Molho, Sabine C. Linn, Florence Coussy, Antonio Di Meglio, Kelly-Anne Phillips, Ava Kwong, Hans Wildiers, Elisa Agostinetto, Robert Fruscio, Alberta Ferrari, Laura De Marchis, Carmen Criscitiello, Katarzyna Pogoda, Meredith M. Regan, Ann H. Partridge, Matteo Lambertini; Dana-Farber Cancer Institute, Boston, MA; U.O. Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, University of Genova, Genova, Italy; Clinical Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; Department of Surgery, Division of breast surgery, University of Ulsan, College of Medicine, Asan Medical Center, Seoul, Songpa-gu, South Korea; Faculty of Medical and Health Sciences, School of Medicine, Tel Aviv, Israel; Department of Medical Oncology-Antoni van Leeuwenhoek Hospital, Netherlands Cancer Institute, Amsterdam, Netherlands; Universite Paris Cité, Institut Curie, Paris, France; Cancer Survivorship Program, INSERM 981, Gustave Roussy, Villejuif, France; Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; The University of Hong Kong, Hong Kong, Hong Kong; University Hospitals Leuven, Leuven, Belgium; Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Institut Jules Bordet,, Brussels, Belgium; University of Milan & Bicocca San Gerardo Hospital, Monza, Italy; Hereditary Breast and Ovarian Cancer (HBOC) Unit and General Surgery 3 - Senology, Breast Cancer Center, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Sapienza University of Rome, Medical Oncology Department, Policlinico Umberto I, Roma, Italy; Istituto Europeo Oncologico, Milano, Italy; Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; Dana-Farber Cancer Institute and IBCSG Statistical Center, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; University of Genova, Genoa, Italy

Background: Systemic treatment decisions for young BRCA carriers with small node-negative breast cancers present unique challenges due to limited evidence on the benefits of chemotherapy in this setting. This study evaluated chemotherapy use and survival outcomes among these patients. **Methods:** The BRCA BCY collaboration (NCT03673306) is an international, multicenter, hospital-based, retrospective cohort study that included carriers of germline pathogenic variants in *BRCA1/2* diagnosed with invasive breast cancer at the age of ≤40 years between January 2000 and December 2020. Among patients diagnosed with T1N0 disease, survival outcomes - disease-free survival (DFS) and overall survival (OS) defined from breast cancer diagnosis - were compared between patients who received chemotherapy and those who did not, using multivariate Cox models adjusted for propensity score (including age at diagnosis, histology, grade, country and year of diagnosis) and risk-reducing surgeries (bilateral risk-reducing mastectomy (RRM) and/or risk-reducing salpingo-oophorectomy (RRSO)), and accounting for the delayed entry at the time of BRCA testing (i.e. left truncation). Subgroup analyses were performed according to tumor subtype (HR+/HER2- vs triple negative breast cancer (TNBC)). **Results:** Out of 5660 from 109 centers, 1280 patients had T1N0 breast cancer: T1mic (n = 14, 1.1%), T1a (n = 92, 7.2%), T1b (n = 303, 23.7%), T1c (n = 778, 60.8%), and T1 size unknown (n = 93, 7.3%). Most patients received chemotherapy (80%), although use was less frequent over time. Among patients who received chemotherapy, the majority were treated with an anthracycline-containing regimen (83.6%) and in the adjuvant setting (85.7%). Patients who received chemotherapy were younger and more likely to have high grade, TNBC or larger tumors compared to those who did not. The median follow-up was 8.7 years (IQR 5.0-13.4 years), during which 428 had DFS events including second primary breast cancer (n = 174), locoregional (n = 130), distant relapse (n = 65), second primary non breast cancer (n = 53), and 88 had died. Overall, 8-year DFS was 69.4%. In multivariate analysis, no significant differences in DFS or OS were observed between patients who received chemotherapy and those who did not (DFS HR = 0.92, 95% CI 0.65-1.31; OS HR = 0.68, 95% CI 0.37-1.24). No significant difference in 8-year DFS was observed between patients with HR+/HER2- breast cancer (n = 474) treated with or without chemotherapy (HR 0.91: 95% CI 0.59-1.43), or between patients with TNBC (n = 637) treated with or without chemotherapy (HR 0.84: 95% CI 0.46-1.53). **Conclusions:** In this global study of young BRCA carriers with T1N0 breast cancer, chemotherapy was not associated with better DFS or OS overall. However, these patients remain at high risk of events and warrant investigation of additional risk-reduction strategies. Research Sponsor: None.

Long-term outcomes of patients with HER2-positive invasive lobular carcinoma in the ALTTO trial (BIG 2-06/NCCTG N063D [Alliance]).

Guilherme Nader Marta, Lieveke Ameye, Giuseppe Viale, Diogo Martins-Branco, Marianne Paesmans, Philippe Georges Aftimos, Christine Desmedt, Anup Choudhury, Antonio C. Wolff, Ian E. Krop, Martine J. Piccart-Gebhart, Evandro de Azambuja; Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Data Center, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium; Department of Pathology and Laboratory Medicine, IEO European Institute of Oncology IRCCS, Milan, Italy; Clinical Trials Support Unit, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium; Department of Medical Oncology, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium; Laboratory for Translational Breast Cancer Research, KU Leuven, Leuven, Belgium; Novartis Healthcare Pvt Ltd., Hyderabad, India; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Yale Cancer Center, New Haven, CT; Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Brussels, Belgium, Brussels, Belgium

Background: Invasive lobular carcinoma (ILC) is the second most common histologic subtype of breast cancer (BC), representing 10–15% of cases. HER2 overexpression is rare in ILC, and there is limited data on the clinical characteristics and outcomes of patients (pts) with HER2-positive (HER2+) ILC treated with adjuvant trastuzumab. This study aims to investigate the prognostic value of ILC histology in this setting. **Methods:** ALTTO was a multicenter, randomized phase III trial evaluating the efficacy of trastuzumab, lapatinib, their sequence, or combination as adjuvant therapy in pts with HER2+ early BC. Pts with pure ILC or invasive BC of no special type (NST) who were enrolled in trastuzumab-containing arms of the ALTTO trial were included in this analysis. Central pathology review confirmed histologic subtype and was used for classification, while local pathology was used when centralized review was unavailable (USA and China). Survival outcomes, including disease-free survival (DFS), and overall survival (OS) were evaluated using Kaplan-Meier method and multivariate Cox regression adjusted for prognostic factors. Patterns of relapse were analyzed and compared across histological subtypes. Time to distant recurrence (TTDR) and time to CNS recurrence were summarized using cumulative incidence functions. **Results:** Among pts in the trastuzumab-containing arms (N = 6281), 84.4% underwent central pathology review, with a concordance rate of 67.4% for ILC diagnosis. A total of 61 pts with pure ILC (1.0% of the cohort) and 5981 pts with NST were included in the analysis. Pts with ILC were older (mean 54.8 vs. 50.9 years; p=0.002), more likely White (95.1% vs. 68.8%; p<0.001), and postmenopausal (72.1% vs. 56.3%; p=0.01). The proportion of pts with ILC (vs NST) was higher in Europe (67.2% vs 53.7%) and lower in Asia-Pacific (8.2% vs 30.6%) (p<0.001). A significantly higher proportion of ILC (vs NST) were hormone receptor-positive (80.3% vs. 57.4%; p<0.001), Grade 1-2 (51.7% vs. 39.3%; p=0.05). At a median follow-up of 9.8 years (IQR 6.9-10.0), no significant differences in DFS (hazard ratio [HR] 1.14, 95% CI 0.66-1.97; adjusted HR [aHR] 1.33,0.77–2.31), OS (HR 0.96, 0.43-2.15; aHR 1.09, 0.48–2.44), or TTDR (HR 1.67, 0.91–3.05) were observed between ILC and NST. Central nervous system (CNS) relapses were more frequent in ILC (13.6% at 10y, 95% CI 7.1–26.1%) than in NST (5.0%, 4.5–5.7%), with an HR of 3.14 (1.52–6.48) for CNS recurrences in ILC when compared to NST. **Conclusions:** Long-term outcomes were comparable between ILC and NST in HER2+ early BC treated with trastuzumab-containing regimens. The higher incidence of CNS metastases in ILC highlights its unique relapse pattern, necessitating further investigation to optimize treatment. High discordance between central and local pathology emphasizes the need for standardized histological review in trials and treatment decisions. Clinical trial information: NCT00490139. Research Sponsor: Novartis.

Cost-effectiveness of HER2/neu 655 genotyping in managing trastuzumab-induced cardiotoxicity risk in HER2-positive breast cancer patients.

Isabel Blancas, Marta Legerén, Lidia Carnerero Córdoba, Carlos Jose Rodriguez Gonzalez, Fernando Rodríguez-Serrano; Hospital Universitario Clínico San Cecilio / Medicine Department, Granada University / Instituto de Investigación Biosanitaria de Granada (ibs Granada), Granada, Spain; Oncology Department, San Cecilio University Hospital, Granada, Spain; Hospital Universitario Clínico San Cecilio / Instituto de Investigación Biosanitaria de Granada (ibs Granada), Granada, Spain; Institute of Biopathology and Regenerative Medicine (IBIMER), University of Granada; Biosanitary Research Institute of Granada (ibs.GRANADA), Granada, Spain

Background: Trastuzumab has significantly improved survival in HER2-positive breast cancer patients. However, around 20% of patients experience cardiotoxicity. Cardiotoxicity has been defined as a ≥10% drop in left ventricular ejection fraction (LVEF) or LVEF <50%, or the appearance of clinical cardiac insufficiency. The HER2/neu 655 A>G polymorphism has been linked to cardiotoxicity risk. This study evaluates the cost-effectiveness of HER2/neu 655 genotyping. **Methods:** Eighty-eight HER2-positive breast cancer patients treated for early disease with trastuzumab were retrospectively analyzed. All were genotyped for HER2/neu 655 A>G (AA: n=53, AG: n=32, GG: n=3). LVEF was monitored by echocardiography or isotopic ventriculography at baseline and regular intervals. Cardiotoxicity was defined as above. Logistic regression adjusting for hormonal status and anthracycline use estimated the association between genotype and cardiotoxicity. Cost data from the Andalusian Regional Health Service included diagnostic tests, cardiology visits, pharmacologic therapy, and hospitalizations. **Results:** Among the 53 patients with the AA genotype, 3.7% experienced a decrease in LVEF, while 9.4% developed clinical symptoms. For the AG genotype (32 patients), 9.3% showed an LVEF reduction, and 28.1% presented clinical symptoms. In the GG genotype group (3 patients), 1 patient (33.3%) developed clinical symptoms. AG carriers had a significantly higher risk of cardiotoxicity than AA patients (OR adjusted for hormonal status and anthracycline treatment =4.42; p=0.037). HER2/neu 655 A>G genotyping costs €38. Asymptomatic LVEF reductions usually required 3 cardiology visits including echocardiography (€121.05 each), and one year of pharmacological treatment (carvedilol and/or enalapril therapy; €84.72 total). Cardiac insufficiency costs range from €2,992.61 (grade 1) to €9,363.56 (grade 4). **Conclusions:** HER2/neu 655 genotyping is cost-effective for identifying patients at higher risk of trastuzumab-induced cardiotoxicity. The low cost of genotyping is outweighed by the potential savings in preventing severe cardiac events. Genotype-driven monitoring and proactive cardiac and targeted cardiovascular risk management in AG carriers could reduce both the incidence and severity of cardiotoxicity. Research Sponsor: None.

Neuromorphological effects of simultaneous exercise during neo-/adjuvant chemotherapy in breast cancer patients: The Exercise Cancer and Cognition (ECCO) study.

David Kiesl, Filip Purgar, Marina Sallaberger, Milan Vosko; Ordensklinikum Linz - Elisabethinen, Linz, Austria; Kepler University Hospital – Med Campus III, Linz, Austria; Technical University Dortmund, Dortmund, Germany; Kepler University Hospital, Department for Neurology, Linz, Austria

Background: Cancer-Related Cognitive Impairment (CRCI) is commonly experienced by breast cancer patients, often linked to chemotherapy. It manifests as deficits in learning, memory, reaction time, and concentration, with the hippocampus—a critical region for cognitive and affective functions—playing a central role. The hippocampus retains neurogenesis potential throughout life, with physical exercise shown to enhance hippocampal volume and memory function. High-intensity exercise appears to have superior cognitive benefits compared to moderate aerobic activity. The ECCO study aimed to assess the neuropsychological and brain morphological effects of high-intensity interval training (HIIT) in breast cancer patients, focusing here on imaging data subanalysis. **Methods:** The ECCO-study was designed as monocentric two-armed 1:1 randomized controlled trial (RCT), including a 12-month intervention group and a control group. Patients in the intervention group were instructed to perform strength- and low-intensity endurance training at least once a week at home according to the American College of Sports Medicine (ACSM) recommendations and to complete a supervised high-intensity interval training (HIIT) once a week at our health center. Patients in the control group were advised physical activity recommendations according to the World Health Organsiation (WHO). Participants randomized to the control arm received usual care and physical activity recommendations have been given according to usual standards. The volume measurements of the brain were performed with an automatic segmentation tool FreeSurfer version 7.4. The FreeSurfer algorithm performs an automatic segmentation of subcortical volumes and reconstructs the cortex after the elimination of non-brain tissue. **Results:** MRI data were available at baseline and after 12 months for a total of 67 patients diagnosed with breast cancer. Randomized into an intervention arm (n = 35) and control arm (n = 32). The groups were comparable in all demographic factors such as age, BMI and VO2max. There were no statistically significant changes ($p < 0.05$) in the volumes between the baseline measurement and the 12-months-follow-up measurement. Other brain areas also showed no significant ($p < 0.05$) alterations between baseline and follow-up. No differences were found in the volume change between the exercise group and the control group. **Conclusions:** This analysis of the ECCO study revealed that there were no significant changes in hippocampal volume or in the more precise categorization into its subfields in either the intervention or control group of breast cancer patients. Contrary to hypotheses suggested in the literature, it was shown that breast cancer therapy does not lead to morphological changes in the hippocampus, indicating that CRCI is not based on morphological damage. Clinical trial information: NCT04789187. Research Sponsor: Verein zur Forschungsförderung der Krebshilfe OÖ.

Effect of a multidisciplinary intervention based on a supervised training program on cardiovascular risk and quality of life in early stage breast cancer patients.

Maria Torrente, Gorka Benitez, Pedro Da Costa Sousa, Enrique Colino, Beatriz Nuñez García, Margarita Diez, Miriam Mendez, Juan Cristobal Sanchez, Marta Mendez, Esther Vielba, Eva Garcia-Zozaya, Mariano Provencio, Blanca Cantos; Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; Universidad NOVA De Lisboa, Lisboa, Portugal; Universidad Francisco de Vitoria, Madrid, Spain; Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; Hospital Universitario Puerta de Hierro, Madrid, Majadahonda, Spain; HU Puerta de Hierro-Majadahonda, Majadahonda, Spain; Hospital Universitario Puerta de Hierro, Madrid, Spain

Background: There is growing evidence that physical activity can enhance cancer care. Exercise programs have been shown to help manage treatment side effects, improve functional outcomes, enhance overall quality of life, and reduce fatigue. Additionally, obesity and cardiovascular disease are among the most common comorbidities in breast cancer survivors. However, despite these benefits, exercise is still not widely prescribed to oncology patients. A multidisciplinary approach involving various healthcare professionals is crucial to ensuring that exercise interventions are tailored to individual needs. Our study aims to determine whether a 12-week exercise intervention can improve physical fitness and reduce cardiovascular risk in patients with early-stage breast cancer after completing oncologic treatment. For the first time, impact is assessed by measuring cardiorespiratory fitness (VO_2 max) and muscle strength, including range of motion, speed, and power. **Methods:** A total of 75 women with histologically confirmed Stage I-III primary breast cancer who have recently completed all cancer-related treatments were included. Through computer-generated simple randomization, participants were assigned to resistance training (RTG; two sessions/week for 12 weeks) or control (CG; general physical activity guidelines recommendations). Outcomes were evaluated at baseline and week 12. Muscular strength (including range of motion, speed, and power) was the primary outcome. Secondary outcomes included cardiorespiratory fitness (measured by VO_2 max-*maximum* rate of oxygen consumption attainable during exercise), cancer-related fatigue and HRQoL. All participants had Performance status 0 or 1 and completed the EUROQOL-5D 5L and EORTC-QLQ-C30 QoL online survey. **Results:** The expected number of 75 patients was enroled in the study (mean age 55.9 ± 7.4 years, all female). Patients assigned to the intervention had a significant positive change in HRQoL total score [mean difference 3.8; 95% confidence interval (CI) 0.2; 7.3; P = .038], body mass index [mean difference −0.7 kg/m2 (95% CI −1.3; −0.1); P = .022], muscle strength [mean difference 2.5 (95% CI 0.1; 5); P = .044; effect size 0.39], and cardiorespiratory fitness (VO2 max) [mean difference 2.7 (95% CI 0.8; 4.6); P = .007]. No significant changes were observed in the control group between week 0 and 12. **Conclusions:** This 12-week supervised exercise-based programme improved HRQoL, body mass index, muscle strength, range of motion, and power in loads while notably enhancing cardiorespiratory fitness. Integrating exercise into standard healthcare practice can significantly improve patient's quality of life and reduce cardiovascular risk. Research Sponsor: SPANISH SOCIETY OF MEDICAL ONCOLOGY.

Survival impact of adjuvant chemotherapy regimens for small (T1mi/a/b), node-negative (pN0), triple-negative breast cancer (TNBC).

Kai Conrad Cecil Johnson, Joanne Kim, Brandon Slover, Andrea House, Blair Hoeting, Brittany Elizabeth Sandoval, Pratik Thakur, Ruth Johnson, Arya Mariam Roy, Dionisia Marie Quiroga, Gilbert Bader, Ashley Pariser Davenport, Nicole Olivia Williams, Mathew Amprayil Cherian, Sagar D. Sardesai, Daniel G. Stover, Margaret E. Gatti-Mays, Sachin R. Jhawar, Roman Skoracki, Robert Wesolowski; The Ohio State University - James Comprehensive Cancer Center, Columbus, OH; The Ohio State University - College of Medicine, Columbus, OH

Background: While triple negative breast cancer (TNBC) represents an aggressive subtype of breast cancer worldwide, clinically low-risk cases are still encountered. When managing such cases, questions remain regarding the true added benefit of adjuvant chemotherapy on survival outcomes given the absence of dedicated prospective trials for this population. Additionally, in the event that systemic therapy is pursued for these patients, it remains unclear whether anthracycline-containing treatments lead to improved long-term outcomes. **Methods:** Given the rarity of stage 1 triple negative breast cancer, we extracted recurrence & survival data from within the ASCO-developed CancerLinQ database to perform an in-depth retrospective analysis involving women with small (pT1mi/a/b), node-negative (pN0), TNBC who underwent curative breast surgery and were diagnosed between the years 2002-2023. For the adjuvant chemotherapy recipients, only those who received a regimen of either taxane chemotherapy plus cyclophosphamide (TC) or an anthracycline & cyclophosphamide combined followed by taxane chemotherapy (AC-T) were included in this study. Our co-primary objectives were to compare the invasive recurrence-free survival (iRFS) and overall survival (OS) of patients who received adjuvant TC or AC-T versus those receiving locoregional therapy alone. Our secondary outcome included an iRFS comparison between AC-T, TC, & locoregional therapy. Clinicopathologic variables were compared with appropriate tests for the categorical and continuous variables. **Results:** Among the 159 patients identified with T1mi/a/b N0 TNBC who met inclusion criteria, 42 had undergone locoregional therapy alone, 77 had received TC chemotherapy, and 40 received AC-T. Baseline demographics found that the locoregional group had a higher proportion of T1mi/a vs T1b patients ($p < 0.001$) & a higher average age ($p < 0.002$). No differences were seen between groups in terms of germline mutations (BRCA1, BRCA1, PALB2, CHEK2, & ATM), tumor grade, lymphovascular invasion, surgery type, race, ethnicity, or average body-mass index. After a median follow up period of 57.2 months overall, we found there was a significant benefit in both iRFS (HR 2.52, 95% CI 1.1-5.83, $p = 0.025$) & OS (HR 6.95, 95% CI 1.62-29.79, $p = 0.0027$) for those who received adjuvant chemotherapy (TC or AC-T) compared to locoregional therapy alone. The 5-year iRFS was 89.9% with AC-T, 77.1% with TC, & 69.1% with locoregional therapy, whereas the 5-year OS was 96.9%, 96.3%, 85.8%, respectively. **Conclusions:** These findings suggest that a recurrence & survival benefit is seen with the application of adjuvant chemotherapy, even among this clinically low-risk population. However, whether it needs to be AC-T or TC appears less significant. Research Sponsor: None.

Obesity, chemotherapy dosing, and toxicity: Results from the Optimal Breast Cancer Chemotherapy Dosing study.

Elizabeth Kantor, Kelli O'Connell, Jenna Bhimani, Victoria S. Blinder, Rachael P. Doud, Grace B. Gallagher, Jennifer J. Griggs, Maria J. Monroy-Iglesias, Tatjana Kolevska, Candyce Kroenke, Cecile Laurent, Raymond Liu, Kanichi G. Nakata, Janise M. Roh, Yashasvini Sampathkumar, Emily Valice, Peng Wang, Elisa Victoria Bandera, Erin Aiello Bowles, Lawrence H. Kushi; Memorial Sloan Kettering Cancer Center, New York, NY; Kaiser Permanente Washington Health Research Institute, Seattle, WA; Rogel Cancer Center, University of Michigan, Ann Arbor, MI; The Permanente Medical Group, Oakland, CA; Division of Research, Kaiser Permanente Northern California, Pleasanton, CA; Kaiser Permanente Northern California, Pleasanton, CA; Department of Hematology Oncology, Kaiser Permanente, San Francisco, CA; Division of Research, Kaiser Permanente Northern California, Oakland, CA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: ASCO guidelines state that most cytotoxic drugs should be dosed according to full body surface area (BSA) without limiting the dose on the basis of obesity. This approach is supported by a lack of evidence to suggest that patients with obesity, when fully-dosed, experience higher risk of toxicity. Indeed, historical evidence suggests that obese, fully-dosed patients may experience lower risk of neutropenia than normal weight patients. However, questions remain regarding the representativeness of historical trial data on which this evidence is based. We examined this issue in the Optimal Breast Cancer Chemotherapy Dosing (OBCD) Study. **Methods:** The OBCD Study is a real-world cohort of 34,109 women diagnosed with stage I-IIIA breast cancer at Kaiser Permanente Northern California and Kaiser Permanente Washington between 2004-2019. Among women receiving the full dose of chemotherapy at treatment initiation ($\geq$90% of intended dose, n = 7,644), we examined risk of toxicities in women with obesity (BMI $\geq$30 kg/m^2) compared to non-obese women (BMI 18.5- $<$ 30 kg/m^2). We examined hematologic (neutropenia, anemia, thrombocytopenia) and non-hematologic (nephrotoxicity, hepatotoxicity, neuropathy, and cardiotoxicity) toxicities. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression, adjusted for covariates including prevalent comorbid conditions. Secondary analyses examined associations pertaining to specific BMI groups and also stratified by administration schedule (standard vs dose-dense). **Results:** Fully-dosed patients with obesity experienced lower risk of neutropenia (HR: 0.80; 95% CI: 0.73-0.88) and any hematologic toxicity (HR: 0.83; 95% CI: 0.75-0.91) but increased risk of neuropathy (HR: 1.34; 95% CI: 1.18-1.52), cardiotoxicity (HR: 2.30; 95% CI: 1.13-4.67), and non-hematologic toxicities overall (HR: 1.31; 95% CI: 1.15-1.48). The strength of these associations increased with increasing BMI category. The inverse association between obesity and hematologic toxicity was evident for standard administration schedules (HR: 0.54; 95% CI: 0.45-0.66) but not dose-dense schedules. However, the positive association between obesity and non-hematologic toxicities persisted regardless of administration schedule. **Conclusions:** Women with obesity given the full BSA-determined chemotherapy dose are less likely to experience neutropenia than fully-dosed non-obese women. Importantly, this holds among patients with more severe obesity, but not when restricted to newer dose-dense administration schedules. Findings also suggest that fully-dosed patients with obesity may experience higher risks for neuropathy and cardiotoxicity. These findings highlight the importance of better understanding the risks and benefits of dosing strategies as treatments and patient populations continue to evolve. Research Sponsor: National Cancer Institute; R37CA222793; National Cancer Institute; U24CA171524; National Cancer Institute; U01CA195565; National Cancer Institute; P30CA008748; National Cancer Institute; P01CA154292; Geoffrey Beene Cancer Research Center at Memorial Sloan Kettering Cancer Center; National Cancer Institute; R50CA211115.

Clinical outcomes of patients with stage I triple-negative breast cancer (TNBC) treated with or without chemotherapy: The Mayo Clinic experience.

Sumeet Kumar Yadav, Sarah K. Reed, David Zahrieh, David W. Hillman, Judy Caroline Boughey, Karthik Giridhar, Dame Idossa, Krishna Rani Kalari, Peter C. Lucas, Fergus Couch, James N. Ingle, Matthew P. Goetz, Roberto Antonio Leon-Ferre; Mayo Clinic Health System, Mankato, MN; Mayo Clinic, Rochester, MN; Mayo Clinic Alliance Statistics and Data Center, Rochester, MN; Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Background: TNBC is associated with higher risk of recurrence and poorer survival rates than other breast cancer subtypes. For node-positive TNBC or tumors larger than 0.5 cm, chemotherapy is generally recommended. For stage I TNBC, the benefit from chemotherapy, the optimal regimen, and whether to administer it in the neoadjuvant versus adjuvant setting remain controversial. Here, we report the treatment patterns and clinical outcomes of patients with stage I TNBC treated at Mayo Clinic. **Methods:** Using the Mayo Clinic Tumor Registry data, we identified patients with stage I TNBC treated between 2010 and 2021. We used the pathologic tumor (T) category for patients treated with upfront surgery and the clinical T category for patients receiving neoadjuvant chemotherapy. We used the Kaplan-Meier method and log-rank test to compare recurrence-free survival (RFS) according to treatment groups, measured from the day of surgery. RFS was reported at a median follow-up of 3.9, 6.2, and 7.3 years for patients who received chemotherapy neoadjuvantly, adjuvantly, and surgery alone with no chemotherapy, respectively. **Results:** A total of 602 patients with Stage I TNBC were included, with a median age of 62 years. 290 (48%) underwent upfront surgery followed by adjuvant chemotherapy (pT1a: 2%, pT1b: 25%, pT1c: 74%), 127 (21%) received neoadjuvant chemotherapy followed by surgery (cT1a: 2%, cT1b: 11%, cT1c: 87%), and 185 (31%) underwent primary surgery without any chemotherapy (pT1mi/T1a: 33%, pT1b: 32%, pT1c: 35%). Most patients treated with neoadjuvant therapy received anthracycline/cyclophosphamide + taxane (70%), while most patients treated in the adjuvant setting received a non-anthracycline containing regimen (60%). The 5-year RFS was 96% (95% CI: 93-100%) for patients who received chemotherapy neoadjuvantly, 95% (95% CI: 92-98%) for those who received chemotherapy adjuvantly, and 85% (95% CI: 80-91%) for those treated with surgery alone and no chemotherapy ($P < 0.0001$). 71 (56%) of the 127 patients who received neoadjuvant therapy achieved a pCR, with only 1 RFS event (at 14 months) in that group, compared to 4 RFS events among those not achieving pCR (at 12, 20, 28 and 75 months, respectively). Among patients not receiving chemotherapy (either adjuvantly or neoadjuvantly), the 5-year RFS rates were 94% for pT1mi/T1a, 92% for pT1b and 72% for pT1c (T1mi/a/b vs T1c, $P = 0.009$). **Conclusions:** In this large cohort of stage I TNBC, patients who received chemotherapy (adjuvantly or neoadjuvantly) had better 5-year RFS compared with those treated with locoregional therapy only. Among patients receiving chemotherapy, 5-year RFS was nearly identical regardless of whether chemotherapy was administered before or after surgery. Interestingly, patients undergoing upfront surgery were more likely to receive an anthracycline-sparing chemotherapy regimen.
Research Sponsor: Mayo Clinic Breast Cancer SPORE P50CA 116201; ASCO, the Conquer Cancer - Breast Cancer Research Foundation Advanced Clinical Research Award.

Clinical validation of a multi-modal Ataraxis AI platform for recurrence prediction in early-stage breast cancer across multiple patient cohorts.

Jan Witowski, Khalil Choucair, Jailan Elayoubi, Elena Diana Chiru, Nancy Chan, Young-Joon Kang, Frederick Matthew Howard, Irina Ostrovnaya, Freya Ruth Schnabel, Waleed Abdulsattar, Yu Zong, Lina Daoud, Marcus Vetter, Jia Wern Pan, Arvydas Laurinavičius, Brian Piening, Carlo Bruno Bifulco, Adam Brufsky, Francisco J. Esteva, Lajos Pusztai; Ataraxis AI, New York, NY; Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI; Department of Hematology and Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI; Cancer Center Baselland, Cantonal Hospital Baselland, Liestal, Switzerland; Perlmutter Cancer Center, NYU Langone Health, New York, NY; Department of Surgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, South Korea; Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, IL; Memorial Sloan Kettering Cancer Center, New York, NY; NYU Perlmutter Cancer Center, NYU Langone Health, New York, NY; Barbara Ann Karmanos Cancer Institute, Detroit, MI; Department of Internal Medicine, Wayne State University, Detroit, MI; Cancer Center Baselland, Liestal, Switzerland; Cancer Research Malaysia, Subang Jaya, Malaysia; Vilnius University, Vilnius, Lithuania; Providence Cancer Institute, Portland, OR; Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR; University of Pittsburgh Medical Center, Pittsburgh, PA; Northwell Health Cancer Institute, New York, NY; Yale Cancer Center, New Haven, CT

Background: Breast cancer (BC) treatment selection is traditionally guided by clinical characteristics. However, as clinical characteristics cannot capture the complexity of a disease, genomic tools have been developed. Recent advances in artificial intelligence (AI) have allowed pathology imaging to be used to build more accurate and comprehensive prognostic/predictive models. In this study, we validated an AI test, powered by a pan-cancer histopathology foundation model, that integrates digital pathology images with clinical variables to predict breast cancer recurrence. **Methods:** The Ataraxis AI prognostic model (ATX) was developed using 4,659 stage I-III BC patients from 10 distinct cohorts. Ataraxis AI platform first extracts novel morphological features from digitized H&E slides using a pre-trained AI foundation model. These morphological features are then integrated with common clinical characteristics, such as TNM staging, ER/PR/HER2 status, age at diagnosis, or lobular or ductal histology to generate a risk score between 0 and 1. We evaluated ATX on 3,502 patients from 5 external cohorts, including 858 patients with available Oncotype DX (ODX) scores. The primary endpoint of this study was disease-free interval (DFI), defined as the time until first recurrence, with deaths prior to recurrence censored. **Results:** Across 3,502 patients spanning five validation cohorts, ATX accurately predicted DFI with a C-index of 0.71 [0.68-0.75] and hazard ratio (HR) of 3.63 [3.02-4.37, $p < 0.01$], computed for every 0.2 unit increase in the test score. Compared to ODX (n = 858), the ATX was more accurate, achieving a C-index of 0.67 [0.61-0.74] versus 0.61 [0.49-0.73]. Additionally, ATX added independent prognostic information to ODX in a multivariate analysis (HR: 3.11 [1.91-5.09, $p < 0.01$]). ATX demonstrated robust accuracy in TNBC (n = 230, C-index: 0.71 [0.62-0.81], HR: 3.81 [2.35-6.17, p = 0.02]) and HER2+ (n = 353, C-index: 0.67 [0.55-0.80], HR: 2.22 [0.99-5.01, p = 0.05]) groups. **Conclusions:** (1) ATX is predictive of breast cancer recurrence, (2) ATX improves upon the accuracy of ODX, (3) ATX demonstrates robust performance in all main BC subtypes. Research Sponsor: Ataraxis AI.

ATX evaluated across 5 cohorts individually and pooled, for both Harrell's C-index and hazard ratio.

Cohort	N	C-index	HR
Karmanos	168	0.62 [0.49-0.75]	3.82 [1.33-10.98, p=0.01]
Basel	269	0.67 [0.58-0.77]	3.98 [1.92-8.25, p<0.01]
TCGA	911	0.70 [0.63-0.77]	3.0 [2.1-4.28, p<0.01]
Providence	1733	0.74 [0.7-0.79]	4.02 [3.09-5.23, p<0.01]
Chicago	421	0.70 [0.60-0.80]	3.25 [1.45-7.31, p<0.01]
Pooled	3502	**0.71 [0.68-0.75]**	**3.63 [3.02-4.37, p<0.01]**

Pathologic complete response to neoadjuvant chemotherapy in early-stage male breast cancer across molecular subtypes and racial/ethnic groups.

Jincong Q. Freeman, Kent Schechter, Long C. Nguyen, Olasubomi Jimmy Omoleye, Jared H. Hara; Department of Public Health Sciences, The University of Chicago, Chicago, IL; Ben May Department for Cancer Research, The University of Chicago, Chicago, IL; Department of Medicine, The University of Chicago Medical Center, Chicago, IL; Department of Radiation Oncology, The Queen's Medical Center, Honolulu, HI

Background: Male breast cancer (mBC) accounts for ~1.0% of all breast cancers in the U.S. Neoadjuvant chemotherapy (NACT) is often used to downsize locally advanced tumors and/or allow for lumpectomy in early-stage breast cancer. However, data on pathologic complete response (pCR) after NACT in mBC is scarce. This study aimed to explore how pCR in male patients with early-stage breast cancer differed by molecular subtype and by race/ethnicity. **Methods:** This retrospective study analyzed data from the 2004-2021 U.S. National Cancer Database registry. Patients were eligible if they were male sex, aged ≥18 years, diagnosed with stage I-III disease, and underwent NACT. pCR (achieved/did not achieve) was defined as ypT0/TisypN0. Molecular subtypes included HR+/HER2−, HR+/HER2+, HR−/HER2+, and TNBC. Racial/ethnic groups included Asian or Pacific Islander, Black, Hispanic, White, and Other. We performed multivariable logistic regression, adjusting for age, race/ethnicity, molecular subtype, clinical T/N, and tumor grade. **Results:** Of 1428 patients, the mean age was 58.5 years (SD=12.8); 69.3% identified as White, followed by 18.8% as Black, 6.2% as Hispanic, 3.4% as Asian or Pacific Islander, and 2.4% as Other. Most (87.2%) patients had invasive ductal carcinoma. 51.3% were HR+/HER2−, 31.9% were HR+/HER2+, 11.7% were TNBC, and 5.1% were HR−/HER2+. Overall, the rate of pCR was 10.9%. Patients with HR−/HER2+ tumors achieved the highest pCR rate (37.3%) compared to 33.8% with TNBC, 14.9% with HR+/HER+, and only 3.7% with HR+/HER2− tumors ($p<.001$). The pCR rate trended higher in Asian or Pacific Islander (14.6%) or Hispanic (13.6%) patients than in Black (11.2%), White (10.4%), or Other (8.8%) patients, though not statistically significant ($p=.728$). On multivariable regression analysis, patients with HR+/HER2+ (adjusted odds ratio [aOR] 3.89, 95% CI: 2.24-6.76; $p<.001$), TNBC (aOR 8.80, 95% CI: 4.76-16.28; $p<.001$), or HR−/HER2+ (aOR 13.45, 95% CI: 6.40-28.28; $p<.001$) tumors had greater odds of having achieved pCR than those with HR+/HER2− tumors. No significant differences in odds of pCR by race/ethnicity were found. Additionally, older age (aOR 0.84 [per 10-year increase], 95% CI: 0.72-0.98; $p=.026$) and grade 1/2 (*vs* grade 3) tumors (aOR 0.39, 95% CI: 0.25-0.60; $p<.001$) were associated with lower odds of pCR. **Conclusions:** In early-stage mBC, the post-NACT pCR rate varied significantly across molecular subtypes, with the lowest rate in HR+/HER2− tumors, mirroring patterns observed in female breast cancer in the neoadjuvant setting. pCR rates were similar by race/ethnicity but lower among patients who were older or had low-grade tumors. These data suggest pCR dependence on tumor biology and could help neoadjuvant treatment selection to achieve optimal outcomes for early-stage mBC. Future research could investigate survival outcomes by pCR in this mBC population. Research Sponsor: National Institute on Aging; T32AG000243; Susan G. Komen Breast Cancer Foundation; TREND21675016.

Artificial intelligence (AI) based spatial assessment of tumor-infiltrating lymphocytes (TIL) and pathologic complete response in early HER2+ breast cancer (BC): Secondary analysis of NSABP B-41.

Ilana Schlam, Gong Tang, Khalid AbdulJabbar, Brent T. Harris, Priya Rastogi, Tanner Freeman, Sai Kumar Maley, Haixi Yan, Isaac Hook, Norman Wolmark, Roberto Salgado, Sandra M. Swain; Dana-Farber Cancer Institute, Boston, MA; NRG Oncology SDMC; Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA; CASE45, London, United Kingdom; MedStar Georgetown University Hospital, Washington, DC; NSABP Foundation, Inc.; UPMC Hillman Cancer Center; and University of Pittsburgh School of Medicine, Pittsburgh, PA; NSABP Foundation, Inc.; University of Pittsburg School of Medicine, Pittsburgh, PA; Nsabp Foundation Inc., Pittsburgh, PA; Case45, London, United Kingdom; NSABP Foundation, Inc., Pittsburgh, PA; GZA, Antwerpen, Belgium; Georgetown University, Washington, DC

Background: Manual quantitative assessment of stromal TILs has shown promise as a biomarker in HER2+ BC. We present an AI-powered single-cell TIL assessment. **Methods:** Manual TIL assessment was completed per guidelines. Zero-shot, AI-powered pipeline (Case45) was used to analyze tumor microenvironment (TME) from H&E slides, focusing on TILs and their spatial interplay with cancer cells. The algorithm identified all cells, deriving three metrics: pct_lymphocyte (lymphocytes/total cells), AI_TIL (adjacent-tumor lymphocyte to stromal cell ratio), hotspot_immune (normalized fraction of immune cell aggregates in relation to cancer/tissue). Spearman correlation coefficients evaluated correlations; logistic regression models assessed the relationship between TIL measurements and pCR, with and without gene expression adjustments. AUC assessed predictive performance, and univariate Cox models examined TILs' association with event-free survival (EFS). **Results:** Our analyses included tumors of 262 patients with early-stage HER2+ BC, 67% estrogen receptor (ER) positive, 51% positive lymph nodes. Poor histologic grade ($p<0.001$), non-luminal ($p=0.006$), and ER- tumors ($p=0.003$) were associated with higher manual TILs. Manual TILs were moderately associated with pct_lymphocyte ($r= 0.34$) and AI_TIL ($r= 0.43$). Perthe table, manual TILs were positively associated with pCR, the association was numerically stronger in ER- tumors (Interaction $p=0.38$). pct_lymphocyte and AI_TIL were positively associated with pCR, regardless of ER status. hotspot_immune was strongly associated with pCR (OR=1.26 for all, 1.29 in ER-, 1.22 in ER+, $p=<0.001$). TILs and *ESR1 and ERBB2* provided complementary prognostic utility in pCR in trastuzumab-treated patients (AUC: 0.699-0.757). Among all subjects, there was no association between manual TILs and EFS ($p=0.2$); there was a marginal association between AI_TIL and EFS ($p=0.06$). **Conclusions:** The spatial characterization of TILs using an AI-powered tool shows promise as a prognostic biomarker in both HER2+/ER+ and HER2+/ER- BC, manual TIL assessment is prognostic in HER2+/ER- BC. The assessment of immune aggregates appears to be highly predictive of pCR. Further validation through prospective-retrospective studies, focused on the spatial immune heterogeneity in the TME, is required before integrating these biomarkers into routine clinical practice. Clinical trial information: NCT00486668. Research Sponsor: BCRF; BCRF 21-156.

TILs measurements and pCR.

Variable (continuous)	Cohort	OR (95% CI)	p-value
Manual TILs %	All	1.13 (1.04, 1.23)	0.004
(10-unit inc.)	ER-	1.16 (1.02, 1.31)	0.02
	ER+	1.07 (0.95, 1.21)	0.27
Percentage of Lymphocyte	All	2.00 (1.30, 3.07)	0.002
(10-unit inc.)	ER-	1.75 (0.95, 3.21)	0.07
	ER+	1.93 (1.02, 3.62)	0.04
AI TILs	All	1.22 (1.06, 1.40)	0.005
(one-tenth inc.)	ER-	1.19 (0.98, 1.44)	0.09
	ER+	1.19 (0.97, 1.46)	0.10

Ultrasensitive circulating tumor DNA (ctDNA) detection for prognostication in triple-negative breast cancer (TNBC) post-neoadjuvant chemotherapy (NAC).

Luc Cabel, Constance Lamy, Kathleen Keough, Charles Abbott, Nicolas Pouget, Jean-Yves Pierga, Marie Paule Sablin, Julie Flavius, Thierry Bronzini, Enora Laas, Lauren Darrigues, Jean Guillaume Feron, Virginie Fourchotte, Claire Bonneau, Anne Vincent-Salomon, Sean Michael Boyle, Richard Chen, Christophe Le Tourneau, Francois Clement Bidard; Institut Curie, Paris and Saint-Cloud, France; Institut Curie, Paris, France; Personalis, Fremont, CA; Personalis, Inc., Menlo Park, CA; Institut Curie, St Cloud, France; Institut Curie, Saint-Cloud, France; Institut Curie, Paris and St Cloud, France; Institut Curie and University of Versailles Saint-Quentin-en-Yvelines-Paris-Saclay University, Paris, France

Background: NAC +/- immune checkpoint inhibitors is the standard of care for most early-stage TNBC patients. After NAC and breast surgery, adjuvant treatment decisions rely on pathological complete response (pCR) status, which does not inform on the presence of distant micrometastases. Blood-based assays for ctDNA enable non-invasive monitoring of residual disease levels at sensitivities down to 1 part-per-million (PPM). We report the prognostic value of ultrasensitive ctDNA detection during NAC in patients with TNBC. **Methods:** Early-stage TNBC patients treated with NAC in the SCANDARE prospective study were evaluated for ctDNA before, during, after NAC/pre-surgery and during post-surgical follow-up. Plasma ctDNA was profiled using NeXT Personal (Personalis), an ultrasensitive tumor-informed MRD assay that tracks up to 1,800 patient tumor-specific variants based on whole genome sequencing to attain sensitivity down to 1-3 PPM with >99.9% specificity. **Results:** Plasma ctDNA was analyzed for 279 samples from 84 TNBC patients (Stage I: 2%, II: 77%, III: 20%), of whom 35 (42%) achieved pCR after NAC. After a median follow-up of 53 months, 16 patients (19%) developed distant metastases, and 18 patients (21%) died. ctDNA was detected before NAC in all 82 patients with an available sample (median=3461 PPM, IQR: 1168-22078), with pretreatment levels in the ultrasensitive range (<100 PPM) in 12%. Most ctDNA detections during (51%) and post-NAC (55%) were <100 PPM. Patients with rates of early on-treatment ctDNA reduction faster than the median, or clearance, had significantly improved distant relapse-free interval (DRFI, log-rank $P=7.7x10^{-3}$) and overall survival (OS, log-rank $P=7.9x10^{-3}$). Patients with post-NAC, pre-surgery ctDNA clearance had significantly improved DRFI (log-rank $P=3.5x10^{-7}$) and OS (log-rank $P=1.4x10^{-11}$), and were enriched for pCR (59% vs 9%, OR=13.9, 95% CI [2.8,137.2], Fisher's exact $P=1.4x10^{-4}$). Multivariable Cox models including pCR and ctDNA detection post-NAC, pre-surgery performed significantly better than models including only pCR for predicting DRFI (LRT $P=8.0x10^{-4}$) and OS (LRT $P=6.6x10^{-4}$). ctDNA detection significantly stratified survival outcomes among patients without pCR (DRFI HR=8.2, 95% CI [1.8,37.0], Cox $P=6x10^{-3}$), with 60% of ctDNA-positive patients developing distant metastases vs 10% of ctDNA-negative patients. During follow-up, all plasma samples from non-relapsing patients were ctDNA-negative. In relapsed patients, ctDNA was detected in 95% of samples collected at relapse or tumor progression. **Conclusions:** Ultrasensitive ctDNA detection informs on the outcome of early TNBC treated by NAC, independently of pCR status. These results, obtained with samples taken post-NAC but before-surgery warrant investigating the benefit of implementing ctDNA detection in an interventional setting. Research Sponsor: Agence National de la Recherche; Site de recherche intégré contre le cancer (SiRIC).

Association of immune, proliferation gene signatures and stromal tumor infiltrating lymphocytes (sTILs) with outcomes in patients with stage I triple-negative breast cancer (TNBC).

Paolo Tarantino, Tianyu Li, Laia Pare, Esther Sanfeliu Torres, Beyza Koca, Ruby Guo, Mercedes Marín-Aguilera, Olga Martínez-Sáez, Olivia Cunningham, Melissa E Hughes, Ashka Patel, Tari A. King, Elizabeth A. Mittendorf, Nancy U. Lin, Fara Brasó-Maristany, Guillermo Villacampa, Patricia Villagrasa, Nabihah Tayob, Aleix Prat, Sara M. Tolaney; Dana-Farber Cancer Institute, Boston, MA; Reveal Genomics Srl, Barcelona, Spain; Reveal Genomics, Barcelona, Spain; Brigham & Women's Hopsital, Boston, MA; Brigham and Women's Hospital, Boston, MA; SOLTI Cancer Research Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Reveal Genomics SL, Barcelona, Spain; Hospital Clínic Barcelona, Barcelona, Spain; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Approximately one third of all TNBC diagnoses are stage 1. No validated biomarker is routinely utilized to guide treatment at this early stage. **Methods:** Samples from patients with stage I TNBC or ER-low (1-10%) breast cancer undergoing surgery at Dana-Farber/Brigham Cancer Center between 2016 and 2021 were identified. The 10-gene Core Immune Gene (CIG) signature and the 4-gene proliferation signature (both part of the TNBC-DX tool) were derived from extracted RNA. Central evaluation of sTILs was conducted at Dana-Farber, with 5% and 20% used as thresholds. All markers were tested for prediction of recurrence free survival (RFS) using the Kaplan-Meier method. **Results:** We identified 253 patients with stage I TNBC (n=218) or ER-low tumors (n=35) treated at Dana-Farber. Median age was 61 (31 – 85), most tumors were ductal (89%), high-grade (73%), 48% were >1 cm and 65% received chemotherapy. 5-year RFS in the overall cohort was 86.8%, with numerical variation by tumor size (T1a 100%, T1b 93.8%, T1c 81.7%, p=0.26). Gene signatures and sTILs were obtained for 117 and 123 patients, respectively (both for 110 patients), with their association with outcomes described in Table 1. Median follow-up was 3 years. A total of 20/117 patients (17.1%) had medium-high CIG score, with none experiencing RFS events prior to year 5. Similarly, no recurrence was observed prior to year 5 in 29 patients (24.8%) at the upper CIG quartile (vs 83-88% 5-year RFS in other quartiles). Worse outcomes were seen among patients in the upper quartile of proliferation (5-year RFS 83%, vs 88-100% in other quartiles). Overall, 33/123 patients (26.8%) had high sTILs (>20%) and experienced the highest 5-year RFS (97%, vs 78% if low sTILs). OS data will be presented. **Conclusions:** High expression of the 10-gene CIG immune signature or high sTILs are associated with numerically improved outcomes in patients with stage I TNBC that did not reach statistical significance, warranting further study as prognostic tools. Research Sponsor: None.

3- and 5-year recurrence free survival (RFS) according to gene signatures and sTILs. P values were obtained via Cox proportional hazard models.

	N	3-year RFS	5-year RFS
CIG score			
- Low	97	91% (85%, 98%)	89% (80%, 98%)
- Med-High	20	100% (100%, 100%)	100% (100%, 100%)
CIG score (quartiles)			
- ≤25%	49	94% (87%, 100%)	88% (74%, 100%)
- 25-50%	10	83% (58%, 100%)	83% (58%, 100%)
- 50-76%	29	87% (74%, 100%)	87% (74%, 100%)
- >75%	29	100% (100%, 100%)	100% (100%, 100%)
Proliferation score			
- Low	58	96% (89%, 100%)	90% (78%, 100%)
- Med-High	59	90% (82%, 99%)	90% (82%, 99%)
Proliferation score (quartiles)			
- ≤25%	30	100% (100%, 100%)	88% (67%, 100%)
- 25-50%	29	90% (77%, 100%)	90% (77%, 100%)
- 50-76%	29	100% (100%, 100%)	100% (100%, 100%)
- >75%	29	83% (68%, 100%)	83% (68%, 100%)
sTILs			
- 1-5%	62	94% (87%, 100%)	78% (63%, 98%)
- >5-20%	28	91% (81%, 100%)	91% (81%, 100%)
- >20%	33	97% (90%, 100%)	97% (90%, 100%)

Association of ImPrintTN signature with survival outcomes by race in basal-type triple negative breast cancer (TNBC): FLEX registry analysis.

Priyanka Sharma, Shane R. Stecklein, Denise M. Wolf, Christina Yau, Laura Esserman, Laura van t Veer, David B. Page, Harshini Ramaswamy, Sahra Uygun, Josien Haan, Nicole Stivers, Andrea Menicucci, William Audeh, Joyce O'Shaughnessy; University of Kansas Medical Center, Westwood, KS; 3901 Rainbow Blvd, Kansas City, KS; University of California, San Francisco, San Francisco, CA; Department of Surgery, University of California, San Francisco, San Francisco, CA; Agendia, The University of California San Francisco, San Francsico, CA; Providence Cancer Institute, Portland, OR; Medical Affairs, Agendia, Inc., Irvine, CA; Agendia, Inc., Irvine, CA; Agendia, Amsterdam, Netherlands; Agendia USA, Sherman Oaks, CA; Baylor University Medical Center, Texas Oncology, Dallas, TX and Sarah Cannon Research Institute, Dallas, TX

Background: ImPrintTN is a triple negative breast cancer (TNBC) immune classifier signature that has been associated with pathological complete response (pCR) to immunotherapy (IO) plus chemotherapy in ISPY2. Real Word data (RWD) from FLEX was utilized to assess the association of ImPrintTN with self-reported race and its impact on clinical outcomes in early stage TNBC. **Methods:** Patients (pts) enrolled in the FLEX (NCT03053193) trial diagnosed with early-stage TNBC and BluePrint Basal molecular subtype with available survival data, who self-identified as Black or White, were eligible for this analysis. ImPrintTN results (+/-) were acquired through whole transcriptome profiling. Chi-squared and Fisher's exact tests assessed differences in clinical characteristics. Association of pCR outcomes and ImPrintTN+/- were tested by binary logistic regression. Recurrence-free survival (RFS) was compared between race and ImPrintTN+/- using Kaplan-Meier estimates and log rank tests. Cox proportional hazards model was used to analyze the association of ImPrintTN, race, and clinical features with RFS. **Results:** Among 279 eligible patients with early stage Basal TNBC, 23.7% were Black, 76.3% were White, 27.7% had node positive disease, 49.8% received neoadjuvant therapy, 47.3% adjuvant therapy, 2.5% IO, and median follow-up was 3 years. 56.6% of pts were ImPrintTN+, similarly distributed by race (Black: 60.6%, White: 55.4%, p=0.761). Among pts treated with neoadjuvant therapy (n=139) no significant differences in pCR rates were observed by race (Black: 26.5%; White: 35.2%; p=0.46). However, a higher pCR rate was achieved in ImPrintTN+ vs ImPrintTN- cancers (39.3% vs 22.0%; OR=2.29, 95% CI [1.04-5.08]; p=0.039). The 3-year RFS was similar for Black (82.5%) and White (83.5%; p=0.91) pts. Significantly improved 3-year RFS was associated with ImPrintTN+ (87.9%) compared to ImPrintTN- (77.5%; p=0.01). Among ImPrintTN+, RFS was similar for Black (89.7%) and White (87.3%; p=0.30) pts. However, ImPrintTN- observed a trend towards lower 3-year RFS in Black (71.1%) compared with White (79.2%; p=0.24) pts. In a multivariate model, RFS probability was significantly associated with ImPrintTN (ImPrintTN+ vs ImPrintTN-: HR= 0.41, 95% CI [0.22-0.75]; p=0.004) and nodal status (LN+ vs LN-: HR= 2.98, 95% CI [1.66-5.37,]; p<0.001), while race and neo/adjuvant therapy were not. **Conclusions:** The analysis found that 56.6% of Basal TNBCs in the FLEX trial were ImPrintTN+, with similar proportions observed among Black and White pts. ImPrintTN status was prognostic for both pCR and RFS in TNBC and was associated with significantly improved RFS across racial groups. However, the negative prognostic impact of ImPrintTN- appeared more pronounced among Black compared with White pts. Ongoing research is focused on exploring biological differences within the ImPrintTN- subgroup by race. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

Real-world (rw) ctDNA testing trends and associated outcomes in patients (pts) with early stage breast cancer (EBC).

Erin Fidyk, Patrick J. Ward, Melissa Estevez, Konstantin Krismer, John James Ritten, Anca Marinescu, Aaron B. Cohen; Flatiron Health, New York, NY

Background: Emerging evidence from prospective studies underscores the prognostic potential of ctDNA to inform risk stratification and clinical decision-making in EBC (stage I-III). However, its use and correlation with outcomes in routine clinical practice remains less understood. We describe tumor-informed ctDNA testing trends and the association of test results with recurrence risk among pts with EBC in the rw setting. **Methods:** Pts with an EBC diagnosis (dx) after 1/1/2018 who had documented HR/HER2 status at initial dx, surgery, and ≥1 commercial ctDNA test in the early stage setting were selected using machine learning models from the Flatiron Health US-nationwide EHR-derived, deidentified, longitudinal database of >750 000 pts with BC (data cutoff 8/31/2024). ctDNA positivity (ctDNA+) was defined as having ≥1 positive test in EBC. Baseline characteristics were stratified by EBC subtype and ctDNA status. To examine the association of ctDNA status with recurrence, unadjusted Kaplan-Meier (KM) plots and adjusted Cox proportional hazards models were performed to assess recurrence-free survival among ctDNA-tested pts, controlling for age, race/ethnicity, stage, ECOG status, dx year, insurance status, practice type, and neoadjuvant/adjuvant treatment. Recurrence was indexed to surgery date and defined as locoregional or metastatic recurrence or death. **Results:** In a cohort of 195 279 pts with EBC, 14 496 ctDNA tests were performed in 4639 pts (median 2 per pt) with most in stage I (43.3%) and II (37.1%). Testing prevalence was highest in HR-/HER2- (4.9%), followed by HR-/HER2+ (3.5%), HR+/HER2+ (2.9%), and HR+/HER2- (1.9%). Testing increased from 1.6% (n = 450) of EBC pts dx in 2020 to 4.25% (n = 1278) in 2023 with a decrease in median time to first test pre- and post-2022 (35 vs 8 months respectively). Among tested pts, 921 (19.9%) had ≥1 positive test and were more likely to be younger (58 vs 64 years) and have stage III disease compared to non-tested pts. ctDNA+ patients had a worse 3-year overall survival (OS) as well as a strong association with recurrence (Table). **Conclusions:** In the largest rw study of ctDNA testing in EBC to date, pts with ctDNA+ disease across all subtypes were more likely to recur, highlighting the potential prognostic value of ctDNA testing to inform pt counseling, monitoring and treatment strategies. These rw results, coupled with findings from prospective randomized trials, support the case for ctDNA+ as a distinct risk category in the management of EBC. Research Sponsor: Flatiron Health, Inc.

	Unadjusted 3-year OS probability (95% CI)		
EBC Subtype	ctDNA- pts	ctDNA+ pts	Adjusted HR (95% CI) All with P <0.01
HR+/HER2- N = 2786	0.98 (0.97-0.99)	0.76 (0.7-0.82)	10.7 (7.08-16.1)
HR-/HER2- N = 1002	0.96 (0.95-0.98)	0.61 (0.52-0.72)	10.7 (6.34-18.1)
HR+/HER2+ N = 592	0.97 (0.95-0.99)	0.85 (0.77-0.94)	11.8 (4.54-30.8)
HR-/HER2+ N = 259	0.97 (0.94-1)	0.78 (0.62-0.97)	8.94 (1.72-46.4)

Association of genetic predisposition to low-grade systemic inflammation with cancer-related fatigue in women receiving chemotherapy for non-metastatic breast cancer in URCC07012 and URCC10055.

Ayo Olowofela, Paul Auer, Michelle Christine Janelsins, Karen Michelle Mustian, Alison Katherine Conlin, Adedayo A. Onitilo, Marianne Melnik, Chin-Shang Li, Umang Gada, Hongying Sun, Sarah L. Kerns; Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI; Division of Biostatistics, Data Science Institute, and Cancer Center, Medical College of Wisconsin, Milwaukee, WI; Department of Surgery, Division of Supportive Care in Cancer and URCC NCORP Research Base, University of Rochester Medical Center, Rochester, NY; Pacific Cancer Research Consortium NCORP, Seattle, WA; Wisconsin NCORP, Marshfield, WI; Cancer Research Consortium of West Michigan, Grand Rapids, MI

Background: Cancer-related fatigue (CRF) is reported by ~75% of patients receiving chemotherapy for breast cancer. CRF has been linked to inflammation. Chronic, low grade systemic inflammation is a polygenic trait, and a polygenic risk score for inflammation (iPRS) might be associated with risk of CRF. **Methods:** Using data from the UK Biobank,we developed an iPRS using the INFLA-score, a composite measure of serum C-reactive protein, white-cell count, platelet count, and neutrophil-lymphocyte ratio. The iPRS was evaluated for association with CRF among women with non-metastatic breast cancer enrolled in one of two completed multisite clinical trials of the University of Rochester Cancer Center NCI Community Oncology Research Program (NCORP) Research Base. CRF was measured before and after standard-of-care chemotherapy using the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). Linear regression evaluated the change in MFSI-SF score from pre- to post-chemotherapy; logistic regression evaluated a binary outcome of any vs no worsening of scores. Analyses were adjusted for patient and treatment factors. **Results:** The NCORP cohort included 802 women who received chemotherapy (anthracycline-based = 51.8%; previous surgery = 85.0%) at a median age of 55 years (range = 22 to 81). There was an increase in MFSI in 55% of the women, with a mean increase of 8 (range=-64 to 71) from prechemotherapy (mean=8, range = -24 to 83) to post-chemotherapy (mean=15.3, range = -24 - 88), indicating an overall increase in CRF. The iPRS was associated with a significant decrease in MFSI-SF (β=-3.29; 95% CI=-6.25 to -0.34; *P*=0.029; covariate-adjusted β=-2.71; 95%CI=-5.50 to 0.08; *P*=0.057) and lower odds of worsening CRF (OR=0.66; 95%CI=0.47-0.93; *P*=0.016; covariate-adjusted OR=0.67; 95%CI=0.47 to 0.96; *P*=0.029). The negative relationship between the iPRS and change in CRF was partially explained by the finding that women with an iPRS in the highest quartile have worse pre-chemotherapy MFSI-SF scores (β=4.33; 95%CI=0.23 to 8.43; *P*=0.038). **Conclusions:** Women with genetic predisposition to low-grade systemic inflammation, indicated by a higher iPRS, have worse CRF pre-chemotherapy that does not worsen, and may improve, over the course of treatment while women with a lower iPRS have less CRF pre-chemotherapy and are at greatest risk of developing new or worsening CRF during treatment. If validated, the iPRS could identify patients in need of supportive care interventions to reduce CRF. This work was supported by the National Institutes of Health National Cancer Institute Contract No. HHSN261201500003I, Task Order No. HHSN261000039 and by UG1CA189961, URCC NCORP Research Base. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; Contract No. HHSN261201500003I, Task Order No. HHSN261000039.

Assessment of ovarian function suppression (OFS)-containing adjuvant endocrine therapy in premenopausal women by Breast Cancer Index.

Ruth O'Regan, Yue Ren, Yi Zhang, Natalia Siuliukina, Catherine A. Schnabel, Roswitha Kammler, Giuseppe Viale, Patrizia Dell'Orto, Olivia Pagani, Barbara Walley, Gini F. Fleming, Prudence A. Francis, Sherene Loi, Marco Colleoni, Kai Treuner, Meredith M. Regan; University of Rochester, Rochester, NY; Dana-Farber Cancer Institute, Boston, MA; Biotheranostics, A Hologic Company, San Diego, CA; Biotheranostics, Inc., San Diego, CA; Biotheranostics, San Diego, CA; ETOP IBCSG Partners Foundation, Bern, Switzerland; Department of Pathology and Laboratory Medicine, IEO European Institute of Oncology IRCCS, Milan, Italy; Istituto Europeo Oncologico, Milano, Italy; Geneva University Hospitals, SAKK, Lugano Viganello, Switzerland; University of Calgary, Calgary, AB, Canada; University of Chicago, Chicago, IL; Peter MacCallum Cancer Centre, Melbourne, Australia; Istituto Europeo di Oncologia, IRCCS, Milan, Italy; Dana-Farber Cancer Institute and IBCSG Statistical Center, Boston, MA

Background: Breast Cancer Index (BCI) previously identified that premenopausal patients with *HOXB13/IL17BR* ratio (H/I)-Low tumors derived greater benefit than BCI(H/I)-High tumors from OFS-containing adjuvant endocrine therapy vs tamoxifen alone in the Suppression of Ovarian Function Trial (SOFT). This translational study of the Tamoxifen and Exemestane Trial (TEXT) was conducted to assess the predictive benefit of BCI (H/I) from exemestane (E) plus OFS over tamoxifen (T) plus OFS and validate the prognostic performance of BCI. **Methods:** Blinded BCI testing was performed in all available tumor samples from patients enrolled in TEXT, of which 1782 of 2660 had BCI successfully assessed and BCI categories assigned per established clinical cutpoints. Primary endpoints were breast cancer–free interval (BCFI) for predictive and distant recurrence–free interval (DRFI) for prognostic analyses. Per pre-specified SAP, a secondary analysis of predictive benefit combined the two OFS arms common to TEXT and SOFT (2896 of 4690 patients); clinicopathologic subgroup analyses were conducted in the combined TEXT+SOFT cohort. Cox proportional hazards models, stratified by chemotherapy use and nodal status, that included treatment assignment, BCI(H/I) status, and interaction term were used to assess BCI predictive performance by testing for treatment-by-BCI(H/I) interaction. The median follow-up was 13 years. **Results:** Among TEXT patients, 58% had BCI(H/I)-Low tumors.Patients with BCI (H/I)-Low tumors exhibited a 6.6% absolute benefit in 12-year BCFI (HR=0.61 [95% CI, 0.44-0.85]) for E+OFS versus T+OFS while those with BCI(H/I)-High tumors had an 6.3% absolute benefit (HR=0.78 [95% CI, 0.57-1.07]) (P-interaction = 0.29). Results were consistent in the combined TEXT+SOFT cohort and adjusting for clinicopathological variables. Clinical subgroup analyses consistently showed benefit of E+OFS vs T+OFS for BCI(H/I)-Low tumors, and more variable relative treatment effects among BCI(H/I)-High tumors, including by age. Post-hoc exploratory time-varying estimates suggested the treatment-by-BCI relationships may differ in years 0-5 vs >5 years. BCI and BCIN+ as continuous indices were prognostic for distant recurrence in N0 ($P = 0.0004$) and N1 ($P < 0.0001$) cancers. The 12-year DRFI was 96.3%, 90.3% and 84.9% for BCI-low, intermediate and high-risk N0 cancers, respectively. **Conclusions:** BCI was confirmed as prognostic in premenopausal women with HR+ early breast cancer enrolled in TEXT. BCI(H/I) status did not clearly predict differential benefit from E+OFS vs T+OFS. The TEXT results complement the prior results from SOFT, indicating premenopausal patients with BCI(H/I)-Low tumors benefit from more intensive endocrine therapy. Research Sponsor: Biotheranostics, Inc., a Hologic company.

Dynamic changes in circulating tumor DNA among Taiwanese early breast cancer patients undergoing upfront surgery: Results from the VGH-TAYLOR study.

Chi-Cheng Huang, Ling-Ming Tseng; Taipei Veterans Genreal Hospital, Taipei City, Taiwan; Taipei Veterans General Hospital, Taipei, Taiwan

Background: Circulating tumor DNA (ctDNA) has emerged as a promising prognostic marker in breast cancer. Post-treatment ctDNA detection is associated with increased recurrence risk and reduced long-term survival. This study evaluated dynamic ctDNA changes in early breast cancer patients with distinct immunohistochemical (IHC) subtypes. **Methods:** Liquid biopsies were performed using the Oncomine Breast cfDNA Assay v2. Samples were collected at baseline (pre-surgery, visit 1), after adjuvant therapy (visit 2), and every six months thereafter (visit 3 and subsequent visits) for patients in the upfront surgery (Group 1A) arm of the VGH-TAYLOR study. Pre-operative and follow-up ctDNA detectability and its impact on recurrence-free survival (RFS) were evaluated. **Results:** A total of 577 early breast cancer patients with at least one ctDNA test were analyzed; the majority (74%, n=425) were hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative. Among 500 pre-operative samples, ctDNA was detected in 24% (n=121) of patients, with *TP53* (21%, n=106) and *PIK3CA* (6%, n=28) being the most prevalent mutations. During follow-up (visit 2 and later), ctDNA was detected in only 3% (n=13) of patients; all harbored *TP53* mutations, with one case also exhibiting an *ERBB3* mutation. All patients with detectable follow-up ctDNA had also tested positive pre-operatively (Table 1). Five-year RFS was 94% in the ctDNA-positive group (n=121) and 95% in the ctDNA-negative group (n=319). Among HR-negative/HER2-positive and HR-negative/HER2-negative subtypes, ctDNA positivity was associated with numerically worse RFS (90% vs. 94% and 88% vs. 89%, respectively). **Conclusions:** Following surgery and adjuvant therapy, most pre-operative ctDNA-positive cases became undetectable (89%, 108/121). Although ctDNA positivity showed a trend toward compromised RFS, particularly in HR-negative/HER2-positive and HR-negative/HER2-negative subtypes with *TP53* mutations, the high clearance rate of pre-surgery ctDNA positivity warrants longer follow-up to fully evaluate its prognostic value and the impact of liquid biopsy in early breast cancer. Clinical trial information: NCT04626440. Research Sponsor: Yonglin HealthCare Foundation.

Dynamic changes of circulating tumor DNA before surgery and after treatment across immunohistochemical subtypes among early breast cancer.

Subtype	Pre-surgery ctDNA positive	Post-treatment/follow-up ctDNA positive
HR+/HER2+	26%(9/35)	0%(0/35)
HR+/HER2-	22.8%(84/369)	1.9%(7/369)
HR-/HER2+	25%(7/28)	7.1%(2/28)
HR-/HER2-	30.8%(20/65)	6.2%(4/65)

HR: hormone receptor, HER2: human epidermal growth factor receptor II, ctDNA: circulating tumor DNA.

Impact of germline *BRCA* status on clinical outcomes of patients with HR+/HER2- early breast cancer.

Antonio Marra, Serena Perazzo, Enzo Martino, Gilda Gaudio, Grazia Castellano, Ambra Carnevale Schianca, Bianca Malagutti, Elisa Giordano, Carmen Criscitiello, Paola Zagami, Mariarosaria Calvello, Monica Marabelli, Monica Milano, Nadia Bianco, Elena Guerini Rocco, Sara Gandini, Elisabetta Munzone, Aliana Guerrieri-Gonzaga, Bernardo Bonanni, Giuseppe Curigliano; Division of Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS, Milan, Italy; Division of Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS, University of Milan, Milan, NA, Italy; Division of Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS, University of Milan, Milan, Italy; Division of Cancer Prevention and Genetics, European Institute of Oncology IRCCS, Milan, Italy; Division of Medical Senology, European Institute of Oncology IRCCS, Milan, Italy; Division of Pathology, European Institute of Oncology IRCCS, University of Milan, Milan, Italy; Department of Experimental Oncology, European Institute of Oncology IRCCS, Milan, Italy; European Institute of Oncology IRCCS, University of Milan, Milan, Italy

Background: Germline pathogenic variants (PVs) in the *BRCA1* and *BRCA2* (g*BRCA1/2*) genes increase the risk for breast cancer (BC) development.The prognostic significance of *gBRCA1/2* in patients with hormone receptor-positive/HER2-negative (HR+/HER2) early BC is still controversial. **Methods:** This cohort study derived from a prospectively-maintained institutional database of all consecutive patients with BC who underwent germline testing, including *BRCA1*, *BRCA2* and *PALB2*, at the European Institute of Oncology (May 2002-Jan 2024). The study population comprised patients with stage I-III HR+/HER2- (estrogen receptor expression >1%) invasive BC who underwent surgery and (neo)adjuvant treatment, as endocrine therapy (ET) +/- chemotherapy (CT) (Jan 2000-Dec 2022). Primary endpoints were distant relapse-free interval (DRFI) and invasive disease-free survival (iDFS) by STEEP 2.0. Univariate and multivariate Cox proportional-hazard models were employed for survival analyses, with left-truncated models to account for the time from BC diagnosis to germline testing. **Results:** A total of 1,730 patients were included in the analyses, with 52 (3%) *BRCA1*, 180 (10%) *BRCA2*, and 9 (0.5%) *PALB2* PV carriers. Compared to non-carriers, patients with *gBRCA1/2* and *gPALB2* PVs were younger (median age: 39 vs 42 yrs, p<.001), had advanced disease stage (stage II-III: 71% vs 58%, p<.001), higher tumor grade (G3: 54% vs 26%, p<.001) and Ki-67 expression (median: 26% vs 20%, p<.001). Patients with *gBRCA1/2* and *gPALB2* PVs were also more likely to receive neoadjuvant (13% vs 6%, p<.001) and/or adjuvant CT (56% vs 36%, p<.001) and mastectomy (56% vs 45%, p=.002). All patients received adjuvant ET, as tamoxifen or aromatase inhibitor +/- GnRH analogue. No patient received adjuvant olaparib or CDK4/6 inhibitor. At a median follow-up of 9.7 (IQR 6-13.9) years, 335 (19%) patients experienced local relapse, 316 (18%) distant metastasis, and 124 (7.2%) died due to BC. At multivariate analyses, *gBRCA2* P/LPVs were independently associated with shorter DRFI (HR 1.46, 95%CI 1.04–2.06, p=.028) and iDFS (HR 1.34, 95 CI 1.01–1.78, p=.045), regardless of stage, nodal status, (neo) adjuvant CT, type of surgery and adjuvant ET, whereas *gBRCA1* were not. Exploratory analyses showed that among 232 *gBRCA1/2* carriers, 47 (20%) and 96 (41%) were eligible for adjuvant olaparib or abemaciclib therapy per OlympiA and monarchE criteria, respectively, with 37 (16%) eligible for both therapies. Additional analyses to unravel interaction of *gBRCA* status with adjuvant treatment are underway. **Conclusions:** Patients with HR+/HER2- early BC harboring *gBRCA2* PVs had a significantly increased risk of recurrence, with a potentially distinct impact of *BRCA2* vs *BRCA1*. Only a small proportion of this population currently qualify to adjuvant treatment escalation with targeted therapies, underscoring the need of expanding the therapeutic options in this setting. Research Sponsor: None.

Cadence of circulating tumor DNA (ctDNA) testing for molecular surveillance in early-stage breast cancer (eBC).

Marla Lipsyc-Sharf, Cheng Cheng, Arielle J. Medford, Maurice J. Berkowitz, Rena Desai Callahan, Aashini Master, Nicholas Patrick McAndrew, Kelly Elizabeth McCann, Juliet Penn, Mina S. Sedrak, Nimmi S. Kapoor, Emily L. Podany, Carolina Reduzzi, Samuel Rivero-Hinojosa, Ekaterina Kalashnikova, Angel A Rodriguez, Minetta C. Liu, Andrew A. Davis, Massimo Cristofanilli, Aditya Bardia; UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA; University of California Los Angeles, Los Angeles, CA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; David Geffen School of Medicine at UCLA, Los Angeles, CA; University of California, Los Angeles, Los Angeles, CA; University of California Los Angeles, Santa Monica, CA; Washington University in St. Louis, St. Louis, MO; Weill Cornell Medicine, New York, NY; Natera, Inc., Austin, TX; Siteman Cancer Center, Washington University in St. Louis, St. Louis, MO

Background: Post-surgical detection of molecular residual disease (MRD) via plasma ctDNA testing is strongly associated with recurrence of eBC. Our prior real-world data suggests that adjuvant MRD testing impacts clinical care for most patients (pts) with positive ctDNA (ctDNA+) results. Ongoing trials are studying whether adjuvant ctDNA testing improves eBC outcomes. While serial testing is known to improve MRD detection rates, the optimal cadence of testing is unknown. Here, we investigated the role of timing, cadence, and quantitative results of real-world ctDNA testing on detection of clinical recurrence of eBC. **Methods:** We identified eBC pts with available recurrence-free survival data who had adjuvant plasma MRD testing via a clinically validated, personalized, tumor-informed mPCR-NGS ctDNA test (Signatera, Natera, Inc.). All tests were ordered in the United States in the real-world clinical setting between 2019-2024; clinical records were reviewed. The cumulative incidence of clinical recurrence after each ctDNA test was used to calculate negative predictive value (NPV) for recurrence within 3, 6, 12, 18, 24, and 30 months (mo) post-test. ctDNA levels at different timepoints prior to recurrence were analyzed separately by ER and HER2 status. **Results:** For 819 pts with stage I-III eBC (ER+/HER2-: 249, HER2+: 68, triple-negative [TNBC]: 502), there were 4689 total plasma samples obtained in the adjuvant setting (median 5.7 time points per patient). Median time of first adjuvant ctDNA testing was 7 mo after surgery (range: 0.1-214.9). Median follow-up was 18.1 mo (range: 0.7-239.4). For pts with ER+/HER2- tumors, median time to first test was 14.6 mo (range: 0.3-214.9) versus 16.1 mo (range: 0.3-151.8) in HER2+ and 7.1 mo (range: 0.1-178.8) in TNBC. Among pts with multiple adjuvant ctDNA tests, median interval between tests was 2.8 mo (consistent across subtypes). For ER+ and TNBC tumors NPV (95%CI) gradually decreased over time from 99.5% (98.8-99.8) and 99.7% (99.2-99.9) at 3 mo to 97.7% (96.7-98.4) and 97.8% (96.6-98.5) at 30 mo, respectively. Among ctDNA+ TNBC pts, quantitative ctDNA levels were higher among those who recurred $<$ 3 mo after a +ctDNA test than those with recurrence in 3-6 mo; median ctDNA levels were lowest in pts who recurred $>$ 6 mos after a ctDNA+ test (median [range], 2.7 [0.03-1089.6] vs 2.0 [0.1-15.3] vs 0.3 [0.3-1.7] MTM/mL, p = 0.0041 and p = 0.0071, respectively). This trend was less pronounced in ER+HER2- disease between pts who relapsed $<$ 6 mo, 6-9 mo, and $>$ 9 mo after a ctDNA+ test (median [range], 11.6 [0.26-299.4] vs 4.5 [0.2-27.0] vs 3.8 [2.3-124.5] MTM/mL, p = 0.5, p = 0.8). **Conclusions:** The data from this real-world analysis of tumor-informed ctDNA testing in pts with eBC during surveillance demonstrate a high NPV for both ER+ and TNBC disease. These data guide future prospective ctDNA-guided studies aimed at therapeutic interception to improve clinical outcomes. Research Sponsor: Conquer Cancer, the ASCO Foundation; Natera, Inc.

Association of lifestyle factors and pathological characteristics in patients with early breast cancer and overweight/obesity: Results from the Breast Cancer Weight Loss (BWEL) trial.

Caterina Sposetti, Karla V. Ballman, Linda Mackie McCall, Pamela Jean Goodwin, Anna Weiss, Cynthia A. Thomson, Olwen Hahn, Dawn L. Hershman, Electra D. Paskett, Lori M. Minasian, Linda Nebeling, Erica L. Mayer, Judith O. Hopkins, Vanessa Bernstein, Vered Stearns, Julia R. White, Eric P. Winer, Ann H. Partridge, Lisa A. Carey, Jennifer A. Ligibel; Dana-Farber Cancer Institute, Boston, MA; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; Alliance Statistics and Data Management Center, Duke University, Durham, NC; University of Toronto/Mount Sinai Hospital, Toronto, ON, Canada; Department of Surgery, University of Rochester, Rochester, NY; University of Arizona, Tucson, AZ; University of Chicago, Alliance for Clinical Trials in Oncology, Chicago, IL; Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY; Department of Internal Medicine, The James Comprehensive Cancer Center, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH; National Cancer Institute, Rockville, MD; National Cancer Institute, Bethesda, MD; Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; SCOR NCORP/Novant Health Cancer Institute, Winston-Salem, NC; University of British Columbia, Vancouver, BC, Canada; Weill Cornell Medical Center, New York, NY; University of Kansas Medical Center Comprehensive Cancer Center, Kansas City, KS; Yale Cancer Center, New Haven, CT; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Obesity and other lifestyle factors are associated with breast cancer (BC) risk and outcomes. These relationships appear to vary in pre- vs postmenopausal women. Here we explore associations between pathological features, diet quality and physical activity (PA) in patients (pts) with BC enrolled in the BWEL (Alliance for Clinical Trials in Oncology A011401) trial, stratifying for menopausal status. **Methods:** BWEL is a phase III trial evaluating the impact of a weight loss intervention on disease outcomes in 3180 pts with stage II-III HER2− BC and body mass index ≥27 kg/m^2. The first 542 BWEL pts underwent assessment of PA (7-Day PA Recall) and diet (24-hour Diet Recall) at enrollment. Healthy Eating Index 2020 (HEI) score (0-100, higher value = healthier diet) and minutes/week (min/wk) of moderate/vigorous PA (MVPA) were calculated. Estrogen receptor (ER) and progesterone receptor (PR) expression level (%) were abstracted from pathology reports. Analyses of links between HEI score, MVPA min/wk, % ER/PR, stratified by menopausal status, were conducted using t-tests; differential associations by menopausal status used linear regression models with interaction term. **Results:** In 523 pts with available pathology data, 76.5% had ER/PR+ BC, 56.2% were postmenopausal. Median HEI score was 50.1 (range 18.1-96.4), median MVPA min/wk was 0 (range 0-630), median time from diagnosis to enrollment was 10.0 months (range 2.4-13.1). In postmenopausal pts, higher diet quality was linked to increased % ER and PR (HEI above vs below median, mean % ER 78.0 vs 66.1, p=0.012; mean % PR 57.7 vs 43.1, p=0.004). The relationship between HEI score and % ER/PR differed significantly by menopausal status (interaction term of menopausal status and % ER: p=0.006; and % PR: p=0.012); there were no significant associations between HEI scores and % ER/PR in premenopausal pts. There were no significant associations between PA and % ER/PR. **Conclusions:** Healthier diet was associated with higher % ER and PR in postmenopausal pts with BC, but no relationship was seen in premenopausal pts. These data suggest that lifestyle factors may influence BC pathologic features related to outcomes in older women. Support: U10CA180821, U10CA180882, UG1CA189823, U24CA196171, https://acknowledgments.alliancefound.org. Clinical trial information: NCT02750826. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180821; National Cancer Institute/U.S. National Institutes of Health; U10CA180882; National Cancer Institute/U.S. National Institutes of Health; UG1CA189823; National Cancer Institute/U.S. National Institutes of Health; U24CA196171; National Cancer Institute/U.S. National Institutes of Health; U10CA180820; National Cancer Institute/U.S. National Institutes of Health; U10CA180868; National Cancer Institute/U.S. National Institutes of Health; U10CA180863; National Cancer Institute/U.S. National Institutes of Health; UG1CA189974; National Cancer Institute/U.S. National Institutes of Health; CCS 707213; Italian Association for Cancer Research (AIRC) / Gianni Bonadonna.

	% ER mean (SD)	*p value*	% PR mean (SD)	*p value*
Post-Menopausal				
HEI* score				
≤50.1 [n=134]	66.1 (43.3)	*0.012*	43.1 (41.8)	*0.004*
>50.1 [n=156]	78.0 (36.8)		57.7 (41.0)	
MVPA† min/wk				
0 [n=147]	74.5 (39.3)	*0.37*	50.0 (41.8)	*0.41*
≥1 [n=147]	70.3 (41.2)		53.0 (42.0)	
Pre-Menopausal				
HEI* score				
≤50.1 [n=124]	70.5 (38.5)	*0.15*	53.5 (41.1)	*0.43*
>50.1 [n=103]	65.5 (43.0)		49.1 (43.0)	
MVPA† min/wk				
0 [n=112]	66.3 (41.0)	*0.99*	49.5 (41.4)	*0.59*
≥1 [n=113]	66.3 (41.2)		52.6 (42.7)	

*Healthy Eating Index.
†Moderate/Vigorous Physical Activity.

Association of infiltration of hematopoietic stem cells (HSC) with cell proliferation and patient survival in breast cancer.

Masanori Oshi, Akimitsu Yamada, Kazutaka Narui, Itaru Endo, Kazuaki Takabe, Rongrong Wu, Takashi Ishikawa; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Yokohama City University Hospital, Yokohama-Shi, Japan; Yokohama City University Medical Center, Yokohama, Japan; Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Kanagawa, Japan; Roswell Park Cancer Institute, Buffalo, NY; Tokyo Medical University Hospital, Shinjuku-Ku, Japan; Breast Surgical Oncology, Tokyo Medical University, Tokyo, Japan

Background: HSCs, also known as blood stem cells, are self-renewable cells that can develop into all types of blood cells. They are found in bone marrow and peripheral blood. However, the clinical relevance of HSCs in the BC TME remains unknown.To elucidate the clinical significance of HSC infiltration in the tumor microenvironment (TME) of breast cancer (BC). **Methods:** In silico analyses were conducted on 5,176 BC patients, including large independent cohorts; The Sweden Cancerome Analysis Network-Breast (SCAN-B) and the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC), as well as multiple single-cell sequenced cohorts. HSC were identified through the xCell algorithm, and patients with high HSC levels were defined as those with HSC expression above the median in each cohort. **Results:** Fraction of HSCs ranged from 0.04-0.50% of all cells in BC TME by single cell transcriptome analyses. HSC infiltration was not correlated with its lineage cells, common myeloid progenitor cells and common lymphoid progenitor cells, but was associated with high infiltration of dendritic cells and stromal-related cells and low infiltration of Myeloid-related cells; M1-macrophages, and eosinophils, and lymphoid-related cells; Th1 cells, Tregs, NK T cells, and memory B cells. HSC high BC enriched TGF-β signaling, myogenesis, coagulation, and angiogenesis gene sets. On the other hand, all the cell proliferation-related gene sets in Hallmark collection; E2F targets, G2M checkpoint, MYC targets-v2, and mitotic spindle, enriched to low HSC BC, and HSC infiltration was significantly lower in high histological grade BC and in Ki67 high expression BC. HSC high patients were significantly associated with better overall survival compared to low patients in ER+/HER2- (both $p<0.02$), but not in TNBC in both cohorts. Interestingly, there was no survival difference by HSC infiltration in ER+/HER2- when neoadjuvant chemotherapy (NAC) was used. Together with our finding that HSC in the TME markedly reduced by NAC, we cannot help but speculate that the loss of HSCs by NAC may have contributed to lose their benefit in patient prognosis. Lastly, high levels of HSC were associated with significantly lower risk of lung metastasis and better survival, but not with brain and bone metastases. **Conclusions:** This is the first report that quantified HSCs using transcriptome in TME and demonstrated that they are rare, associated inversely with cell proliferation and with better survival in ER+/HER2- BC patients. Survival benefit of HSC infiltration was lost with NAC that reduce its infiltration. HSC high BC was associated with lower risk of lung metastasis and with better survival, but not with brain nor bone metastasis. Research Sponsor: National institutes of healthes.

MRI-based radiomic signature and its association with genomic complexity in breast tumor heterogeneity.

Joonoh Lim, Young Seok Ju, Jeong Seok Lee, Brian Baek-Lok Oh, Ryul Kim, Sangmoon Lee, Won-Chul Lee, Jeongmin Lee; Inocras Inc., San Diego, CA; Inocras, Inc., San Diego, CA; Genome Insight, Inc., San Diego, CA; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Breast cancer is inherently heterogeneous, posing challenges for effective treatment. Uncovering the relationship between imaging features and genomic profiles could improve patient stratification. In this study, we evaluated whether radiomic features can capture the underlying genomic complexity of breast tumors, potentially offering a non-invasive means to better characterize tumor heterogeneity. **Methods:** We analyzed 284 breast cancer patients using an integrated radiogenomic approach. MRI-derived radiomics features were extracted and clustered using unsupervised learning methods, resulting in 12 distinct clusters. We then analyzed these clusters against matched whole-genome sequencing and transcriptome data, focusing on heterogeneity-related radiomics features. Clustering was performed using dynamic tree cutting after hierarchical clustering of 10 principal components derived from 214 radiomic features. **Results:** We identified distinct patterns of tumor heterogeneity among the 12 identified clusters, named according to descending cluster size (range: 10-46). Clusters 9, 4, and 3 exhibited the highest homogeneity (in that order), with cluster 9 being the most homogeneous overall. Cluster 12, 11, 8, 7, and 5 showed varying degrees of heterogeneity, while clusters 1 and 2 were moderately heterogeneous. Cluster 1-3 were HER2-enriched (PAM50). Clusters 1 and 2 together had *ERBB2* amplifications (33%; Fisher's exact test, $P = 0.056$), whereas cluster 3 was HER2-positive (IHC) without amplifications. Cluster 1 leaned toward the basal-like subtype, while 3 leaned toward luminal A. Cluster 2 was enriched in luminal B (50%; $P = 0.012$). Cluster 1-3 were distinguishable by their degree of radiomics-quantified heterogeneity. Cluster 4 was enriched in high *Myc* expression (17%; $P = 0.059$). Cluster 5 was enriched in whole-genome-based HRD (40%; $P = 0.01$) and basal-like (52%; $P = 0.001$). Cluster 6 was deprived of *TP53* mutations (37%; $P = 0.04$), had low tumor mutational burden, and was characterized by small volume but higher surface-volume ratio, suggesting irregular shape. Cluster 8 was enriched in *PIK3CA* mutations (60%, $P = 0.046$), cluster 10 was enriched in *CHEK2* mutations (9%; $P = 0.039$), cluster 11 showed high *TERT* (40%, $P = 0.005$) and *CDKN2A* (40%; $P = 0.048$) expression, cluster 12 was predominantly post-menopausal (80%; $P = 0.47$), and both clusters 10 and 12 exhibited low *ESR1* expression (20%; $P = 0.035$). **Conclusions:** This comprehensive radiogenomic analysis demonstrates that MRI-based radiomics features can effectively capture tumor heterogeneity patterns that correlate with specific genomic alterations in breast cancer. The identification of 12 distinct clusters, each with characteristic genomic features, provides new insights into the biological basis of tumor heterogeneity, potentially opening new avenues for breast cancer subtyping. Research Sponsor: None.

Pregnancy-associated breast cancer: Tumor infiltrating lymphocytes TILting the balance?

Carsten F.J. Bakhuis, Natalie D. ter Hoeve, Sabine C. Linn, Stefan Prekovic, Elsken Van Der Wall, Paul J. van Diest, Carmen van Dooijeweert; University Medical Center Utrecht, Utrecht, Netherlands; Department of Medical Oncology-Antoni van Leeuwenhoek Hospital, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Pregnancy-Associated Breast Cancer (PABC), which includes breast cancer diagnosed during pregnancy (PrBC) or postpartum (PPBC), is often more aggressive and diagnosed at more advanced stage compared to breast cancer in non-pregnant young women. The aggressive tumor growth in PABC may be influenced by the maternal shift towards immunotolerance during pregnancy, aimed at safely harboring the semi-allogenic fetus. Potentially, this shift allows cancer cells to evade immune detection. In recent years, the importance of stromal tumor-infiltrating lymphocytes (sTILs) as a marker of the anti-cancer immune response has become evident. Given the aforementioned relevance of immunotolerance in PABC development, we have evaluated the presence and prognostic importance of sTILs in PrBC and PPBC patients in this most extensive study to date. **Methods:** We assessed tumor tissues from the Dutch Pregnancy-Associated Breast Cancer Cohort, which includes PrBC and PPBC (≤1 year postpartum) patients diagnosed between 1988 and 2022. Whole slide images (H&E) of tumors from 200 patients were uniformly reviewed, and sTILs were scored according to international guidelines. Given the lack of previous sTIL cutoffs for PABC, a data-driven approach was chosen. **Results:** Our initial analysis revealed a clear survival benefit for a sTIL score of at least 20%. Therefore, our PrBC/PPBC patient group was divided into a "Low sTILs" ($< 20\%$, n = 153) and a "High sTILs" ($\geq 20\%$, n = 47) group. High sTIL scores were associated with a higher histologic grade (89% grade III versus 73% in the low sTIL group, p = 0.043) and more frequent triple negativity (68% versus 43%, p = 0.021) Despite this more aggressive histopathology, higher sTILs were associated with a significantly better 5-year overall survival (OS) probability (94% versus 69%, $p < 0.001$). In a multivariable analysis, correcting for disease stage, intrinsic subtype and tumor grade, high sTIL scores remained a strong prognostic indicator in PABC (HR 7.3, 95% CI 2.24 – 23.9). In a subgroup analysis for triple negative disease only (n = 93), patients with a high sTIL score (n = 30) showed a better 5-year OS probability (93% versus 60%, p = 0.002), which also persisted in a multivariable analysis (HR 4.7, 95% CI 1.4 – 15.7). **Conclusions:** Despite the immunotolerance in pregnancy, this study demonstrates the presence and prognostic importance of sTILs in PABC. Importantly, patients with high sTILs ($\geq 20\%$) had a markedly better prognosis despite having more aggressive disease characteristics, regardless of subtype. Therefore, sTILs may be an important prognostic indicator and may aid in selecting patients to forgo adjuvant systemic therapy, especially during pregnancy. Research Sponsor: A Sister's Hope for Breast Cancer Research; Private philantropist (unrestricted funding for this project).

Effect of allostatic load and measures of segregation on cancer detection and false positive rate after screening mammography.

Niam Abeysiriwardena, Braelyn Wekwerth, Nathaniel Mercaldo, Sarah Bell, Ruth C. Carlos; Massachusetts General Hospital, Boston, MA; University of Michigan, Ann Arbor, MI; Columbia University, New York, NY

Background: Allostatic load (AL), a cumulative stress measure and residential segregation (MRSs) have been associated with breast cancer (BC) outcomes. We assess the association of AL and MRSs on breast screening outcomes. **Methods:** From the Mass General Brigham Biobank, we retrospectively identify women aged ≥40, who underwent screening mammography from Jan 1, 2021 to Dec 31, 2021. We collected age, self-reported race/ethnicity, and zip code. Five MRSs were computed: Dissimilarity, Isolation (BI), Delta Index, Absolute Centralization, and Spatial Proximity. To compute AL, we assessed cardiovascular, metabolic, immune and renal lab values. AL was assigned one point for each lab value in the worst quartile and summed. We assessed any false positive (FP) and cancer diagnoses within 12 months after the index screen. Multiple imputation was performed for missing covariates. Multivariable logistic regression models were constructed to assess age, race, AL, and each MRSs association with cancer detection and FP rates. Rubin's rules were applied to estimate overall odds ratios (OR), confidence intervals (CI), and p-values for all covariates. **Results:** Of 13,754 women assessed, 1.2% (n=169) women received a cancer diagnosis. Most of the women were White (87.6%), 2.6% Asian, 5.3% Black; 1.5% self-identified as Hispanic; mean age, 64.4±11.3SD. Each point increase in AL increased the risk of cancer detection after screening mammography by 15% (OR=1.15,95% CI[1.06, 1.25],p=0.001). No association was detected between each MRS and cancer detection (all p>0.22). BI, the expected proportion of neighbors belonging to the same group, was associated with FP rate, with BI > 0.6 increasing the odds of FPs (OR=2.80[1.13-6.92],p=0.026). After adjusting for AL and MRSs, age and race were not significantly associated with cancer detection, but 5-year changes in age were associated with lower FP rate (OR=0.82 [0.80, 0.84],p<0.001). **Conclusions:** AL was associated with an increased risk of cancer detection after screening mammography after adjusting for age, race, and MRSs. The MRS BI above 0.6 was associated with an increased false positive rate. Further work is needed to confirm these observations. Clinical Relevance Statement: AL and MRS (i.e., BIS) may represent potential biomarkers for personalized mammographic screening for BC. Research Sponsor: None.

Prognostic value of systemic inflammation in early-stage breast cancer in the CANTO cohort (SIM-CANTO).

Julia Dixon-Douglas, Julie Havas, Federica Giugliano, Thi Hoai Hoang, Alessandro A. Viansone, Jean Zeghondy, Anne-Laure Martin, Dominique Delmas, Barbara Pistilli, William Jacot, Coureche Kaderbhai, Olivier Tredan, Paul H. Cottu, Mario Campone, Carole Tarpin, Fabrice Andre, Antonio Di Meglio, Ines Luis, Chayma Bousrih, Joana M. Ribeiro; Peter MacCallum Cancer Centre, Hobart, Australia; Cancer Survivorship Group, INSERM Unit 981, Gustave Roussy, Villejuif, France; Gustave Roussy, INSERM U981, Department of Medical Oncology, IHU-National PRecISion Medicine Center in Oncology, Villejuif, France; INSERM Unit 981, Gustave Roussy, Villejuif, France, Paris, France; Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France, Villejuif, France; Gustave Roussy, Villejuif, France; Unicancer, Le Kremlin-Bicêtre, France; Unicancer, Paris, France; Breast Cancer Unit, Gustave Roussy, Villejuif, France; Department of Medical Oncology, Institut du Cancer de Montpellier, Université de Montpellier, Montpellier, France; Georges François Leclerc Comprehensive Cancer Care Centre, Dijon, France; Medical Oncology, Centre Léon Bérard, Lyon, France; Medical Oncology, Institut Curie, Universite, Paris, France; Institut de Cancérologie de l'Ouest-René Gauducheau, Centre de Recherche en Cancérologie, Saint-Herblain, France; Institut Paoli-Calmettes, Marseille, France; Gustave Roussy, INSERM U981, Université Paris-Saclay, IHU-National PRecISion Medicine Center in Oncology, Villejuif, France; Cancer Survivorship Program, INSERM 981, Gustave Roussy, Villejuif, France; Gustave Roussy, Cancer Survivorship Program, INSERM U981, IHU-National PRecISion Medicine Center in Oncology, Villejuif, France; Gustave Roussy, Department of Medical Oncology, France, Villejuif, France; Gustave Roussy, Department of Medical Oncology, IHU-National PRecISion Medicine Center in Oncology, France, Villejuif, France

Background: The importance of host anti-tumor immunity in early-stage breast cancer (eBC) is now well recognised. Neutrophil / lymphocyte ratio (NLR) is a peripheral blood-based measure of systemic inflammation and immune status that has been associated with prognosis in other tumour types.We aimed to evaluate the prognostic value of NLR in a large prospective cohort of eBC. **Methods:** Patients with eBC (stage I-III) in the national French CANTO (NCT01993498) cohort with baseline peripheral blood counts (obtained after diagnosis and before any eBC treatment, including surgery) were included, regardless of systemic (neo) adjuvant therapy. The independent variable of interest was baseline NLR assessed as a continuous variable. Outcomes included invasive- and distant-disease-free survival (iDFS, DDFS) and overall survival (OS). We performed univariable analysis followed by multivariable Cox regression models sequentially adjusting for age, biologic subtype, TNM stage and treatment. Main analyses were conducted in the overall cohort, while additional analyses explored the role of NLR in subtypes (ER+/HER2-, HER2+, TNBC). For a cohort of patients receiving neoadjuvant therapy we tested the impact of NLR or pCR using Wilcoxon test. Sensitivity analyses used NLR as a categorical variable (using median NLR as cutoff to define high vs low NLR). **Results:** Overall, 10 470 patients were included. Median follow-up was 6.7 years (5.1 – 8.5). The median age at diagnosis was 56.4 years. Most (78%) of patients had stage I/II eBC, 77% ER+/HER2-, 13% HER2+ and 9% TNBC. The median NLR was 2.03. In the univariate analysis, there was a significant association between increasing NLR and worse DDFS in the overall cohort (HR: 1.1, p = 0.004; 95% CI:1.1 – 1.16) and in the ER+/HER2- cohort (HR: 1.1; p = 0.03; 95%CI:1.1 – 1.2). In a model adjusted by age and biologic subtype, NLR showed significant associations with DDFS (HR 1.07; p = 0.04) in the global cohort, but these associations did not maintain significance after further adjustment for TNM stage and treatment. Similarly, in the ER+/HER2- cohort, NLR was significantly associated with DDFS when adjusted for age (HR 1.08; p = 0.02), which was no longer significant after adjusting for TNM stage. No statistically significant differences were observed across other subtypes for DDFS, iDFS or OS, nor for pCR in the neoadjuvant cohort. Sensitivity analysis showed consistent results, in particular low NLR was significantly associated with improved DDFS (HR: 0.8, p = 0.03; 95%CI: 0.7 – 0.9) in the ER+/HER2- subgroup. **Conclusions:** Systemic inflammation, as measured by baseline NLR, was associated with significantly shorter DDFS in the overall CANTO cohort and in the ER+/HER2- subgroup in univariable and age- adjusted analysis. However, this association disappeared after adjustment for known clinicopathologic prognostic characteristics. Research Sponsor: None.

Exploring tumor genomics and clinical outcomes in in adolescent and young adult (AYA) breast cancer.

Faris Tamimi, Kamal Hosni Al-rabi, Baha' Sharaf, Tamer Moh'd Waleed Al-Batsh, Anas Mohammad Zayed, Osama El Kahtib, Hikmat Abdel-Razeq, King Hussein Cancer Center; King Hussein Cancer Center, Amman, Jordan; KHCC, Amman, Jordan; King Hussein Medical Center, Amman, Jordan

Background: Breast cancer in adolescents and young adults (AYAs, defined as individuals aged 39 or younger) often exhibits aggressive biological behavior and distinct clinical patterns compared to older patients. This research investigates the somatic mutations and clinical features that distinguish AYA breast cancer, aiming to uncover unique genomic and prognostic characteristics. **Methods:** We analyzed data from the METABRIC cohort using cBioPortal, focusing on 173 genes sequenced from 2,509 breast cancer cases. The dataset included information on copy number variations, gene expression, and long-term clinical outcomes. Tumor characteristics, mutation frequencies, and relapse-free survival (RFS) outcomes were compared between AYAs and older patients. Statistical methods employed included Chi-square tests for categorical data, Wilcoxon Rank-Sum tests for medians, and Cox regression for survival analysis. The 10 most commonly altered genes across the dataset were examined. **Results:** Of 2,498 patients included in the analysis, 143 were AYAs (5.7%) and 2,355 were older patients (94.3%). Compared to older patients, AYAs demonstrated: Lower ER-positive rates (37.8% vs. 74.9%), Higher ER-/HER2- subtype prevalence (25.2% vs. 11.6%), Greater lymph node positivity (52.4% vs. 41.3%), and Worse Nottingham Prognostic Index scores (median 5.04 vs. 4.04). Genomic analysis revealed significantly higher TP53 mutation frequencies in AYAs (58.9% vs. 33.2%, $p < 0.01$) and lower PIK3CA alterations (28.1% vs. 42.1%, $p < 0.01$). Other significantly altered genes in AYAs included TG, TRPS1, CASC8, POU5F1B, MYC, CASC11, NDRG1, and LINC02912. However, stratification by receptor subtypes (ER-/HER2-, ER+/HER2-, HER2+) showed no significant differences in TP53 or PIK3CA alterations between AYAs and older patients. AYA status (< 40 years) was associated with worse recurrence-free survival (RFS) in univariable analysis and remained a significant predictor in multivariable analysis, adjusting for ER status, HER2 status, and nodal involvement (HR: 1.33, 95% CI: 1.00–1.77, $p = 0.048$). **Conclusions:** AYA breast cancer is marked by distinct genomic and clinical features, including higher TP53 mutation rates, lower PIK3CA mutation rates, more aggressive subtypes such as ER-/HER2-. While some genomic differences are less pronounced within biomarker-matched subgroups, AYAs remain at higher risk for recurrence. These findings highlight the urgent need for age-specific therapeutic strategies to improve outcomes in this population. Research Sponsor: None.

Gene alteration event frequency by age group (AYA versus >39 years).

Gene	AYA	>39	p-Value	q-Value
TP53	58.90% (86/146)	33.16% (780/2352)	<0.001	<0.001
PIK3CA	28.08% (41/146)	42.05% (989/2352)	<0.001	0.0442
TG	35.62% (52/146)	23.72% (558/2352)	<0.01	0.0645
NDRG1	29.45% (43/146)	19.56% (460/2352)	<0.01	0.126
TRPS1	30.82% (45/146)	23.04% (542/2352)	0.0347	0.340
CASC8	30.14% (44/146)	21.51% (506/2352)	0.0178	0.231
LINC02912	29.45% (43/146)	20.88% (491/2352)	0.0167	0.229
CASC11	30.14% (44/146)	21.73% (511/2352)	0.0235	0.268
MYC	30.14% (44/146)	21.68% (510/2352)	0.0234	0.268

Global trends and regional disparities in young-onset breast cancer: Age-specific patterns from 1990 to 2021.

Muzamil Khan, Waseem Nabi, Nouman Aziz, Shree Rath, Reem Eisa, Munaza Afaq, Adnan Bhat, Mir Shahnawaz, Maryam Inam Zaroo; The George Washington University School of Medicine and Health Sciences, Washington, DC; Wyckoff Heights Medical Center, Brooklyn, NY; All India Institute of Medical Sciences, Bhubaneswar, Bhubaneswar, India; Ain Shams University, Cairo, Egypt; University of Florida, Gainesville, FL; Government Medical College Srinagar, Srinagar, India; Bangladesh Medical College Hospital, Jigatala, Bangladesh

Background: Young-onset breast cancer (YOBC), defined as breast cancer in women under 40, is a growing global health concern with unique biological and clinical implications. Analyzing its patterns and distribution is essential for developing effective healthcare strategies and ensuring efficient resource allocation. **Methods:** Data on incidence, prevalence, mortality, and morbidity indicators (DALYs, YLD, and YLL rates per 100,000) were obtained from the Global Burden of Disease (GBD) 2021 database for women under 40 from 1990 to 2021. The dataset, covering 204 countries, was stratified into five age groups: 35–39, 30–34, 25–29, 20–24, and < 20 years. Linear regression was used to calculate average annual percent change (AAPC) and 95% confidence intervals (CI) for each indicator and age group. Statistical significance was set at $p < 0.05$. **Results:** Between 1990 and 2021, YOBC accounted for 16,783,674 deaths globally. Incidence increased across all age groups, with the largest increases in women under 30. AAPC for incidence was 2.27 (95% CI: 2.21–2.33) in those under 20, 2.18 (95% CI: 2.11–2.24) for ages 20–24, and 1.60 (95% CI: 1.51–1.70) for ages 25–29 (all $p < 0.0001$). Prevalence showed similar increases: 2.35 (95% CI: 2.29–2.41), 2.24 (95% CI: 2.18–2.30), and 1.64 (95% CI: 1.54–1.73), respectively (all $p < 0.0001$). Mortality AAPCs were 1.54 (95% CI: 1.46–1.61) for under 20, 1.35 (95% CI: 1.23–1.46) for ages 20–24, and 0.68 (95% CI: 0.59–0.76) for ages 25–29, while older cohorts saw declines, including -0.38 (95% CI: -0.53 to -0.23, $p < 0.0001$) for ages 35–39. DALYs also increased in younger groups, with AAPCs of 1.56 (95% CI: 1.49–1.63) for under 20 and 1.37 (95% CI: 1.26–1.48) for ages 20–24 but declined in older cohorts. Regionally, Turkey had the highest AAPCs across metrics, Malawi had the highest incidence and YLL for those under 20, and Zimbabwe, Yemen, and Lesotho reported the highest incidence, prevalence, YLL, and DALY. In contrast, Ukraine, Mariana Island and Armenia experienced the greatest declines in incidence, prevalence, YLL, and DALY. **Conclusions:** The global burden of YOBC has risen sharply, especially in the youngest cohorts (< 20 and 20–24 years), with significant increases in low- and middle-income regions like Turkey, Sub-Saharan Africa, and the Middle East. Age-specific interventions, early detection, and preventive measures are needed to address the growing YOBC rates. Research Sponsor: None.

Interferon signaling and outcomes in triple-negative breast cancer (TNBC) in FinXX, CALGB 40603 (Alliance) and real-world clinico-genomic data.

Saranya Chumsri, Yi Liu, Sachin Kumar Deshmukh, Jodi Carter, Heikki Joensuu, Roberto Antonio Leon-Ferre, David Zahrieh, Judy Caroline Boughey, James N. Ingle, Fergus Couch, Evanthia T. Roussos Torres, Maryam B. Lustberg, Daniel G. Stover, William M. Sikov, Ann H. Partridge, Lisa A. Carey, George W. Sledge Jr., Matthew P. Goetz, Keith L. Knutson, E. Aubrey Thompson; Mayo Clinic Florida, Jacksonville, FL; Department of Quantitative Health Sciences, Mayo Clinic, Phoenix, AZ; Caris Life Sciences, Phoenix, AZ; Dept of Oncology, Edmonton, AB, Canada; Helsinki University Hospital, Helsinki, Finland; Mayo Clinic, Rochester, MN; USC, Los Angeles, CA; Department of Medical Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; The Ohio State University - James Comprehensive Cancer Center, Columbus, OH; Women and Infants Hospital of Rhode Island; Warren Alpert Medical School of Brown University, Providence, RI; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Mayo Clinic Comprehensive Cancer Center, Jacksonville, FL

Background: Several studies established the prognostic role of both the amount and locations of tumor-infiltrating lymphocytes (TILs) in TNBC. Three distinct immunotypes were described based on the amount and locations of TILs: immune enriched (IN), immune excluded, and immune desert. Using single-cell spatial transcriptomic analysis in the Mayo Clinic TNBC cohort, our previous studies showed the central role of interferon (IFN) signaling in IN phenotype. Herein, we evaluated the association between IFN and outcomes in TNBC in 3 independent datasets. **Methods:** NanoString IO360 was performed in 114 samples from FinXX (NCT00114816) to generate 22-gene IFNα and 33-gene IFNγ signatures. RNA sequencing was performed in 388 samples from CALGB 40603 (NCT00861705). 3038 TNBC samples were tested by WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ). Median values were used as cut-offs for high vs low IFNγ RNA expression and 18-gene IFNγ signature scores. Caris Life Science CODEai was used to evaluate real-world overall survival (OS) obtained from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier estimates. Chi-square, Mann-Whitney U, ANOVA, and Cox regression were used. **Results:** A high 22-gene IFNα signature score was associated with significantly improved recurrence-free survival (RFS) in FinXX (hazard ratio [HR] 0.32, 95% confidence interval [CI] 0.14-0.74, p 0.007) and OS (HR 0.28, 95%CI 0.12-0.66, p 0.003). Similar findings were observed with 33-gene IFNγ signature with significant improvement in RFS (HR 0.21, 95%CI 0.09-0.51, $p < 0.001$) and OS (HR 0.18, 95%CI 0.08-0.44, $p < 0.001$). Furthermore, in CALGB 40603, both IFNα and IFNγ scores were positively associated with pathologic complete response (pCR: IFNα p 0.019 and IFNγ p 0.007) and residual cancer burden (RCB: IFNα p 0.044 and IFNγ p 0.013). Using the Caris data platform to further validate, we identified 2899 TNBC patients (pts) with genomic and clinical outcome data. High IFNγ expression was associated with significant improvement in OS (25.95 vs 17.43 months; HR 0.65, 95% CI 0.59 – 0.72, $p < 0.001$). Similarly, pts with high IFNγ signature scores had significant improvement in median OS (25.79 vs 16.22 months; HR 0.66, 95% CI 0.6 – 0.73, $p < 0.001$). **Conclusions:** This study underscores the pivotal role of IFN signaling in TNBC. High IFNα and IFNγ signatures were consistently associated with improved RFS, OS, higher pCR rates, and lower RCB across clinical trial cohorts and real-world data. These findings signify IFN signaling as a potential key biomarker and therapeutic target in TNBC. Support: U10CA180821, U10CA180882, U24CA196171; Breast Cancer Research Foundation, Mayo Clinic Breast Cancer SPORE (P50CA116201-17), Bankhead Coley, W81XWH-15-1-0292, P50CA015083, R35CA253187; https://acknowledgments.alliancefound.org. Genentech. Clinical trial information: NCT00114816 and NCT00861705. Research Sponsor: U.S. National Institutes of Health; U10CA180821, U10CA180882, U24CA196171; Mayo Clinic Breast Cancer SPORE (P50CA116201-17), P50CA015083, R35CA253187; Bankhead Coley; Breast Cancer Research Foundation; U.S. Department of Defense; W81XWH-15-1-0292; Genentech.

MHC class I expression and outcomes in breast cancer in the real-world clinico-genomic data and the FinXX trial.

Yi Liu, Sachin Kumar Deshmukh, Yaohua Ma, Jodi Carter, Sharon Wu, Joanne Xiu, Nadine Norton, Kathryn Jean Ruddy, Kathryn Jean Ruddy, Edith A. Perez, Shipra Gandhi, Priscila Barreto Coelho, Maryam B. Lustberg, Matthew P. Goetz, Heikki Joensuu, George W. Sledge Jr., E. Aubrey Thompson, Saranya Chumsri; Department of Quantitative Health Sciences, Mayo Clinic, Phoenix, AZ; Caris Life Sciences, Phoenix, AZ; Mayo Clinic, Jacksonville, FL; Dept of Oncology, Edmonton, AB, Canada; Mayo Clinic Florida, Jacksonville, FL; Mayo Clinic, Rochester, MN; Roswell Park Comprehensive Cancer Center, Buffalo, NY; University of Miami, Miami, FL; Department of Medical Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT; Helsinki University Hospital, Helsinki, Finland

Background: Major histocompatibility complex class I (MHC I) plays a critical role in immune surveillance by binding peptides derived from intracellular proteins and presenting them on the cell surface for recognition by CD8+ T cells. Loss or downregulation of MHC I expression has been identified as a key mechanism of immune evasion in cancers. Here, we evaluated MHC I expression and outcomes in all subtypes of breast cancer (BC). **Methods:** 9,038 BC samples were analyzed via NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ), including triple-negative BC (TNBC) 3,038, HER2-positive (HER2+) 1,082, and hormone receptor-positive (HR+HER2-) 4,918. Immune cell fractions were estimated using WTS deconvolution (Quantiseq). MHC I (*HLA-A*/*HLA-B*/*HLA-C*)-high (H) and -low (L) were classified by RNA expression above or below the 25th percentile. Real-world overall survival (OS) was derived from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier. NanoString IO360 was performed in 114 samples from the FinXX trial (NCT00114816). Statistical significance was assessed using chi-square, Mann-Whitney U, ANOVA, and Cox regression with multiple comparison adjustments ($q<.05$). **Results:** TNBC had higher expression of *HLA-A* and *HLA-B* (median TPM: 169 and 191) compared to HER2+ (146.6 and 170, $q<0.05$) and HR+HER2- (141.7 and 157.5, $q<0.05$). However, there was no significant difference in *HLA-C* expression across 3 BC subtypes. In TNBC, MHC I-H tumors had higher frequencies of PD-L1 positivity (66.2% vs. 13.1%) as well as higher infiltration of B cells (4.5% vs. 3.2%), M1 macrophages (5% vs. 1.5%), M2 macrophages (4% vs. 2.1%), Tregs (2.8% vs. 0.8%), $CD8^+$ T cells (1.8% vs. 0%), dendritic cells (3.2% vs. 2.8%), higher T-cell inflamed score (137 vs. -144), and IFN*g* score (0.02 vs. -0.49) compared to MHC I-L TNBC (all $q<.05$). MHC I-H TNBC was associated with significant improvement in median OS (30.1 vs. 15.2 months, HR 0.55, 95% CI 0.46-0.65, $p<0.0001$). However, this survival difference was not observed in patients with MHC I-H vs. MHC I-L in HER2+ (HR 1.04, 95% CI 0.74-1.47, $p = 0.81$) and HR+HER2- (HR 0.87, 95% CI 0.75-1.02, $p= 0.09$) BC subtypes. We further validated the MHC I expression in the FinXX trial. Similarly, patients with MHC I-H had significant improvement in recurrence-free survival (HR 0.27, 95%CI 0.11-0.66, $p = 0.002$) and OS (HR 0.23, 95% CI 0.09-0.57, $p = 0.0005$) compared to MHC I-L. **Conclusions:** Our findings demonstrate that higher MHC I expression is associated with higher immune infiltration and improved outcomes in TNBC but not in HER2+ or HR+HER2- BC subtypes. These results suggest that MHC I expression plays a critical role in the tumor microenvironment of TNBC. Future studies are needed to evaluate the prognostic value and potential therapeutic target of MHC I in TNBC. Support: Breast Cancer Research Foundation, Bankhead Coley, W81XWH-18-1-0564. Clinical trial information: NCT00114816. Research Sponsor: None.

Impact of HER2 low status on pathologic response after neoadjuvant chemotherapy in TNBC: A large scale retrospective cohort study.

Julia Tchou, Macy Goldbach, Anupma Nayak, Payal Deepak Shah; University of Pennsylvania, Philadelphia, PA; Hospital of University of Pennsylvania, Philadelphia, PA; Penn Medicine Abramson Cancer Center, Philadelphia, PA

Background: HER2 low status, defined as HER2 1+ or HER2 2+ and nonamplified by in-situ hybridization, has demonstrated the ability to identify a population of patients with triple-negative disease who benefit from trastuzumab deruxtecan in the metastatic setting. The implications of HER2 low status in the early-stage setting is unclear. This study evaluated whether HER2 low status impacts rates of pathologic complete response in response to neo-adjuvant chemotherapy (NAC). **Methods:** Using the national cancer database (NCDB), patients with clinically invasive non-metastatic breast cancer between 2010-2021 were retrospectively identified (n=1,926,979). Patients with unknown receptor status or who did not have triple negative breast cancer (n=1,755,897) and those who did not have surgery (n=9,849) were excluded. Clinicopathologic, treatment, and outcome variables were compared using chi-square and anova tests. Subgroup analysis was performed among patients who received NAC and had available pathologic response results. Multivariable binary logistic regression was performed to assess clinical variables associated with pCR after NAC. Cox proportional hazards model was performed to assess clinical variables associated with overall survival (OS) in TNBC receiving NAC. **Results:** Of the 161,233 individuals eligible for analysis, 79,268 (49.4%) had HER2 low disease. The proportion of HER2 0, HER2 1+ and HER2 2+/ish negative (HER2 2+) were 50.6, 34.8, and 14.6% respectively. Overall, 49,994 (31%) individuals received NAC with an overall pCR rate of 42.9%. The pCR rate was significantly lower in those with HER2 2+/ish negative compared to those with HER2 0 TNBC at 39.9 vs. 44.2%, p <0.001. On multivariable analysis, HER2 1+ status trended towards a lower likelihood of pCR R 0.95, 95% CI 0.91-1.00, p=0.06) while HER2 2+/ish negative status was significantly associated with a lower likelihood of pCR (OR 0.87, 95% CI 0.82-0.94, p<0.001) compared to HER2 0 disease. Cox proportional hazards model analysis demonstrated that the strongest clinical factor for worse OS was non-pCR with HR 3.76, 95% CI 3.48 – 4.05, p<0.001 while neither HER2 1+ or HER2 2+/ish negative was associated with worse OS. **Conclusions:** In this analysis, tumors that were HER2 2+/ish negative were associated with a significantly lower pCR rate after NAC compared with HER2 0 tumors. This is the first large-scale study to demonstrate that HER2 low status may be prognostically unfavorable in early-stage TNBC. Examination of novel neoadjuvant therapeutic approaches tailored based on HER2 status including trastuzumab deruxtecan may be warranted to improve pCR rates and outcomes in patients with HER2-low early-stage breast cancer. Research Sponsor: None.

pCR rate stratified by HER2 low status.

	HER2 0		HER2 1+		HER2 2+	
n	81605		56109		23519	
Neoadjuvant	26458	32.4%	16841	30.0%	6695	28.5%
pCR	11690	44.2%	7064	41.9%	2672	39.9%

Reframing hormone-positive DCIS management: Effects of adjuvant therapies and surgical extent on any invasive recurrence.

Thomas O'Keefe, Christina Yau, Sophie Lin, Nicolas Prionas, Gillian L. Hirst, Rita Mukhtar, Anne M. Wallace, Michael Alvarado, Laura Esserman; University of California, San Francisco, San Francisco, CA; University of California San Francisco, San Francisco, CA; Department of Radiation Oncology, University of California, San Francisco, San Francisco, CA; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of California, San Diego, La Jolla, CA

Background: The treatment of DCIS is still primarily informed by trials that are now decades old. We have learned since then that only invasive subsequent events, not in situ ones, increase a woman's risk of eventual metastasis and breast cancer mortality, and may necessitate more aggressive systemic treatment. This suggests a need for the reassessment of the impact of adjuvant therapies. **Methods:** Women diagnosed with a first breast cancer of unilateral hormone positive DCIS undergoing breast conserving surgery were identified in the Surveillance, Epidemiology and End Results Program registry. Propensity-matching was performed between treatment groups using age, race, lesion size and grade. Competing risks methods were used to estimate the cumulative incidence of any invasive event at 10 years and subdistribution hazard ratios (sHRs) were calculated from multivariate models adjusting for the same covariates used for matching. **Results:** A total of 14,189 patients diagnosed from 2007 to 2011 were eligible for matching, among whom 900 (6.3%) suffered a subsequent invasive event.A cohort was developed by matching from the smallest treatment group, lumpectomy with endocrine therapy. There were 2,996 matched patients, among whom 511 (17.1%) had an invasive subsequent event. Adjuvant endocrine therapy was associated with reduced risk of any invasive event (sHR=0.38, p<0.001) compared to patients undergoing lumpectomy without adjuvant therapy. Radiotherapy alone was not associated with reduced risk (sHR=1.03, p=0.81): it was associated with reduced risk of an ipsilateral invasive event (sHR=0.65, p=0.006) but an increased risk of a contralateral invasive event (sHR=1.50, p=0.01). In subgroup analyses, lumpectomy with radiation therapy was noted to be non-significantly associated with increased risk of any invasive disease in patients younger than 60 years (sHR=1.38, p=0.053) and with decreased risk in patients 60 years or older (sHR=0.79, p=0.12). **Conclusions:** Our results suggest that endocrine therapy may confer the greatest risk reduction to the development of any subsequent invasive recurrences, and whole-breast radiotherapy may be associated with increased risk for younger women. The risk posed by DCIS as a high-risk marker may outweigh its risk as a premalignant lesion. Research Sponsor: None.

Any invasive subsequent breast cancer, and subgroup analyses by age. Only treatment effect shown, but results are adjusted for race, grade, age, and lesion size.

	Any Invasive, Any Age		Any Invasive, < 60 years old		Any Invasive, ≥ 60 years old	
	sHR (95% CI)	p	sHR (95% CI)	p	sHR (95% CI)	p
Treatment						
BCS	Ref	-	Ref	-	Ref	-
BCS + ET	0.38 (0.29-0.51)	<0.001	0.34 (0.21-0.54)	<0.001	0.40 (0.28-0.58)	<0.001
BCS + RT	1.03 (0.82-1.28)	0.81	1.38 (1.00-1.91)	0.053	0.79 (0.59-1.07)	0.12

sHR = Subdistribution hazard ratio.
BCS=Breast conservation surgery.
ET=Endocrine therapy.
RT=Radiation therapy.

Impact of postmastectomy radiotherapy on health-related quality of life and safety in breast cancer patients undergoing breast reconstruction: A multi-center cross-sectional study (Reborn-02).

Hirohito Seki, Noriyuki Watanabe, Shinsuke Sasada, Naomi Nagura, Akiko Ogiya, Ayaka Koike-Shimo, Natsue Uehiro, Wakako Tsuji, Shoichi Tomita, Takahiro Tsukioki, Tatsuya Uchida, Hirotsugu Isaka, Tomohiro Shiraishi, Yutaka Nishida, Shigeru Imoto, Chikako Yamauchi; Department of Breast Surgery, Kyorin University School of Medicine, Tokyo, Japan; Department of Breast and Endocrine Surgery, Osaka International Cancer Institute, Osaka, Japan; Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan; Department of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan; Department of Breast Surgery, Japanese Red Cross Medical Center, Tokyo, Japan; Department of Breast and Endocrine Surgery, St. Marianna University School of Medicine, Kanagawa, Japan; Breast Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Breast Surgery, Shiga General Hospital, Moriyama Shiga, Japan; Department of Plastic and Reconstruction Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan; Department of Plastic Surgery, Okayama University Hospital, Okayama, Japan; Department of Breast Surgery Kyorin University School of Medicine, Tokyo, Japan; Department of Plastic Surgery, Kyorin University Scool of Medicine, Mitaka-Shi, Japan; Center for Data Science Education and Research, Kyorin University, Tokyo, Japan; Kyorin University Hospital, Mitaka-Shi, Japan; Department of Radiation Oncology, Shiga General Hospital, Shiga, Japan

Background: Postmastectomy radiotherapy (PMRT) is the standard treatment for improving the prognosis of patients with high-risk breast cancer. Expanded indications for breast reconstruction (BR) will likely increase the number of patients undergoing BR who require PMRT, but combining BR with PMRT raises concerns about complications and aesthetics. Evaluating the impact of PMRT on the health-related quality of life (HR-QOL) in Japanese patients is essential for shared decision-making (SDM). This study assessed differences in postoperative HR-QOL and complications between patients who underwent BR with or without PMRT. **Methods:** We conducted a multicenter cross-sectional study using a questionnaire survey of patients with primary breast cancer who underwent BR between January 2008 and December 2022 at participating institutions, which was approved by the respective institutional review boards. We used the Japanese version of the BREAST-Q questionnaire and questions on patient backgrounds. **Results:** We included 1078 patients with primary breast cancer. The questionnaire response rate was 77.0% (830/1078). The non-PMRT and PMRT groups comprised 616 and 214 patients, respectively. The PMRT group had higher rates of axillary lymph node dissection (11.7% vs. 52.4%; P<0.001), adjuvant hormonal therapy (67.2% vs. 90.6%; P<0.001), and perioperative chemotherapy (31.8% vs. 84.0%; P<0.001) than the non-PMRT group. Moreover, the overall complication rate (45.3% vs. 76.2%, P<0.001) and the rates of dermatitis (9.9 vs. 48.1%; P < 0.001), skin necrosis (2.9 vs. 9.8%; P<0.001), breast asymmetry (17.0% vs. 24.3%; P=0.002), capsular contracture (4.9 vs. 16.4%; P<0.001), and lymphedema of the upper limb (1.1% vs. 7.5%; P<0.001) were higher in the PMRT group. Multivariate analysis revealed PMRT as an independent risk factor for dermatitis, skin necrosis, and capsular contracture. In the BREAST-Q assessment, the PMRT group showed lower satisfaction with the breast (55 vs. 49; P<0.001), and with physical (85 vs. 76; P<0.001), psychosocial (55 vs. 49; P<0.001), and sexual well-being (36 vs. 34; P=0.021) than the non-PMRT group. Multiple regression analysis revealed PMRT as an independent factor associated with low BREAST-Q scores for breast satisfaction and physical and psychosocial well-being in patients with BR. **Conclusions:** This is the first large-scale, multi-institutional study to use patient-reported outcomes to assess the effects of PMRT on HR-QOL in Japanese patients with breast cancer who underwent BR. PMRT was associated with an increased risk of complications and decreased HR-QOL in patients with BR. Of note, these findings do not negate the role of PMRT in patients undergoing BR, but highlight the importance of SDM based on realistic HR-QOL expectations after breast reconstruction surgery with PMRT. Research Sponsor: None.

Development and validation of prediction models for 5-year and 10-year ipsilateral breast tumor recurrence after breast-conserving surgery.

Yasuaki Sagara, Atsushi Yoshida, Yuri Kimura, Makoto Ishitobi, Yuka Ono, Yuko Takahashi, Takahiro Takahiro, Kouji Takada, Yuri Ito, Tomo Osako, Takehiko Sakai; Department of Breast Surgical Oncology, Social Medical Corporation Hakuaikai Sagara Hospital, Kagoshima, Japan; St Luke's International Hospital, Tokyo, Japan; Breast Medical Oncology, Breast Center, The Cancer Institute Hospital of JFCR, Tokyo, Japan; Osaka Habikino Medical Center, Habikino, Japan; Kyoto University, Kyoto, Japan; Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan; Osaka Metropolitan University, Osaka, Japan; Osaka Medical and Pharmaceutical University, Takatsuki, Japan; The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Breast Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Ipsilateral breast tumor recurrence (IBTR) remains a critical concern for patients undergoing breast-conserving surgery (BCS). Reliable prediction tools for IBTR risk can support personalized surgical strategies and adjuvant treatment decisions, especially in the era of evolving systemic therapies. This study aimed to develop and validate prediction models for 5-year and 10-year IBTR. **Methods:** This multi-center retrospective cohort study included 10,089 women who underwent partial mastectomy for invasive breast cancer between 2008 and 2017. Cases involving conversion to mastectomy, use of neoadjuvant chemotherapy, bilateral/multiple cancers, or missing key data were excluded. Prediction models were developed using Cox proportional hazards regression and validated via bootstrap resampling. Model performance was assessed using Harrell's C-index, Brier scores, calibration plots, and goodness-of-fit tests. The cumulative incidence of IBTR, which served as the baseline for the prediction model, was calculated using the Fine and Gray model, treating death as a competing risk. **Results:** The median age of patients was 55 years [interquartile range (IQR): 46–65]. During a median follow-up of 8.9 years (IQR: 6.4–10.8), IBTR occurred in 292 patients (3.1%). The initial model, based on variables from Sanghani et al. (JCO 2010), achieved a Harrell's C-index of 0.70. Incorporating hormonal receptor status, HER2 status, radiotherapy, and targeted therapy as predictors reduced the C-index to 0.60, despite their clinical relevance. Importantly, the inclusion of these factors improved calibration, demonstrating better alignment between predicted and observed IBTR probabilities. The final Cox model exhibited strong clinical and statistical robustness ($p < 0.001$), providing individualized IBTR risk estimates. Cox-Snell residual analysis confirmed goodness-of-fit, with the cumulative hazard closely following the 45-degree line up to 0.3, indicating reliable model performance for observed events. While hazard ratios (HRs) for chemotherapy and radiotherapy were consistent with results of EBCTCG meta-analyses (MA), HR for endocrine therapy was lower than reported in MA. Consequently, HRs from MA were adopted to account for treatment effects in our prediction model. **Conclusions:** We have developed and validated a new prediction model for 5-year and 10-year IBTR using Cox regression and bootstrap methods. A web-based tool is under development to enable individualized risk assessment and treatment planning. Future research will focus on external validation and the integration of genetic and novel therapeutic data to enhance model robustness and clinical utility. Research Sponsor: Japanese Breast Cancer Society.

Regional node recurrence after sentinel lymph node biopsy for ycN0 patients treated with primary chemotherapy in cT1-3N1M0 breast cancer (second report from SHARE study).

Shigeru Imoto, Rikiya Nakamura, Shigeki Minami, Noriaki Wada, Tomohiko Aihara, Kimiyasu Yoneyama, Hiroyuki Yasojima, Shinichiro Kashiwagi, Masayuki Yoshida, Takahiro Nakayama, Masaya Kawada, Tomoko Ogawa, Uhi Toh, Sayaka Kuba, Masahiro Kitada, Akimitsu Yamada, Toru Ohtake, Hiroshi Matsumoto, Mari Saito-Oba, Junichi Sakamoto; Kyorin University, Mitaka, Japan; Department of Breast Surgery, Chiba Cancer Center, Chiba, Japan; Nagasaki Medical Center, Omura, Japan; Tokyo Dental College Ichikawa General Hospital, Ichikawa, Japan; Aihara Hospital, Minoh, Japan; Hiratsuka City Hospital, Hiratsuka, Japan; NHO Osaka National Hospital, Osaka, Japan; Osaka Metropolitan University Hospital, Osaka, Japan; Seirei Social Welfare Community, Seirei Center for Health Promotion and Preventive Medicine, Hamamatsu, Japan; Osaka International Cancer Institute, Osaka, Japan; Tonan Hospital, Sapporo, Japan; Mie University Hospital, Tsu, Japan; Department of Surgery, School of Medicine, Kurume University, Kurume-Shi, Japan; Nagasaki University Hospital, Nagasaki-Shi, Japan; Asahikawa Medical University Hospital, Asahikawa, Japan; Yokohama City University Hospital, Yokohama-Shi, Japan; Fukushima Medical University Hospital, Fukushima, Japan; Saitama Prefectural Cancer Center, Saitama, Japan; National Center of Neurology and Psychiatry, Kodaira, Japan; Tokai Central Hospital, Kakamigahara Gifu, Japan

Background: Axillary management after sentinel lymph node biopsy (SLNB) is still debated for clinically node-positive breast cancer (BC) patients treated with neoadjuvant chemotherapy (NAC). The Japanese Society for Sentinel Node Navigation Surgery conducted a prospective non-randomized phase 2 study (SHARE study, UMIN000030558). False-negative rate (FNR) as the primary endpoint was reported at ASCO2023. In brief, it was 11.5% (90% confidence interval, 5.5% and 20.5%). When multimodal imaging, 1 nodal metastasis, multiple tracers, multiple sentinel lymph nodes were considered for subset analysis, the FNR was 12.1%, 9.1%, 11.1%, and 10.6%, respectively. Here we report a short-term prognosis of ycN0 BC patients. **Methods:** Clinical T1-3N1M0 BC was eligible. Nodal metastasis was histologically confirmed. In case of ycN0 BC, SLNB was planned and lymphatic mapping depended on each institutional practice. In cases of pN0(sn), pN0(i+)(sn) and pN1mi(sn), SLNB followed by lymph node sampling (LNS) had been allowed instead of axillary lymph node dissection (ALND). **Results:** Between February 2018 and May 2021, 185 patients from 19 institutes were registered. Twenty-seven cases were exculded by protocol deviation, non-ycN0 or withdrawal of SLNB. Among the 158 ycN0 cases, sentinel lymph nodes were detected in 153 cases. The median age was 52 years old. Clinical stage was IIA in 40 cases, IIB in 105 and IIIA in 8. Luminal subtype classified by ER, PR and HER2 expression was found in 60 cases, HER2 in 34, Luminal-HER2 in 35 and triple-negative in 24. SLNB alone was performed in 37 cases, SLNB and LNS in 72 and SLNB followed by ALND in 44. Regional nodal irradiation was planned in 63 cases. At the median follow-up of 24 months, 13 cases relapsed and 5 died of BC. Regional node recurrence-free survival rate at 2 years after surgery, disease-free survival rate and overall survival rate were 98.6%, 92.6% and 97.3%, respectively. **Conclusions:** SLNB-guided axillary management is feasible and safe in ycN0 BC after NAC. Clinical trial information: 000030558. Research Sponsor: The Japanese Society for Sentinel Node Navigation Surgery.

Preoperative axillary US and MRI in early-stage breast cancer: Potential to prevent unnecessary axillary surgery.

Xin Wang, Haitong Xie, Weijing Liu, Ruixian Chen, Jie Chen; West China Hospital (China), Chengdu, China; West China Hospital, Chengdu, China; Breast Center, West China Hospital, Sichuan University, Chengdu, China; Department of Breast Surgery, West China Hospital, Sichuan University, Chengdu, China; West China Hospital of Sichuan University, Chengdu, China

Background: Recent studies, including the INSEMA and SOUND trials, have demonstrated that omitting sentinel lymph node (SLN) biopsy does not adversely affect survival outcomes. Notably, patients with positive axillary findings on ultrasound (US) tended to show more extensive axillary nodal metastasis on final histopathological examination. Thus, we aimed to focused on the advanced utility of preoperative axillary US and Magnetic Resonance Imaging (MRI) in preventing unnecessary axillary surgery in a large series of patients with early-stage breast cancer treated with both breast surgery and SLN biopsy. **Methods:** Between January 2012 to December 2023, a total of 7879 patients who underwent breast surgery for clinical T1–2/N0 cancers and SLN biopsy with or without axillary lymph node dissection were included. Preoperative axillary US and MRI findings were compared with clinical-pathologic variables, considering the presence of SLN metastasis. Patients with positive results routinely underwent US-guided fine needle aspiration biopsy (FNAB), and negative FNAB results were also considered. Multivariate logistic regression analysis was used to identify factors associated with SLN metastasis. **Results:** A total of 7879 eligible patients (47.48% with clinical T1 cancer and 52.52% with T2 cancer) were included in our study. Among them, 2048 (25.99%) had positive SLN biopsy, and 1971 (25.02%) underwent axillary lymph node dissection due to positive SLN biopsy. Patients with SLN metastasis were younger and had a higher frequency of positive axillary findings on US and MRI, as well as clinical T2 stage ($P<0.05$). At multivariate analysis, positive axilla at US (P =0.001), positive axilla at MRI (P =0.02), clinical T2 stage (P =0.004), grade 3 (P =0.004) and lymphovascular invasion (P=0.001) were significantly associated with SLN metastasis. The number of nodal metastases increase with increasing tumor size. Among 3595 (45.06%) patients with negative axilla at US and MRI and clinical T1 stage cancer, 698 (8.75%) had SLN metastasis. For these people, the median follow-up was 73.6 months. The estimated 5-year invasive disease–free survival rate was 96.8%, while the 5-year overall survival rate was 98.6%. The analysis of the first primary-outcome events (occurrence or recurrence of invasive disease or death from any cause), showed apparent differences between the positive axilla at US and MRI and clinical T1 stage cancer group and negative axilla at US and MRI and clinical T1 stage cancer group in the incidence of recurrence (4.7% vs. 3.2%) and death (2.0% vs. 1.4%). **Conclusions:** Preoperative axillary US and MRI results, along with clinical T stage are significant predictors of SLN metastasis in patients with early-stage breast cancer. The results of this study suggest that preoperative axillary US and MRI can help select patients at minimal risk of SLN metastasis, for whom axillary surgery could be omitted. Research Sponsor: National Natural Science Foundation of China; National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University; Natural Science Foundation of Sichuan Province.

Use of local estrogen therapy among breast cancer patients in SEER-MHOS database.

Olivia Mitchel, Paul Hsu, Jennifer Erdrich; University of Arizona- College of Medicine Tucson, Tucson, AZ; University of Arizona Mel and Enid Zuckerman College of Public Health Department of Epidemiology and Biostatistics, Tucson, AZ; University of Arizona Cancer Center, Tucson, AZ

Background: Anti-hormonal therapy with tamoxifen or aromatase inhibitors is a key component in the treatment of hormone receptor-positive breast cancers. One of the adverse effects of this type of therapy is genitourinary syndrome of menopause, which may be treated with vaginal estrogen. It remains unclear whether local vaginal estrogen use carries any increased risk of recurrence or mortality in patients with a history of breast cancer. This has led to conflicting advice in the clinical setting and potentially unnecessary avoidance of hormone-based products that could possibly provide women symptomatic relief. Further exploration of the relationship between local estrogen therapy and breast cancer outcomes is warranted. **Methods:** A retrospective cohort study of 18,620 female breast cancer patients $\geq$ 65 years of age diagnosed between 2010-2017 in the SEER-MHOS registry was performed, comparing the breast cancer patients who used local vaginal estrogen (n=800) to those who did not (n=17,820), to assess whether local vaginal estrogen exposure was associated with any difference in overall survival as a primary outcome. Breast cancer specific survival was analyzed as a secondary outcome. Missing data was excluded by complete case analysis. Wilcoxon rank-sum tests were performed to compare continuous variables, Chi-square tests to compare categorical variables, Kaplan-Meier estimation to summarize overall survival, and sub-distribution hazard regression was performed to evaluate breast cancer specific survival by group. Multivariate regression models controlled for age, race, cancer stage, treatment (i.e. surgery, radiation, anti-hormonal therapy), and year of diagnosis. The research protocol was approved by our Scientific Review Committee and submitted for IRB approval. **Results:** There was a statistically significant increase in overall survival (HR=0.56, $p<0.0001$) as well as breast cancer-specific survival (HR=0.53, p=0.014) among breast cancer patients who used vaginal estrogen compared to those who did not. Among those who used vaginal estrogen, there was a statistically significant increase in overall survival for those with a duration of use >7 years (median duration of use) compared to those with a duration of use <7 years (HR=0.01, $p<0.0001$). Subset analysis restricted to patients with hormone positive breast cancer showed a statistically significant increase in overall survival for those who used vaginal estrogen compared to those who did not (HR=0.62, p=0.0007), and a nonsignificant increase in breast cancer specific survival (HR=0.62, p=0.08). **Conclusions:** The use of vaginal estrogen among this SEER-MHOS cohort of breast cancer patients showed improved survival outcomes. These findings add to a rising contemporary paradigm shift that local hormone therapy is not associated with increased risk to overall or breast cancer specific survival, which has important clinical implications. Research Sponsor: Departmental funding from the University of Arizona College of Medicine - Tucson Department of Surgery.

Efficacy and safety of post-mastectomy radiation therapy for patients with breast cancer after breast reconstruction: A retrospective multicenter cohort study (Reborn-03).

Wakako Tsuji, Shinsuke Sasada, Noriyuki Watanabe, Shoichi Tomita, Ayaka Koike-Shimo, Natsue Uehiro, Takahiro Tsukioki, Naomi Nagura, Hiroko Nogi, Kei Yamaguchi, Kazuhiko Yamagami, Akiko Ogiya, Hiromi Suetsugu, Yuki Nakamura, Hirotsugu Isaka, Tomohiro Shiraishi, Chikako Yamauchi, Hirohito Seki; Department of Breast Surgery, Shiga General Hospital, Moriyama Shiga, Japan; Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan; Department of Breast and Endocrine Surgery, Osaka International Cancer Institute, Osaka, Japan; Department of Plastic and Reconstruction Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan; Department of Breast and Endocrine Surgery, St. Marianna University School of Medicine, Kanagawa, Japan; Breast Surgical Oncology, Breast Oncology Center, Cancer Institute Hospital Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan; Department of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan; Department of Breast and Endocrine Surgery, Jikei University School of Medicine, Tokyo, Japan; Department of Breast Surgery, Saitama Medical Center, Saitama, Japan; Shinko Hospital, Kobe, Japan; Department of Breast Surgery, Japanese Red Cross Medical Center, Tokyo, Japan; Department of Breast Surgery, Kyoto City Hospital, Kyoto, Japan; Department of Breast Surgery, Kyoto University Hospital, Kyoto, Japan; Department of Breast Surgery Kyorin University School of Medicine, Tokyo, Japan; Department of Plastic Surgery, Kyorin University Scool of Medicine, Mitaka-Shi, Japan; Department of Radiation Oncology, Shiga General Hospital, Shiga, Japan; Department of Breast Surgery, Kyorin University School of Medicine, Tokyo, Japan

Background: A cornerstone of multidisciplinary treatment for breast cancer, breast reconstruction has recently been extended to high-risk patients with breast cancer who require post-mastectomy radiation therapy (PMRT). PMRT reduces the 10-year risk of locoregional recurrence; however, its association with postoperative complications remains unclear. This study aimed to evaluate the efficacy and safety of PMRT in patients with high-risk breast cancer who underwent breast reconstruction. **Methods:** This retrospective cohort study included patients with high-risk breast cancer who underwent immediate or delayed breast reconstruction after mastectomy between 2008 and 2018. High-risk patients were defined as those with positive axillary lymph nodes, clinical tumor size of >5 cm, chest wall invasion, or skin invasion. Patient data were collected from participating institutions and analyzed retrospectively. **Results:** Of the 1,138 patients, 427 (37.5%) underwent PMRT and 711 (62.5%) did not. The median age at surgery was 46 years (range, 23–76years), and the median follow-up period was 8 years. The number of patients meeting more than two high-risk criteria was 149 (23.9%) and 81 (11.4%) in the PMRT and non-PMRT cohorts, respectively. Breast reconstruction using silicone breast implants (SBI) was performed in 70% and 71.4% of patients in the PMRT and non-PMRT cohorts, respectively. The locoregional recurrence rates were 7.7% and 12.7% in the PMRT and non-PMRT cohorts, respectively (P=0.034). Multivariate analysis revealed that PMRT was an independent predictive factor for reducing locoregional recurrence (P<0.001) (Table 1). Complications occurred in 130 patients (30.4%) in the PMRT cohort and 168 (23.6%) in the non-PMRT cohort (P=0.016). The reoperation rates due to complications were 46 (35.4%) in the PMRT cohort and 61 (36.3%) in the non-PMRT cohort (P = 0.100). In the PMRT cohort, 62 patients (14.5%) experienced grade 2 radiation-induced dermatitis, and three patients (0.7%) developed grade 2 radiation-induced pneumonia. **Conclusions:** Although the incidence of adverse events was slightly higher in the PMRT cohort, the reoperation rates due to complications were comparable between the cohorts. PMRT is a safe and effective modality that provides substantial benefits for locoregional recurrence reduction in patients with high-risk breast cancer undergoing breast reconstruction. Research Sponsor: None.

Multivariate analysis for locoregional recurrence in patients with high-risk breast cancer who underwent breast reconstruction.

Factors	Hazard ratio	95% Confidence interval	P-value
PMRT	0.40	0.251-0.623	<0.001
Neoadjuvant therapy	3.43	2.29-5.12	<0.001
pT (>5 cm)	1.95	1.25-3.03	0.003
Surgical margin	1.96	1.01-3.81	0.047

Implications for sentinel lymph node biopsy (SLNB) omission in patients with early-stage node-negative HR+/HER2- breast cancer undergoing mastectomy.

Jennifer Hechao Chen, Kerollos Wanis, Mahdia Rahman, Ayushi Gianchandani, Isabelle Bedrosian, Nina Tamirisa, Min Yi, Akshara Singareeka Raghavendra, Puneet Singh, Mediget Teshome, Susie Sun, Henry Mark Kuerer, Kelly Hunt, Funda Meric-Bernstam, Taiwo Adesoye; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas at Austin, Austin, TX; Imperial College London School of Medicine, London, United Kingdom; University of Texas MD Anderson Cancer Center, Houston, TX; UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: The SOUND and INSEMA trials demonstrated non-inferiority of SLNB omission in HR+/HER2- early-stage breast cancer (BC) patients with negative axillary ultrasound (AUS) undergoing breast conserving therapy (BCT). However, it remains unclear if this approach may be applied to patients receiving mastectomy. We evaluated outcomes in a similar patient population receiving BCT versus mastectomy. **Methods:** Using an institutional database (2010-2023), we identified patients with cT1N0M0 HR+/HER2- unifocal invasive ductal carcinoma with negative AUS who underwent upfront BCT (breast conserving surgery + Radiation therapy [RT]) or mastectomy +/- RT. All patients underwent SLNB. Clinicopathologic and treatment characteristics were compared by surgery type as well as clinical outcomes. **Results:** Among 1,506 patients, median age was 59 years (IQR 51-67), and 80% were postmenopausal. BCT was performed in 78.2% (n=1,178) while 21.8% (n=328) underwent mastectomy. Patients who underwent mastectomy were more likely to be younger, premenopausal, with larger and higher grade tumors (Table). SLN positivity rate was 7.7% with no significant differences by surgery type (7.6% vs 8.2%, p=0.684). Only 4 (1.2%) and 2 (0.2%) patients had pN2 disease in the mastectomy and BCT cohorts, respectively. More patients undergoing mastectomy had axillary lymph node dissection compared to patients undergoing BCT (6.96% vs 0.3%, p<0.001). Among mastectomy patients, 10.1% received RT with higher rates in node-positive patients (52.9% vs 5.1%, p<0.0001). Similarly, chemotherapy use was higher among node-positive mastectomy patients (76.5% vs 22.5%, p=0.0001). Among SLN-positive postmenopausal patients with 21-gene recurrence score (RS) <25, chemotherapy use was 16.6% (2/12) after BCT and 0% (0/4) after mastectomy. When RS was >26, chemotherapy use was 60% (27/45) after BCT and 85.7% (12/14) after mastectomy. Median follow up was 25.3 months (IQR 13.2-58.9). There were 3 (0.2%) axillary recurrences with 2 recurrences after mastectomy (1 of whom received RT). There were 7 (0.46%) distant recurrences, with 2 following mastectomy. **Conclusions:** Among patients with cT1N0M0 HR+/HER2- invasive ductal carcinoma with negative AUS, positive SLNs were identified in 7.7% with only 0.46% having pN2 disease. Low axillary and distant recurrence rates were observed regardless of surgery type. However, given that nodal status impacts RT use among mastectomy patients, further research investigating omission of SLNB in this cohort is warranted. Research Sponsor: None.

	BCT (N, %)	TM (N, %)	p-value
Age (median, IQR)	60.8 (53.2-67.8)	55.7 (46.9-64.9)	<0.00001
Premenopausal	198 (16.8)	101 (30.8)	<0.00001
Grade 3	146 (16.7)	66 (22.8)	0.035
cT stage			0.002
T1mic	14 (1.2)	12 (3.7)	
T1a	56 (4.8)	19 (5.8)	
T1b	376 (31.9)	80 (24.4)	
T1c	732 (62.1)	217 (66.1)	
pT size (median, IQR)	1.4 (0.9-4)	1.35 (0.8-2.1)	0.022

Serial circulating tumor DNA (ctDNA) monitoring in early-stage, HR+/HER2-, invasive lobular carcinoma (ILC) of the breast and impact on clinical outcomes.

Julia Foldi, Samuel Rivero-Hinojosa, Sandro Satta, Sara L. Bristow, Ekaterina Kalashnikova, Steffi Oesterreich, Adrian V. Lee, Marija Balic, Angel A. Rodriguez, Minetta C. Liu; University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; Natera, Inc., Austin, TX; University of Pittsburgh, Pittsburgh, PA

Background: ILC accounts for ~10-15% of breast cancer (BC) cases in the US with difficult-to-diagnose patterns of metastasis. Loss of E-cadherin (*CDH1*) is the pathogenomic feature of ILC. Tumor-informed ctDNA assays detect molecular residual disease in patients who completed definitive therapy for early-stage BC. However, little is known about the ctDNA dynamics and its prognostic relevance in ILC specifically. Here, we assessed actionable genomic alterations and correlated ctDNA dynamics with clinical outcomes in patients with HR+/HER2- ILC. **Methods:** We utilized Natera's proprietary real-world database linked to commercially available claims data and commercial ctDNA testing via a clinically validated, personalized, tumor-informed mPCR-NGS ctDNA assay (Signatera, Natera, Inc.) to identify patients with early-stage, HR+/HER2- ILC. Tumors with *CDH1* truncated alterations from tumor whole exome sequencing were categorized as ILC. HR+/HER2- tumors were categorized using treatment regimens from insurance claim codes. Targetable alterations in *PIK3CA*, *AKT*, *PTEN*, *BRCA1*, *BRCA2*, *ESR1*, NF1, and *ERBB2* were assessed. ctDNA positivity rates and distant recurrence-free survival (DRFS) were evaluated using longitudinal ctDNA status (ctDNA + or -). The timing of ctDNA+ after primary BC surgery was divided into two categories: <2 years (y) and >2y. **Results:** 430 patients with early-stage HR+/HER2- ILC and ctDNA testing were identified. The most common targetable alterations co-mutated with *CDH1* were in *PIK3CA* (54.4%), *AKT1* (5.1%), *NF1* (4.9%), and *ERBB2* (4.6%). The first ctDNA test was performed on 258 (59.3%) and 172 (39.5%) patients within or after 2y surgery, respectively. Of 430 patients, 88 (20.2%) had >1 ctDNA+ test. A ctDNA+ result was reported in 31/258 (12%) and in 57/172 (33.1%) patients with testing within or after 2y surgery, respectively. Longitudinal ctDNA+ was associated with DRFS based on distant secondary malignant neoplasm claim codes. Among patients with a ctDNA- test within 2y, only 2.83% (6/212) presented a DRFS event compared to 48% (12/25) of ctDNA-+ cases (Odds ratio 31, p-value=1.42E-9). In patients with a ctDNA- test after 2y, only 2.06% (2/95) presented a DRFS event compared to 37.5% (9/24) of ctDNA+ cases (Odds ratio 27, p-value=4.92E-6). **Conclusions:** To our knowledge, this is the first large-scale analysis of the landscape of targetable genomic alterations and matching longitudinal ctDNA and outcomes in patients with early-stage, HR+/HER2- ILC. We find that *PIK3CA* is most frequently co-mutated with *CDH1*, and a comparison with the *CDH1* wildtype cohort will be presented. These data provide insights into the ability of ctDNA to detect recurrence earlier, including sites associated with challenges in the interpretation of imaging results in the early-stage ILC setting. Research Sponsor: None.

TROP2 overexpression as predictor of outcome in patients with early triple-negative breast cancer. Exploratory analysis from the GEICAM_CIBOMA trial.

Federico Gustavo Rojo Todo, Sara Lopez-Tarruella Cobo, Carlos H. Barrios, Laura Torrecillas Torres, Manuel Ruiz, Jose Bines, Jose Segalla, Jose A. García-Sáenz, Roberto Torres, Juan De La Haba, Francisco Ayala, Henry Leonidas Gomez, Antonio Llombart-Cussac, María Rodríguez de la Borbolla, Jesús Herranz, Raul Rincon, Rosalia Caballero, Begona Bermejo, Miguel Martin, Angel Guerrero; Hospital Universitario Fundación Jiménez Díaz; CIBERONC-ISCCIII; GEICAM Spanish Breast Cancer Group, Barcelona, Spain; Hospital General Universitario Gregorio Marañón; CIBERONC-ISCIII. GEICAM Spanish Breast Cancer Group, Madrid, Spain; Latin American Cooperative Oncology Group (LACOG) - Porto Alegre, Brazil Oncoclinicas Group, Porto Alegre, Brazil; ISSSTE CMN 20 De Noviembre. LACOG, Centro Urbano Presidente Alemán, DF, Mexico; Hospital Virgen del Rocio. GEICAM Breast Cancer Group, Seville, Spain; Instituto Nacional de Câncer; LACOG (Latin American Cooperative Oncology Group), Rio De Janeiro, Brazil; Hospital Amaral Carvalho,, San Paolo, Brazil; Instituto de Investigación Sanitaria Hospital Clinico San Carlos (IdISSC), Madrid, Spain; Instituto Nacional del Cáncer; LACOG (Latin American Cooperative Oncology Group), Santiago De Chile, Chile; Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC); University Reina Sofia Hospital, Universidad de Córdoba; GEICAM Spanish Breast Cancer Group, Córdoba, Spain; Hospital General Universitario Morales Meseguer; GEICAM Spanish Breast Cancer Group, Murcia, Spain; Instituto Nacional de Enfermedades Neoplásicas (INEN), Universidad Ricardo Palma; LACOG (Latin American Cooperative Oncology Group), Surquillo, Peru; Servicio Oncologia Medica, Hospital Arnau de Vilanova-Lliria, Valencia, Spain; Hospital Universitario Virgen de Valme. GEICAM, Spanish Breast Cancer Group, Sevilla, Spain; GEICAM Spanish Breast Cancer Group, Madrid, Spain; Hospital Clinico Universitario de Valencia, CIBERONC-ISCIII, GEICAM Spanish Breast Cancer Group, Valencia, Spain; Instituto de Investigación Sanitaria Gregorio Marañón, CIBERONC, Universidad Complutense de Madrid, GEICAM Breast Cancer Group, Madrid, Spain; Instituto Valenciano de Oncología (IVO). GEICAM Spanish Breast Cancer Group, Valencia, Spain

Background: Antibody-drug conjugates (ADCs) have emerged as a promising therapeutic strategy for triple-negative breast cancer (TNBC), a subtype with limited treatment options and poor prognosis. Understanding the biological and prognostic/predictive implications of biomarkers for these ADCs could help refine appropriate adjuvant treatment for high-risk TNBC. TROP2-targeted ADC sacituzumab govitecan has demonstrated significant improvements in progression-free and overall survival in clinical trials involving the advanced TNBC setting. We sought to explore the prognostic/predictive value of TROP2 expression by immunohistochemistry (IHC) in early TNBC patients (pts) from the GEICAM_CIBOMA trial (NCT00130533). **Methods:** We evaluated TROP2 expression by IHC using an anti-TROP2 monoclonal antibody (clone ERP20043, Abcam) in tumors from a subset of 70 TNBC pts included in the trial. These patients received either 6 months therapy with capecitabine (n=35) or observation (n=35) after receiving standard (neo)adjuvant chemotherapy (trial recruitment between 2006 and 2011). Semi-quantitative Histoscore (H-score) was estimated to consider the following TROP2 expression categories: H-score 0 to <100: TROP2 low; H-score 100-200: TROP2 medium; H-score ≥200: TROP2 high. Median TROP2 H-score was also explored for pts categorization. Cox regression models were assessed to predict DRFS (primary endpoint), DFS and OS (secondary endpoints). Multivariate models were adjusted for confounding factors, including histological grade, stage, chemotherapy regimen, and treatment. **Results:** The TROP2 H-score median value was 165. Medium/high TROP2 expression (H-score ≥100) was observed in 27 (77%) pts treated with capecitabine, and 25 (71%) in the observation group. Higher TROP2 expression was associated with higher histological grade (p=0.032). Medium/high TROP2 expression significantly associated with better DRFS (univariate analysis, HR=0.41; 95%CI 0.19-0.90; p=0.026; multivariate analysis, HR=0.24; 95%CI 0.10-0.60; p=0.002). This prognostic value was confirmed at DFS (multivariate analysis, HR=0.33; 95%CI 0.14-0.77; p=0.010) and OS (multivariate analysis, HR=0.29; 95%CI 0.11-0.76; p=0.011). High TROP2 expression by median value (H-score ≥165) was also associated with better clinical outcome (DRFS univariate analysis, HR=0.43; 95%CI 0.19-0.97; p=0.041; multivariate analysis, HR=0.44; 95%CI 0.19-1.02; p=0.057). TROP2 expression categorization did not demonstrate predictive value of capecitabine benefit (DRFS interaction with treatment, p=0.852). **Conclusions:** In this GEICAM_CIBOMA trial sub-study, TROP2 overexpression by IHC was observed in 74% of the analyzed cases and significantly associated with better clinical outcome in early TNBC pts, in terms of DRFS, DFS, and OS. Clinical trial information: NCT00130533. Research Sponsor: Sociedad Española de Oncologia Medica SEOM (SEOM/FECMA Grant 2022).

Disparities in demographics and outcomes of breast cancer in females undergoing mastectomy in rural vs. urban teaching centers.

Harkaran Shergill, Simran Dahiya, Abhinav Malik, Yara Alnaber, Dhruvkumar Gadhiya, Anaiya Singh, Saisree Reddy Adla Jala, Hemamalini Sakthivel, Kamleshun Ramphul, Suma Sri Chennapragada; Maulana Azad Medical College, New Delhi, India; Freelance Physician, New Delhi, India; The University of Jordan, Jordan, Jordan; St. Luke's University Health Network Anderson Campus, Easton, PA; LSU Health, Shreveport, LA; Mission Hospital, Asheville, NC; Department of Internal Medicine, Christus St. Michael Hospital, Texas, TX; Independent Researcher, Triolet, Mauritius

Background: Breast cancer (BC) sensitization, awareness, and increased screening have led to significant improvements in prevention, management, and survival rates over the last three decades. Recent reports have shown that the use of prophylactic and therapeutic mastectomy is on the rise. Previous studies have revealed healthcare disparities between rural (RC) and urban teaching centers (UTC), which may influence outcomes. In this retrospective study, we propose to explore the presence of similar disparities among BC patients undergoing mastectomy in rural hospitals vs. UTC. **Methods:** For this study, we extracted procedures of mastectomy among BC females through the hospitalization records of the National Inpatient Sample (NIS). We stratified our sample into procedures performed at RC and UTC. Procedural and postprocedural complications were compared through multivariable regression models. **Results:** We studied 75915 BC patients who underwent mastectomy between 2016 and 2022. Around 93.2% of our sample involved procedures performed at UTC, with 6.8% conducted at RC. Procedures at RC involved an older group(mean age 66.18 years vs. 57.19 years, $p < 0.01$), with a higher Charlson Comorbidity Index (CCI) score(mean score 3.79 vs. 3.53, $p < 0.01$). An estimated 91.6% of all procedures were performed on an elective basis(88.8% of rural and 91.9% of UTC, $p < 0.01$). Metastasis was present in 25.5% of all cases (25.4% of UTC and 25.8% of rural cases, $p = 0.591$). Mastectomies performed at RC had higher odds of bleeding (aOR 1.170, 95% CI 1.075-1.272, $p < 0.01$), sepsis (aOR 2.163, 95% CI 1.557-3.004, $p < 0.01$), postprocedural respiratory failure (PPRF) (aOR 2.667, 95% CI 1.479-4.808, $p < 0.01$), need for mechanical ventilation (MV) (aOR 2.732, 95% CI 1.845-4.046, $p < 0.01$), ischemic stroke (aOR 5.073, 95% CI 2.884-8.922, $p < 0.01$), and cardiac arrest (aOR 8.443, 95% CI 4.861-14.666, $p < 0.01$). Acute kidney injury events were similar (aOR 1.160, 95% CI 0.945-1.423, $p = 0.155$). The odds of all-cause death were higher among RC procedures (aOR 5.401, 95% CI 3.456-8.442, $p < 0.01$). **Conclusions:** The findings of this study have significant implications for healthcare policies. BC patients undergoing mastectomy in rural areas were significantly older and had a higher CCI score. Moreover, rural procedures reported higher risks of bleeding, sepsis, stroke, cardiac arrests, PPRF, MV use, and death. These results highlight the need for additional studies to establish the causes of these disparities, which may reflect the need for improving healthcare services in rural areas. Furthermore, encouraging RC to set up review protocols on their adverse events through Ishikawa diagrams may help identify probable healthcare inequities compared to UTC, which can then be remedied. This research has the potential to influence policy changes that could improve outcomes for rural BC patients. Research Sponsor: None.

Changes in the degree of satisfaction and quality of life in breast cancer patients who are candidates for breast conservation but opted for mastectomy: A single-center prospective study.

Changhoon Lee, Changjin Lim, Eunhye Kang, Ji-Jung Jung, Hong-Kyu Kim, Han-Byoel Lee, Wonshik Han, Hyeong-Gon Moon; Department of Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; Department of Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Seoul, South Korea

Background: Randomized trials have shown that breast-conserving surgery (BCS) and total mastectomy (TM) provide comparable survival outcomes for early breast cancer patients. Consequently, the choice of surgery is now considered a preference-based shared decision-making process. While studies have examined quality of life (QoL) in TM and BCS patients, it remains unclear how choosing TM over BCS affects postoperative QoL and satisfaction. This single-center prospective trial investigated the longitudinal impact of TM on QoL and satisfaction in the BCS-eligible patients who voluntarily opted for TM. **Methods:** We prospectively screened newly diagnosed breast cancer patients who are eligible for BCS based on the preoperative clinical assessment between Nov 2021 and June 2024 at Seoul National University Hospital. Patients were allowed to choose between TM and BCS through the shared decision-making process, and were enrolled according to the selected surgical method. A series of surveys were conducted using the BREAST-Q questionnaire and Decision Regret Scale (DRS) before and between 6-24months following surgery and then compared the results between two groups. **Results:** A total of 68 patients were enrolled; 28 opted for TM, and 40 underwent BCS, with two patients lost to follow-up in the TM group. The TM group was significantly older than the BCS group (57.92 vs. 51.43 years, p=0.015), and had larger preoperative tumor sizes (25.77mm vs. 17.88mm, p=0.001). Postoperatively, satisfaction with the breast (62.0 vs. 53.3, p=0.013) and physical well-being (chest) (83.9 vs. 77.5, p=0.004) decreased significantly. Satisfaction with the breast was significantly lower in the TM group compared to BCS (62.7 vs. 38.7, $p<0.001$). Psychosocial well-being (80.3 vs. 58.1, $p<0.001$), sexual well-being (55.3 vs. 24.2, $p<0.001$), and physical well-being (80.9 vs. 72.9, p=0.043) were all lower in the TM group. When comparing pre- and postoperative scores, the TM group experienced greater declines in breast satisfaction (-1.38 vs. -21.34, p=0.007), psychosocial well-being (5.71 vs. -8.40, p=0.004), and sexual well-being (1.55 vs. -17.83, p=0.004). The TM group also had significantly higher DRS scores (21.92 vs. 13.52, p=0.036), indicating greater regret. **Conclusions:** Our data demonstrates that patients who opted for TM over BCS for their breast cancer surgery may experience more profound decline in QoL and higher degree of regret after their surgery. These findings should be incorporated into the shared decision-making process when choosing optimal surgical treatment in early breast cancer patients who are eligible for BCS. Research Sponsor: None.

Bilateral mastectomy and breast cancer morality for invasive lobular carcinoma: A SEER-based study.

Richa Jaiswal, David Wai Lim, Vasily Giannakeas; Women's College Hospital, University of Toronto, Toronto, ON, Canada; Women's College Hospital, Toronto, ON, Canada

Background: Many women with unilateral breast cancer opt for bilateral mastectomy. While removing the unaffected contralateral breast lowers the risk of second primary cancers, there is no benefit on breast cancer mortality. Studies have not investigated whether this holds true for invasive lobular carcinoma (ILC). To estimate the 20-year risk of breast cancer mortality in women with stage I-III unilateral ILC and compare survival outcomes between unilateral lumpectomy, unilateral mastectomy and bilateral mastectomy. **Methods:** This retrospective cohort study used the Surveillance, Epidemiology, and End Results (SEER) database to identify women diagnosed with unilateral invasive lobular carcinoma (ILC) between 2000 and 2020. The cohort was followed for up to 20 years to assess contralateral breast cancer and breast cancer-specific survival. We estimated crude mortality rates, 20-year cumulative breast cancer mortality, and hazard ratios by surgical treatment group. Kaplan-Meier was used for cumulative risk, and Cox proportional hazards models for unadjusted and adjusted hazard ratios with 95% confidence intervals. P-values < 0.05 were considered significant. **Results:** We identified 58,861 women with unilateral ILC. Of which, 34,561 (59%) had lumpectomy, 18,894 (32%) had unilateral mastectomy, and 5406 (9.1%) had bilateral mastectomy. The mean age (in years) was 64 $\pm$11 for unilateral lumpectomy, 62 $\pm$13 for unilateral mastectomy, and 57$\pm$11 for bilateral mastectomy ($p < 0.0001$). The mean tumour size was smallest in the lumpectomy group (1.9$\pm$1.5 cm) compared with 3.6$\pm$ 3 cm in both unilateral and bilateral mastectomy groups ($p < 0.0001$). The 20-year cumulative invasive contralateral breast cancer risk was 7.3% for lumpectomy, 7.5% for unilateral mastectomy, and 0.3% for bilateral mastectomy. The 20-year cumulative breast cancer mortality was 13.4% in the lumpectomy group, 30.2% in unilateral mastectomy group and 24.3% in bilateral mastectomy group. However, after adjusting for demographic, clinical, and treatment variables, we observed no difference in breast cancer mortality rates among unilateral mastectomy patients versus lumpectomy patients (adjusted hazard ratio [aHR], 1.01; 95% CI, 0.94–1.08), and a statistically significant reduction in breast cancer mortality rates among bilateral mastectomy patients compared to lumpectomy patients (aHR, 0.90; 95% CI, 0.82–1.00; p value 0.04). **Conclusions:** In this cohort of invasive lobular breast cancer, bilateral mastectomy patients had a significantly lower risk of contralateral breast cancer and, after adjusting for differences in the surgical treatment groups, had a 10% lower rate of breast cancer mortality as compared to lumpectomy patients. Research Sponsor: None.

Evaluating the outcome of cardiovascular risk factors in breast cancer patients.

Michelle Koifman, Rabia Iqbal, Samridhi Sinha, Ana Maria Ramos Colon, Sobha Atluri, Surbhi Singh, Jayalekshmi Jayakumar, Mrunanjali Gaddam, Sujana Sanka, Siddharth Karipeneni, Tushar Kumar, Shreya Goyal, Maxim Shulimovich; The Brooklyn Hospital Center, Brooklyn, NY; University of Washington, Seattle, WA

Background: Breast cancer patients are at increased risk of cardiovascular disease due to factors such as treatment-related toxicity and shared comorbidities. This study analyzes demographics and outcomes of cardiovascular risk factors in hospitalized breast cancer patients using nationwide data to guide improved care strategies. **Methods:** We used the National Inpatient Sample Database (2016 to 2020) to perform the analysis. ICD-10 codes were used to make the primary diagnosis of patients with breast cancer admitted to hospitals, and secondary diagnosis of various cardiac risk factors. We used the chi-square test and the student's T-test to analyze categorical and continuous variables. Multivariable regression analysis was used to adjust for confounders and calculate adjusted odds ratio (aOR). Statistical significance was set at $p < 0.05$. **Results:** A total of 855394 patients were detected with primary diagnosis of breast cancer. Out of them, 11% had coronary artery disease (CAD), 13% had congestive heart failure (CHF), 6% had atrial fibrillation, 1% had ventricular arrhythmias and 0.06% had endocarditis. The prevalence of cardiac risk factors was mostly in older adults. The mean age of patients with CAD and CHF was 73 years, atrial fibrillation was 75 years, ventricular arrhythmias was 69 years and endocarditis was 71 years. The mortality was found to be higher in patients with cardiac risk factors as well. The patients with coronary artery disease had aOR of 1.9 (p-value 0.02), congestive heart failure had 1.3 (p-value <0.001), atrial fibrillation had aOR 1.1 (p-value 0.001), for ventricular arrhythmias was 3 (p-value <0.001) and for endocarditis was 1.4 (p-value 0.3). **Conclusions:** Breast cancer patients with cardiovascular risk factors experience significantly higher mortality rates compared to those without. These findings emphasize the need for early cardiovascular risk assessment and proactive management in breast cancer patients to improve outcomes and reduce complications. Research Sponsor: None.

Outcomes of cardiovascular disease in breast cancer patients.

Mortality	With Cardiac Risk Factors	Without Cardiac Risk Factors	Adjusted Odds Ratio	Adjusted Odds Ratio
Coronary Artery Disease	4.7%	4.5%	1.9	0.02
Congestive Heart Failure	6.6%	4.3%	1.3	<0.001
Atrial Fibrillation	5.5%	4.5%	1.1	0.01
Ventricular arrhythmias	12%	4.5%	3.0	<0.001
Endocarditis	6.6%	4.6%	1.4	0.3

Gene expression signatures (GES) derived from digital histology to predict pathologic complete response (pCR) to neoadjuvant chemotherapy (CT) in ISPY2 and other trial/real world cohorts.

Frederick Matthew Howard, Raghunath Babu, James M. Dolezal, Dezheng Huo, Alexander D. Borowsky, W. Fraser Fraser Symmans, Michael J. Campbell, Denise M. Wolf, Gillian L. Hirst, Sara Venters, Adam Asare, Sai Kanaparthi, Kim Blenman, Naing Lin Shan, Charles M. Perou, Laura Esserman, Laura van t Veer, Lajos Pusztai, Rita Nanda, Alexander T. Pearson, ISPY2 Investigators; University of Chicago, Chicago, IL; Geisinger Health System, Danville, PA; Department of Public Health Sciences, The University of Chicago, Chicago, IL; University of California, Davis, Davis, CA; The University of Texas MD Anderson Cancer Center, Alliance for Clinical Trials in Oncology, Houston, TX; University of California, San Francisco, San Francisco, CA; UCSF Comprehensive Cancer Center, San Francisco, CA; UCSF, San Francisco, CA; Quantum Leap Health Care Collaborative/UCSF, San Francisco, CA; Quantum Leap Health Care, San Francisco, CA; Yale University, New Haven, CT; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Surgery, University of California, San Francisco, San Francisco, CA; Department of Laboratory Medicine, University of California, San Francisco, San Francisco, CA; Yale Cancer Center, New Haven, CT; University of Chicago Medicine, Chicago, IL; Department of Medicine, University of Chicago, Chicago, IL

Background: GES predictive of response to therapy across multiple breast cancer subtypes are commercially available or in development. Deep learning models can predict GES from digital histology, and may serve as a lower-cost alternative immediately available at the time of biopsy. **Methods:** Transformer-based models trained to predict 38 distinct breast cancer signatures from pathology (all with Pearson correlation > 0.5 versus true GES) were previously developed using cases from The Cancer Genome Atlas. These models were applied to digital H&E from pre-treatment biopsies from HER2- cases treated with CT or CT + immunotherapy (IO) from the ISPY2 trial. The histology-derived GES most predictive of pCR in ISPY2 (as per area under the ROC curve [AUROC]) was tested in two external neoadjuvant cohorts - a subset of a trial from Yale of durvalumab + CT (NCT02489448) with TIL annotations, and patients receiving standard of care CT at University of Chicago. AUROC significance was assessed with 1000x bootstrapping, with Benjamini Hochberg correction applied in ISPY2 to account for testing multiple GES models. Tertiles of predicted expression calculated in ISPY2 defined groups with low, medium, and high likelihood of pCR; these cutoffs were tested in the external cohorts. **Results:** Accuracy for pCR prediction was tested in 578 patients from seven arms of ISPY2 – with breakdown by treatment and hormone receptor (HR) status shown in Table. A histology model for a GES defined by estrogen regulated genes (Oh et al, JCO 2006) – including proliferation, apoptosis, and interferon-response genes – predicted pCR with the highest AUROC (0.794) in ISPY2, and outperformed a logistic regression fit on grade, HR status, and tumor / nodal stage (AUROC 0.705, p for comparison 0.0001). Tertiles of predicted expression for this GES (computed in ISPY2) identified groups with low / high pCR rates which were robust to treatment, HR status, and consistent in validation cohorts (Table). This digital signature (AUROC 0.737) compared favorably to pathologist TIL annotation (AUROC 0.664) from the external Yale cohort. An explainability tool demonstrated that patterns of lymphocytic infiltrate and poor differentiation contributed to high signature predictions from histology. **Conclusions:** A digital histology-derived GES consistently identifies patients at low / high likelihood of pCR with neoadjuvant CT or CT + IO, and may improve treatment personalization. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Subgroup	n	AUROC	p	% pCR (low expression)	% pCR (mid expression)	% pCR (high expression)
ISPY2	579	0.794	2×10^{-28}	7.6	26.7	58.6
ISPY2, CT + IO	459	0.810	3×10^{-26}	8.0	28.2	64.1
ISPY2, CT only	120	0.726	0.001	6.4	20.0	36.8
ISPY2, HR-	239	0.704	4×10^{-7}	14.8	29.2	58.4
ISPY2, HR+	340	0.817	1×10^{-15}	6.5	24.8	59.0
UChicago HR-	151	0.746	3×10^{-7}	11.1	27.3	55.1
UChicago HR+	63	0.847	1×10^{-5}	5.5	12.0	70.0
Yale HR-	41	0.737	0.005	0.0	50.0	61.5

Neoadjuvant penpulimab combined with taxanes and carboplatin in triple-negative breast cancer: A single-arm, open-label, multi-center phase II clinical study (neoTAPPL).

Wenting Yan, Guozhi Zhang, Long Yuan, Dandan Ma, Yan Liang, Ye Zhang, Jing Liu, Qiyun Shi, Jun Jiang, Yi Zhang, Xiaowei Qi; Department of Breast and Thyroid Surgery, Southwest Hospital, Army Medical University; Key Laboratory of Minimally Invasive Surgery and Precision Treatment for Breast Cancer of Chongqing Municipal Health Commission, Chongqing, China; Department of Breast and Thyroid Surgery, Southwest Hospital, Army Medical University, Chongqing, China; Breast and Thyroid Surgery, Southwest Hospital, Army Medical University, Key Laboratory of Minimally Invasive Surgery and Precision Treatment for Breast Cancer of Chongqing Municipal Health Commission, Chongqing, China; Department of Breast and Thyroid Surgery, Southwest Hospital, Army Medical University; Department of Thoracic Surgery, the Eighth Medical Center of Chinese PLA General Hospital, Chongqing, China

Background: The integration of immunotherapy with neoadjuvant chemotherapy has been shown to enhance pathologic complete response (pCR) and survival outcomes in patients with triple-negative breast cancer (TNBC). Nonetheless, additional research is required to ascertain the optimal neoadjuvant regimen. Here we present a prospective phase II NeoTAPPL trial in which evaluated the efficacy and safety of penpulimab (anti-PD-1 antibody) in combination with taxanes and carboplatin for TNBC patients. **Methods:** In this open-label, multi-center phase II study, patients with untreated, histologically confirmed TNBC in stage II-III were enrolled. Patients received 6 cycles of neoadjuvant therapy with penpulimab (200 mg, d1, q3w) plus taxanes (docetaxel 75 mg/m^2 or nab-paclitaxel 260 mg/m^2, d1, q3w) and carboplatin (AUC=6, d1, q3w). Patients who either completed or discontinued the neoadjuvant treatment would undergo breast surgery. Adjuvant chemotherapy and immunotherapy were at the discretion of the treating physician, and radiation therapy was per standard of care. The primary endpoint was the rate of pCR based on the definition of ypT0/Tis ypN0. Secondary endpoints included residual cancer burden (RCB), event free survival (EFS), overall survival (OS), adverse events (AE), and immune response biomarkers. **Results:** 50 patients were enrolled, among which 37 patients received neoadjuvant treatment and underwent breast surgery. The median age was 51 years (range, 32-72). 33 (89.2%) patients had stage II breast cancer at diagnosis. 21 of the 37 patients achieved pCR (56.7%; 95% CI, 40.9%-71.3%), and 29 patients achieved RCB 0-1 (78.4%; 95% CI, 62.8%-88.6%). The ORR and DCR were 86.5% (95% CI, 72.0%-94.1%) and 91.9% (95% CI, 78.7%-97.2%), respectively. Subgroup analysis showed that 60.6% (20/33) patients with stage II had achieved pCR, 25% (1/4) patients with stage III reached this outcome. The pCR rate was 56.5% (13/23) in patients with negative lymph nodes, and 57.1% (8/14) in those with positive lymph nodes. Treatment-emergent adverse events (TEAEs) of any grade occurred in all 37 pts, in which 20 (54.1%) were grade ≥3. The most common grade ≥3 TEAEs were neutropenia (43.2%), leukopenia (24.3%), anemia (21.6%), and thrombocytopenia (18.9%). 15 patients (40.5%) experienced immune related adverse events (irAEs), all of which were hypothyroidism. **Conclusions:** In this trial, we demonstrated that an anthracycline-free neoadjuvant regimen consisting of penpulimab, carboplatin and taxanes in TNBC showed promising antitumor efficacy and manageable safety profile. The study is still ongoing. Clinical trial information: ChiCTR2300071925. Research Sponsor: Development Center for Medical Science & Technology National Health Commission of the People's Republic of China WKZX2023CX010002.

Neoadjuvant low-dose carboplatin and docetaxel in combination with toripalimab for early or locally advanced triple-negative breast cancer (NeoTOP): A single-arm phase 2 trial.

Jun Tang, Ning Li, Tian Du, Yan Wang, Hao Wu, Gehao Liang, Zixuan Zhao, Xinhua Xie, Jin Wang, Yanan Kong, Peng Liu, Zeyu Shuang; Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Neoadjuvant immunotherapy combined with chemotherapy improves the rate of pathological complete response (pCR) and prognosis of triple-negative breast cancer (TNBC). However, chemo-immunotherapy treatment is frequently associated with adverse events, resulting in dose reduction and delays. Approaches to deescalate chemo-immunotherapy without compromising outcomes for TNBC patients are needed. Evidence suggests that low-dose carboplatin potentiates the anti-tumor effect of PD-1 inhibitors through many mechanisms. The NeoTOP trial aimed to assess the efficacy and safety of low-dose carboplatin and docetaxel in combination with toripalimab as neoadjuvant therapy for early or locally advanced TNBC. **Methods:** This is a single-arm, open-label, phase 2 trial. Patients with untreated stage IIA-IIIC TNBC were enrolled. Eligible patients received carboplatin (AUC=4), docetaxel (75 mg/m^2) and toripalimab (240 mg), every 21 days for a total of 6 cycles. Toripalimab (240mg, every 3 weeks) continued post-operatively for a further 11 cycles. The primary endpoint was the rate of pCR (ypT0/Tis ypN0). The secondary endpoints included safety, objective response rate (ORR), residual cancer burden (RCB) rate, event-free survival and overall survival. This study used Simon's two-stage design. **Results:** From January 2022 to September 2024, 51 patients were enrolled. Among them, 29 patients (56.9%) had stage II, and 22 (43.1%) had stage III. Four patients prematurely discontinued study treatment due to adverse events (three patients) or tumor progression (one patient), including two discontinued toripalimab only and two discontinued both toripalimab and chemotherapy. One of the four patients who discontinued treatment achieved a pCR when proceeding to surgery. One patient achieved clinical CR after neoadjuvant therapy and refused to receive surgery. After surgery, pCR in both breast and lymph nodes was achieved in 29 of 50 patients, resulting in a pCR rate of 58.0%. For all the 51 patients who received at least one dose of neoadjuvant therapy, the ORR was 90.2%. The proportions of RCB-0, RCB-1, RCB-2, and RCB-3 were 58%, 12%, 22%, and 8%. All 51 (100%) patients reported any grade of treatment-related adverse events (TRAEs). Grade ≥3 TRAEs occurred in 23 (45.1%) patients. Serious adverse events were reported in 5 (9.8%) patients. The regimen was well tolerated, and no new toxicity signals were noted. **Conclusions:** The combination of low-dose carboplatin, docetaxel, and toripalimab showed promising efficacy and manageable safety, suggesting the feasibility of this regimen in the neoadjuvant setting for TNBC. Further randomized phase III trials are warranted. Clinical trial information: NCT06618014. Research Sponsor: None.

Post-treatment MRI to predict pathological complete response in triple-negative breast cancer following neoadjuvant chemoimmunotherapy.

Toulsie Ramtohul, Derek Lollivier, Justine Spriet, Maxime Jin, Lounes Djerroudi, Thomas Gaillard, Claire Bonneau, Delphine Loirat, Diana Bello Roufai, Youlia M. Kirova, Pierre Loap, Caroline Malhaire, Anne Vincent-Salomon, Francois Clement Bidard, Anne Tardivon, Audrey Mailliez, Lauren Wallaert, Luc Ceugnart, Caroline Nhy, Luc Cabel; Institut Curie, Paris, Ile de France, France; Institut Curie, 26 Rue D'ulm, Ile de France, France; Oscar Lambret, Lille, France; Institut Curie, Paris and St Cloud, France; Institut Curie, Paris, France; Institut Curie, Medical Oncology Department and D3i, Paris, France; Institut Curie, Saint Cloud, France; Institute Curie, Department of Radiation Oncology, Paris, France; Institute Curie, Paris, France; Institut Curie and University of Versailles Saint-Quentin-en-Yvelines-Paris-Saclay University, Paris, France; Oscar Lambret Comprehensive Cancer Center, Lille, France; Institut Godinot, Reims, France; Institut Curie, Paris and Saint-Cloud, France

Background: Neoadjuvant chemoimmunotherapy (NACI) has significantly improved pathological complete response (pCR) rates in early-stage triple-negative breast cancer (TNBC). However, the predictive accuracy of post-treatment MRI for pCR remains unexplored. Our objective was to assess the performance of post-treatment MRI in predicting pCR in TNBC patients treated with NACI. **Methods:** In this prospective, multicenter study (August 2021–June 2024), women with early-stage TNBC were recruited from three centers. Post-treatment dynamic contrast-enhanced (DCE) MRI data were analyzed across multiple vendors. The predictive performance of radiological complete response (rCR) on MRI for pCR was evaluated using the area under the curve (AUC) of receiver operating characteristics. A multivariable logistic regression model incorporating rCR, nodal involvement, and Ki-67 levels was developed and validated. For patients with residual enhancement, a radiomics score was generated using first-order and shape-based features. **Results:** The study included 175 women in a training set from centers #1 (mean age 49 ± 11 years) and 84 in an external test set from centers #2 and #3 (mean age 52 ± 12 years). MRI rCR achieved an AUC of 0.83 (95% CI: 0.75–0.92) for pCR prediction. A combined model with rCR, nodal status, and Ki-67 levels yielded an AUC of 0.88 (95% CI: 0.81–0.96) in the test set. Among patients with rCR, no nodal involvement, and Ki-67 >30%, the false-positive rate was 3.6% and 3.5% in the training and test sets, respectively, with all cases limited to Residual Cancer Burden-I. For patients with residual enhancement, a model incorporating a radiomics score and lesion count achieved an AUC of 0.80 (95% CI: 0.69–0.90). **Conclusions:** Post-treatment MRI effectively predicts pCR in early-stage TNBC after NACI, suggesting its potential role in identifying candidates for breast cancer surgery omission trials. Research Sponsor: Institut Curie.

Accuracy of rCR for predicting pCR.

Set	Subgroup	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	F1 score (%)
Training	N0 and Ki-67>30%	81 (54/67) [71,90]	86 (12/14) [67, 99]	96 (54/56) [92, 99]	48 (12/25) [28, 68]	88
External test	N0 and Ki-67>30%	82 (28/34) [70, 95]	92 (11/12) [76, 99]	97 (28/29) [90, 99]	65 (11/17) [42, 87]	89

Note-Unless otherwise specified, the data are presented as percentages, with the numbers of participants in parentheses and 95% CIs in brackets; pCR = pathological complete response; PPV = positive predictive value; NPV = negative predictive value.

Efficacy and safety of neoadjuvant TQB2102 in women with locally advanced or early HER2-positive breast cancer: A randomized, open-label, multi-centre phase 2 trial.

Junjie Li, Qingyuan Zhang, Xiaohua Zeng, Wenjuan Zhang, Li Chen, Jiong Wu, Guangyu Liu, Zhihong Wang, Xiaobo Hu, Zhiming Shao; Shanghai Cancer Center, Shanghai, China; Harbin Medical University Cancer Hospital, Harbin, China; Chongqing University Cancer Hospital, Chonqqing, China; Fudan University Shanghai Cancer Center, Shanghai, China; Cancer Center, Fudan University, Shanghai, China; Fudan University Shanghai Cancer Center and Key Laboratory of Breast Cancer, Shanghai Medical College, Fudan University, Shanghai, China; The Affiliated Cancer Hospital of Guizhou Medical University, Guiyang, China; Breast Surgical Department 1, Hunan Cancer Hospital, Changsha, Changsha, China; Fudan University Shanghai Cancer Center/Cancer Institute, Shanghai, China

Background: Standard neoadjuvant regimens for HER2-positive breast cancer include trastuzumab and pertuzumab combined with chemotherapy, and the efficacy and safety of third-generation HER2-direted antibody-drug conjugate (ADC) is unknown. TQB2102 is an anti-HER2 antibody-drug conjugate that targets two non-overlapping epitopes of HER2 (ECD2 and ECD4). It consists of a humanized HER2 IgG1 bispecific antibody conjugated to a topoisomerase I inhibitor via a cleavable linker, and the DAR value is 6. **Methods:** This open-label, randomized, multi-centre phase 2 study enrolled HER2-positive patients aged 18-75 years with stage II—III disease. Patients were randomly assigned to receive neoadjuvant TQB2102 6mg/kg every 3 weeks for 6 cycles or for 8 cycles. The primary endpoint was pathological complete response (pCR). Safety was analysed in patients who received at least one dose of study medication. **Results:** Between 05 February 2024 and 24 Sep 2024, we randomly assigned 52 patients to neoadjuvant TQB2102 6 cycles (Arm A, n=26), 8 cycles (Arm B, n=26). The baseline characteristics were well balanced; approximately 50% of the patients were hormone receptor (HR)-positive, and 63% of the patients were stage III. The pCR rate was 57.7% in Arm A (95%CI 36.9%-76.7%), 76.9% in TQB2102 Arm B (95%CI 56.3%-91%). In patients with HR positive disease, the pCR rate was 53.8% in Arm A and 58.3% in Arm B; in patients with HR negative disease, the pCR rate was 61.5% and 92.9%. Grade 3 or higher adverse events occurred 23.1% in Arm A, and 30.8% in 8 Arm B, 7.69% with increased alanine aminotransferase and aspartate transferase. Dose reduction rate and discontinuation was 3.8% and 19.2% in Arm A, 3.8% and 23.1% in Arm B, and no treatment-related deaths occurred. **Conclusions:** This is the first study to report the efficacy and safety of third-generation duel-HER2-directed ADC in the neoadjuvant setting for HER2-positive breast cancer. TQB2102 is highly efficient and well tolerated. Clinical trial information: NCT06198751. Research Sponsor: None.

pCR in All patients and by HR status.

	6 cycles	8 cycles
All	57.7%	76.9%
HR positive	53.8%	58.3%
HR negative	61.5%	92.9%

Early on-treatment (on-Rx) tumor volume reduction (TVR) to predict response to the KEYNOTE-522 (KN-522) regimen in early stage triple negative breast cancer (TNBC).

Clinton Yam, Miral Patel, Jia Sun, Beatriz E. Adrada, Akshara Singareeka Raghavendra, Jennifer Keating Litton, Jason A. Mouabbi, Adaeze Nwosu Iheme, Sadia Saleem, Giancarlo Moscol, Matthew David Wright, Aman Buzdar, Rashmi Krishna Murthy, Anil Korkut, Vicente Valero, Debasish Tripathy, Tanya W. Moseley, Peng Wei, Lei Huo, Gaiane M. Rauch; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Monitoring clinical response by breast ultrasound (US) during neoadjuvant therapy is considered standard of care. We previously demonstrated that suboptimal on-Rx TVR after neoadjuvant doxorubicin and cyclophosphamide (AC) predicts non-pCR after sequential taxane-based chemo. However, it is unknown if on-Rx TVR has the similar predictive value in pts receiving the KN-522 chemo-immunotherapy regimen. **Methods:** Pts with early stage TNBC planned to receive the KN-522 regimen were enrolled on the prospective ARTEMIS trial (NCT02276443). Breast US was performed at baseline and after 6 weeks of paclitaxel + carboplatin + pembrolizumab. TVR was defined as the percent reduction of tumor volumes calculated using 3 perpendicular measurements of the index breast lesion. Pathological complete response (pCR) was defined as ypT0/isN0. Logistic regression was used to examine associations between covariates and pCR. Receiver operating characteristic (ROC) analyses were utilized to assess the predictive value of TVR and determine an optimal TVR threshold. **Results:** 150 pts were included. Clinicopathological characteristics are described in Table 1. The pCR rate was 63%. In uni- and multi-variable analyses, TVR was the only covariate to demonstrate statistically significant association with pCR (aOR:1.9 per 10% TVR, $p<0.001$). In ROC analyses, the area under the ROC curve (AUC-ROC) was 0.74 (95% CI: 0.66-0.82). TVR>50%, selected based on the Youden index, predicted pCR with the following performance characteristics: positive predictive value: 73%; negative predictive value: 79%; sensitivity: 94%; specificity: 41%. **Conclusions:** Early on-Rx TVR by breast US outperforms clinicopathological covariates in the prediction of pCR in pts with TNBC receiving the KN-522 regimen and should be leveraged for risk stratification and design of response-adapted neoadjuvant clinical trials for pts with TNBC. Clinical trial information: NCT022766443. Research Sponsor: Conquer Cancer, the ASCO Foundation; 12238.

	pCR (n=95)	Non-pCR (n=55)	Odds ratio (OR)	p value (univariable)	Adjusted OR (aOR)	p value (multivariable)
Median 6w TVR – % (interquartile range [IQR])	84 (72-90)	69 (38-83)	1.5	**<0.001**	1.9	**<0.001**
Median age – years (IQR)	51 (40-61)	51 (43-64)	0.98	0.25	1.0	0.73
	N (%)					
Ethnicity						
White	50 (53)	33 (60)	1		1	
Black	15 (6)	10 (18)	1.1	0.84	0.9	0.91
Hispanic/Latino	25 (26)	6 (11)	2.4	0.08	1.9	0.32
Asian	5 (5)	6 (11)	0.6	0.36	0.2	0.12
T stage						
T1/2	79 (83)	46 (84)	1		1	
T3/4	16 (17)	9 (16)	1.0	0.94	1.2	0.77
Nodal status						
Positive	31 (33)	24 (44)	1		1	
Negative	64 (67)	31 (56)	1.60	0.18	1.4	0.55
Germline *BRCA* status						
Mutant	8 (8)	2 (3)	1		1	
Wild Type	84 (88)	51 (93)	0.41	0.27	0.3	0.31
Unknown	3 (3)	2 (4)				
Histology						
Ductal	87 (92)	48 (87)	1		1	
Metaplastic	3 (3)	5 (9)	0.33	0.14	0.3	0.26
Other	4 (4)	2 (4)	1.1	0.91	2.0	0.59
Unknown	1 (1)	0				
Histologic grade						
2	13 (14)	14 (25)	1		1	
3	81 (85)	41 (75)	2.1	0.08	2.0	0.59
Unknown	1 (1)	0				
Ki67						
≤35%	5 (5)	8 (15)	1		1	
>35%	67 (71)	38 (69)	2.82	0.09	4.6	0.09
Unknown	23 (24)	9 (16)				

Use of artificial intelligence (AI)–powered spatial analysis to predict pathologic complete response (pCR) in HR+ HER2- breast cancer (BC) patients treated with neoadjuvant chemotherapy (NAC).

Dae-Won Lee, Soyean Kwon, Jiwon Koh, Woochan Hwang, Jimin Moon, Seongho Keum, Chan-Young Ock, Changhee Park, Han Suk Ryu, Hong-Kyu Kim, Han-Byoel Lee, Hyeong-Gon Moon, Wonshik Han, Kyung-Hun Lee, Seock-Ah Im; Seoul National University Hospital, Seoul, South Korea; Lunit Inc., Seoul, South Korea; Lunit, Seoul, South Korea; Department of Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Seoul, South Korea; Department of Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea; Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul National University, Seoul, N/S, South Korea; Seoul National University College of Medicine, Cancer Research Institute, Seoul National University, Seoul, South Korea

Background: In the KEYNOTE(KN)-756 study, adding pembrolizumab to NAC increased pCR in high-risk HR+ HER2- BC. There is an unmet need to discover who will benefit from adding immune checkpoint inhibitors (ICIs). This study aims to investigate the role of pCR in HR+ HER2- BC and to identify whether AI-powered TIL analysis could predict pCR in patients treated with NAC without ICIs. **Methods:** This is a single-center study conducted in Seoul National University Hospital, Korea. H&E whole-slide images (WSIs) of archival breast tumor tissues at diagnosis were analyzed by Lunit SCOPE IO, an AI-powered spatial TIL analyzer. Tumors with a high proportion of area with high intratumoral TIL were classified as immune-inflamed, those with a high proportion of area with low intratumoral but high stromal TIL as immune-excluded, and the remaining as immune-desert. Recurrence risk prediction AI model was trained and validated on independent 1,552 H&E WSIs to predict OncotypeDx score. Patients with histologic grade 3 and tumor size ≥2 cm with node-positive status, or tumor size ≥5 cm were classified as those eligible for KN-756 study. **Results:** A total of 425 BC patients who were treated with NAC without ICIs between January 2015 and October 2018 were included. The median age was 47 (range 24-80), 67.1% had stage III disease, 93.6% had node-positive disease, and 23.5% were eligible for KN-756 study. pCR was achieved in 57 (13.4%) patients and was higher in patients with whom were eligible for KN-756 study (20% vs 11.4%, p= 0.041). Patients who achieved pCR had better 5-year event free survival (EFS, 92.9% vs 77.7%, p= 0.010). AI-powered spatial analysis was performed in 340 patients. There were 125 (36.8%) with immune-desert tumor, 138 (40.6%) with immune-excluded tumor, and 77 (22.6%) with immune-inflamed tumor. Patients with inflamed tumor had higher pCR rate compared to those with immune-excluded or immune-desert in the whole population (Table) and in patients not eligible for KN-756 study (25.6% vs 11.9% vs 5.7%, p = 0.013). Patients with inflamed or excluded tumor had better EFS compared to desert group (80.9% vs 71.2%, p = 0.0275). In addition, recurrence prediction model showed that those who were predicted to have OncotypeDx score ≥ 26 had higher pCR rate (18.2% vs 4.3%, p= 0.002). **Conclusions:** Achieving pCR was associated with favorable EFS in HR+ HER2- patients treated with NAC. Patients with immunogenic tumor microenvironment had higher pCR rate and better EFS. Investigating the role of immune checkpoint inhibitors according to tumor microenvironment may be promising.
Research Sponsor: None.

	Desert (N=125)	Excluded (N=138)	Inflamed (N=77)	p-value
pCR	8 (6.4%)	18 (13.0%)	23 (29.9%)	<0.001
Stage III	85 (68.0%)	88 (63.8%)	51 (66.2%)	0.32
LN +	114 (91.2%)	132 (95.7%)	72 (93.5%)	0.34
HG 3	21 (16.8%)	31 (22.5%)	38 (49.4%)	<0.001
KN-756 eligible	20 (16.0%)	29 (21.0%)	34 (44.2%)	<0.001

SHR-A1811 as neoadjuvant therapy for HR-positive, HER2-low breast cancer: A single-arm, phase II clinical study.

Zhenzhen Liu, Dechuang Jiao, Jiujun Zhu, Chengzheng Wang, Zhenduo Lu, Xianfu Sun, Xiuchun Chen, Min Yan, Lianfang Li, Jianghua Qiao, Jianfei Wang; Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; Henan Breast Cancer Centre, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background: Human Epidermal Growth Factor Receptor (HER2)-low breast cancer accounts for approximately 55% of all breast cancer cases, and it is more prevalent in hormone receptor-positive (HR+) breast cancer. Recent breakthroughs in anti-HER2 antibody-drug conjugates (ADCs) have revolutionized the therapeutic landscape for breast cancer treatment, particularly for HER2-low breast cancer. SHR-A1811 is an anti-HER2 ADC and has demonstrated acceptable tolerability and encouraging antitumor activity in HER2-low advanced breast cancer. Therefore, we conducted the phase 2 trial to investigate the efficacy and safety of SHR-A1811 as a neoadjuvant treatment in patients with HR+/HER2-low breast cancer. **Methods:** This is an open-label, two-stage, phase II clinical trial. In the first stage, 35 participants will be enrolled, and if at least 18 participants achieve an objective response rate (ORR), the trial will proceed to the second stage, enrolling an additional 31 subjects. Eligible patients are women aged 18-70 years; treatment-naïve; histologically confirmed invasive breast cancer stage cT2-3/N0-2M0; HR+/HER2-low, and the expression of Ki-67 exceeds 14%. Eligible patients receive SHR-A1811 as neoadjuvant therapy. SHR-A1811 is administered intravenously at a dose of 6.4 mg/kg once every three weeks for a total of eight cycles. The primary endpoint is ORR. Secondary endpoints include safety, residual cancer burden (RCB) 0-1, and pathologic complete response (pCR). **Results:** A total of 66 patients enrolled in this study. The median age was 49 years, with 84.8% (56/66) aged ≥ 40 years. Of all patients, 66.7% (44/66) were premenopausal, 66.7% (44/66) had node-positive disease, 86.4% (57/66) had stage II, 13.6% (9/66) had stage IIIA, and 74.2% (49/66) had HER2 expression of IHC 2+/FISH-, while 25.8% (17/66) were IHC 1+. In the modified intention-to-treat population (mITT, patients who received at least one cycle of study treatment and at least one post-baseline MRI assessment), 81.5% (53/65) of patients achieved an ORR, and two patients achieved a pathological complete response, resulting in a pCR rate of 3.1% (2/65). Additionally, the proportion of patients with RCB 0 or RCB I was 9.3% (6/65). 97% (64/66) of patients experienced at least one treatment-related adverse event (TRAE). Grade 3 or higher TRAEs occurred in 39.4% (26/66) of patients, with the most prevalent being neutropenia (27.3%, 18/66), leukopenia (16.7%, 11/66), and anemia (13.6%, 9/66). No interstitial lung disease (ILD) and treatment-related deaths were reported. **Conclusions:** As a neoadjuvant treatment, SHR-A1811 achieves a significant improvement in ORR and brings both pCR and RCB 0-I benefits in patients with HR+/HER2-low breast cancer. These outcomes support further exploration of SHR-A1811 in this patient population. Clinical trial information: NCT05911958. Research Sponsor: None.

Computational pathology-informed immune biomarker for trastuzumab benefit in HER2+ breast cancer: Validation in NSABP B-41 clinical trial.

Satvika Bharadwaj, Germán Corredor, Sebastian R. Medina, Sahar Almahfouz Nasser, Tilak Pathak, Pingfu Fu, Sunil S. Badve, Anant Madabhushi; Wallace H. Coulter Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, GA; Emory University, Atlanta, GA; Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, Atlanta, GA; Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, OH; Emory University School of Medicine, Atlanta, GA

Background: Trastuzumab, a targeted therapy, considerably improves survival outcomes in HER2+ breast cancer patients (pts). However, identifying pts most likely to benefit from trastuzumab and those who might avoid it, remains a challenge. Data from the NSABP B-41 randomized clinical trial which evaluated lapatinib-containing regimens against trastuzumab, each given concurrently with chemotherapy in the neoadjuvant setting, holds potential for computational pathology to uncover treatment response patterns. In this study, we present DeSTIL (Density and Spatial Architecture of Tumor Infiltrating Lymphocytes [TILs]), a predictive biomarker derived from Hematoxylin and Eosin (H&E) images, to evaluate the immune microenvironment and identify HER2+ pts that benefit from trastuzumab. **Methods:** Digitized and quality-controlled H&E slides from HER2+ pts in The Cancer Genome Atlas (TCGA; n=175) were used to develop DeSTIL and was independently validated on NSABP B-41 (n=221) pts. Following nuclei segmentation, TILs were identified, and their density and spatial architecture features were quantified. A lasso-regularized Cox proportional hazards model was used to select features and compute a continuous DeSTIL risk score, which was then dichotomized at the median into DeSTIL-positive and DeSTIL-negative groups in the training set. The locked model was validated on NSABP B-41 to predict event-free survival (EFS) in pts receiving neoadjuvant chemotherapy with trastuzumab, lapatinib, or a combination of trastuzumab and lapatinib. Within the DeSTIL-stratified groups, treatment-specific progression was analyzed to evaluate the potential benefit of trastuzumab-based therapies. **Results:** Among 221 HER2+ pts from the NSABP B-41 trial, 61 pts (28%) were classified as DeSTIL-positive and 160 (72%) as DeSTIL-negative, based on the median training threshold. DeSTIL-positive pts demonstrated a significant benefit with the trastuzumab-alone arm compared to the combination regimen (HR=0.09, 95% CI=0.01-0.77, p=0.0061) (interaction term p=0.024) and against lapatinib plus the combination regimen (HR = 0.11, 95% CI = 0.01-0.9, p = 0.01) (interaction term p = 0.05). In contrast, no significant benefit was observed in DeSTIL-negative pts when comparing trastuzumab to the combination regimen (HR=1.33, 95% CI=0.47-3.75, p=0.5840) or to lapatinib plus the combination regimen (HR=1.01, 95% CI=0.45-2.30, p=0.9701). **Conclusions:** DeSTIL, a biomarker based on the density and spatial architecture of TILs, may help identify HER2+ pts more likely to benefit from trastuzumab. Further validation through prospective trials is warranted. Additionally, this biomarker offers a practical framework for comparing HER2-targeted therapies, with the potential to minimize unnecessary treatments, reducing associated cardiotoxicity and financial burden. Research Sponsor: U.S. National Institutes of Health; R01CA268287A1, R01CA26820701A1, R01CA249992-01A1, R01CA202752-01A, 1R43 EB028736-011, R01CA208236-01A1, R01CA216579-01A1, R01CA220581-01A1, R01CA25 7612-01A1, 1U01CA239055-01, 1U01CA248226-01, 1U54CA254566-01, 1R01HL15127701A1, R01HL15807101A1, W81XWH-19-1-0668.; sponsored research agreements from Bristol Myers-Squibb, Boehringer-Ingelheim, Eli-Lilly and Astrazeneca.

Exploration of the new classification of hormone receptor-positive breast cancer: Based on the genomic landscape of 2111 early to mid-stage Asian patients.

Cuiyun Zhang, Qin Li, Tingjie Wang, Chi Yan, Junnan Feng, Jiuzhou Zhao, Pengfei Ren, Huanhuan Wang, Jie Ma, Bing Wei; The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China; Geneplus-Beijing Institute, Beijing, China; The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, Zhengzhou, China

Background: The molecular classification of breast cancer using omics data has led to varied prognoses; however, with the increase of targeted therapy options, current classifications may not adequately guide treatment strategies. **Methods:** This study analyzed 2,111 HR^+ Asian breast cancer patients using next-generation sequencing of 1,021 genes for targeted therapy classification. **Results:** The majority of patients had invasive ductal carcinoma (67.0%) and were at stages 0 to III (89.6%), with 29.7% being HER2 positive. Variations were widespread, with SNV/Indel mutations found in 99.4% and CNV detected in 44.6% of the samples, respectively. The key signaling pathways, including PAM, RTK/RAS, DDR, and TP53, each showed a prevalence of 50% or higher and co-existed. Interestingly, 76.1% of patients had actionable mutations, predominantly in the PAM (54.8%), RTK/RAS (22.2%), and DDR (11.7%) pathways, which were found to be mutually exclusive ($p < 0.01$). Subsequently, Patients were categorized into two groups, C and M, based on CNV presence, revealing significant differences in the prevalence of actionable genes and pathways. The C group stood out for its high prevalence of PAM (43.7%) and HER2 (38.4%), while the M group exhibited prominence in PAM (64.1%) and DDR (15.0%). Notably, responses to neoadjuvant treatment (NAT) varied as well, with higher pCR rates (51.9% vs. 22.1%, $p < 0.001$) for the combination of chemotherapy and HER2-targeted therapy (Chemo + HP) and lower pCR rates (6.0% vs. 15.2%, $p = 0.017$) for chemotherapy alone (Chemo) observed in the C group compared to those in the M group. Additionally, subsequent subgroup analyses based on actionable signaling pathways between the two groups showed similar patterns, with the C-$HER2^+$ subgroup having the highest pCR rate (64.1%) for Chemo + HP and M-PAM^--DDR^- subgroup showing the highest pCR rate (21.5%) for Chemo. Besides, clinical characteristics among the various groups and subgroups showed differences. For instance, the M-PAM^--DDR^+ subgroup had an earlier onset ($p < 0.001$) and included more premenopausal individuals ($p=0.034$), along with higher ER and PR expression ($p < 0.001$) and lower Ki-67 levels ($p < 0.001$). Multivariate logistic regression analysis identified HER2 amplification, PR negativity, and TP53 mutation as independent risk factors for the efficacy of Chemo + HP NAT. **Conclusions:** The study suggested that classifying breast cancer patients based on CNVs and actionable pathways may enhance neoadjuvant pCR rates. This underscored the potential implications for expanding neoadjuvant treatment strategies and facilitating tailored precision treatment options based on distinct molecular profiles and therapy responses. Research Sponsor: None.

Analysis of event-free survival (EFS) of stromal tumor infiltrating lymphocytes (sTILs), PD-L1 expression, and their early dynamics in the NeoTRIP trial.

Giampaolo Bianchini, Giulia Viale, Matteo Dugo, Chiun-Sheng Huang, Daniel Egle, Maurizio Callari, Hamid Ali, Begoña Bermejo, Claudio Zamagni, Xiao Qian Wang, Marc Thill, Antonio Anton, Stefania Russo, Eva Maria Ciruelos, Richard Greil, Vladimir Semiglazov, Marco Colleoni, Lucia Del Mastro, Giuseppe Viale, Luca Gianni; Università Vita-Salute San Raffaele, Milan, Italy; IRCCS Ospedale San Raffaele, Milan, Italy; National Taiwan University Hospital, College of Medicine, National Taiwan University and Taiwan Breast Cancer Consortium, Taipei, Taiwan; Medical University Innsbruck, Innsbruck, Austria; Fondazione Michelangelo, Milan, Italy; CRUK Cambridge Institute, University of Cambridge, Department of Histopathology, Addenbrookes Hospital, Cambridge, United Kingdom; Medical Oncology, Hospital Clínico Universitario de Valencia, Biomedical Research Institute INCLIVA, Valencia, Spain; IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; CRUK Cambridge Institute, University of Cambridge, Cambridge, United Kingdom; Agaplesion Markus Krankenhaus, Frankfurt Am Main, Germany; Universidad de Zaragoza, Instituto Investigación Sanitaria Aragón, Hospital Universitario Miguel Servet. GEICAM Spanish Breast Cancer Group, Zaragoza, Spain; Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; Hospital Universitario 12 de Octubre, Madrid, Spain; Paracelsus Medical University Salzburg, Salzburg Cancer Research Institute-CCCIT, Cancer Cluster Salzburg, Salzburg, Austria; N.N. Petrov Research Institute of Oncology, Saint Petersburg, Russian Federation; Istituto Europeo di Oncologia, IRCCS, Milan, Italy; University of Genova; IRCCS Ospedale Policlinico San Martino, Genova, Italy; Department of Pathology and Laboratory Medicine, IEO European Institute of Oncology IRCCS, Milan, Italy

Background: We demonstrated that pre-treatment sTILs and PD-L1, and on treatment sTILs but not PD-L1 were associated with pathological Complete Response (pCR) to neoadjuvant therapy in patients (pts) with triple-negative breast cancer (TNBC) enrolled in NeoTRIP (NCT02620280) trial (Bianchini G ESMO 2020). Here we assess the association between the same biomarkers and EFS. **Methods:** NeoTRIP randomized 280 pts to nab-paclitaxel/carbo for 8 cycles (CT) or with atezolizumab (CT/A). As Per-Protocol Population, 258 pts were evaluable for EFS, the primary endpoint of the study.We collected samples at baseline (n=258/258; 100%) and on Day 1 Cycle 2 (D1C2) (n=230/258; 89.2%]. We centrally assessed sTILs (cut-off ≥30% to be considered high) and PD-L1 expression (SP142) on immune cells (IC) (IC≥1% considered positive). Association with EFS was investigated. Imaging mass cytometry (IMC) (Wang Nature 2023) was used to investigate the biology linked to PD-L1 dynamic over-expression. **Results:** Median follow-up was 54 months. Pre-treatment high sTILs and PD-L1+ were associated with lower risk of recurrence in CT arm (HR 0.35 [0.12-0.99], p=0.049 and HR 0.31 [0.15-0.64], p=0.001, respectively). In CT/A arm neither pre-treatment marker was significantly associate with EFS. At D1C2 in CT arm, high sTILs but not PD-L1+ was significantly associated with lower risk of recurrence (HR 0.34 [0.15-0.81], p=0.015 and HR 0.65 [0.28-1.48], p=0.30, respectively). In CT/A arm both high sTILs and PD-L1+ were strongly associated with lower risk of recurrence (HR 0.23 [0.07-0.78], p=0.019 and HR 0.25 [0.11-0.57], p=0.001, respectively). Only in CT/A arm, on-treatment PD-L1 provided prognostic information independent of baseline biomarkers, on-treatment sTILs and pCR (adjHR = 0.25 [0.11-0.58], p=0.001). In patients with baseline PD-L1- tumors and paired D1C2 samples (n=87), conversion from PD-L1- to on-treatment PD-L1 positivity occurred in 64.3% and 17.8% in CT/A and CT arms, respectively (p= $7.39x10^{-6}$). The tumors converted to PD-L1+ status were significantly associated with better outcome in CT/A arm (HR 0.23 [0.08-0.68], p=0.008) but not in CT arm (HR 0.82 [0.24-2.85], p=0.76). Notably, in CT/A arm, patients with baseline PD-L1- tumors had similarly low pCR rate regardless of PD-L1 status on D1C2 (20% and 25.9% in PD-L1- and PD-L1+ D1C2 groups, respectively). The IMC results for the biological characterization of tumors with induction of PD-L1+ will be presented. **Conclusions:** In NeoTRIP on-treatment high sTILs (both CT and CT/A arms) and PD-L1 positivity (only in CT/A arm) were significantly associated with lower risk of recurrence independently of pCR and baseline biomarkers. The findings suggest up-regulation of PD-L1 as new candidate pharmacodynamic biomarker of benefit from atezolizumab. Whether this observation hold also for pembrolizumab remain to be defined. Research Sponsor: Fondazione AIRC per la ricerca sul cancro (AIRC); IG 2018 - ID. 21787, Grant to GB; Breast Cancer Research Foundation (BCRF); 20-181, Grant to LG; Breast Cancer Research Foundation (BCRF); 18-181, Grant to LG; Fondazione AIRC per la ricerca sul cancro (AIRC); IG 2024 - ID. 30919, Grant to GB.

Long-term outcomes in triple-negative breast cancers (TNBC) treated with talimogene laherparepvec (TVEC) in combination with neoadjuvant chemotherapy (NACT).

Hatem Hussein Soliman, Amal Daas, Hyo S. Han, Blaise Mooney, Ricardo L. Costa, Marie Catherine Lee, Bethany Niell, Alec Chau, Shannon Falcon, Nazanin Khakpour, Aixa Elena Soyano Muller, Avan J. Armaghani, Robert J. Weinfurtner, Susan Hoover, John Kiluk, Brian J. Czerniecki; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of South Florida, Tampa, FL; Moffitt Cancer Center and Research Institute, Tampa, FL

Background: TVEC is an engineered herpes simplex oncolytic virus (HSV OV) approved for the treatment of melanoma. We published a phase 1/2 trial combining TVEC with NACT in early stage TNBC demonstrating increased pathologic complete response (pCR) compared to expected rates with NACT. We are presenting updated long term follow up data on this cohort of both phase 1 and 2 evaluable patients. **Methods:** Stage II-III TNBC pts were enrolled into a single arm, optimal phase 1/2 trial with TVEC (10^6 PFU 1st dose then 10^8 PFU x 4 doses) weeks 1,4,6,8,10 + weekly paclitaxel (80mg/m2) IV x 12, followed by dose dense AC (doxorubicin/cyclophosphamide 60/600 mg/m2) IV q2weeks x 4 alone (wT-AC) given preoperatively. Primary endpoint was pCR rate. Secondary endpoints included 5 year disease free survival/overall survival rates (DFSR/OSR), safety, immune correlates. **Results:** Forty six patients were enrolled at Moffitt (5/2018 – 4/2020) and evaluable for response and outcomes. Study demographics: median age 49 (27-66), 69.5% White, 13% Black, 13% Hispanic, clinical stage II 80% and III 20%, node + 45%. The pCR rate for the phase 1/2 cohort was 45.6% (95% CI 30.9-60.9). Additionally, 10 patients had residual cancer burden (RCB) 1 responses (associated w/ favorable outcomes) 21.7% (95% CI 10.9-36.3%). At median follow up of 70 months (range 17-98), six patients have had a breast cancer recurrence DFSR=86.9% (95% CI 73.7-95.0) and four patients died OSR=91.3% (95% CI 79.2-97.6). DFSR in pCR group = 95.2% (95% CI 76.1 – 99.9) and non-pCR group = 80% (95% CI 59.3 – 93.1%). All but one of the recurrences occurred in patients with non-PCR responses (RCB 2-3) to TVEC+NACT. Clinical stages at presentation for patients with recurrences were 5 stage II and 1 stage III. No patients had any HSV reactivation or autoimmunity events during the post study surveillance period. Greater immune enrichment of B and T cell subsets in pCR vs. non-pCR tumors was observed during TVEC treatment. **Conclusions:** To our knowledge, this is the first report on longer term outcomes for early TNBC treated with OV. TVEC plus wT-AC demonstrates promising long term outcomes when compared to the more intensive KEYNOTE 522 checkpoint regimen. Additional investigation of oncolytic viruses administered during NACT for TNBC is warranted to confirm this benefit. Clinical trial information: NCT02779855. Research Sponsor: Amgen.

Neoadjuvant cadonilimab (anti-PD-1/CTLA-4 bispecific antibody) plus chemotherapy in early or locally advanced triple-negative breast cancer: A single-arm phase II trial (CABIN study).

Tao Wu, Yong Xu, Ke Gong, Lan Zhuang, Hailin Tang, Yutian Zou, Wei Deng, Wei Du, Pixiao Zhou, Ziqin Chen, Ruomin Xiao, Liping Liao, Cong Liu; Changde Hospital, Xiangya School of Medicine, Central South University, Changde, China; University Hospital, Central South University, Changsha, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Changde Hospital, Hunan University of Traditional Chinese Medicine, Changde, China; The First People's Hospital of Xiangtan City, Xiangtan, China

Background: Neoadjuvant chemotherapy for triple-negative breast cancer (TNBC) can improve surgical outcomes; however, many patients fail to achieve pathological complete response (pCR). Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 show promise, but responses are limited. This phase II trial evaluates cadonilimab (AK104), a bispecific PD-1/CTLA-4 antibody, combined with nab-paclitaxel and carboplatin in neoadjuvant TNBC to improve pCR rates and assess safety. **Methods:** This phase II, single-arm trial enrolled patients aged 18-75 with treatment-naïve, stage IA-IIIC triple-negative breast cancer (TNBC). Patients received cadonilimab (10 mg/kg) plus nab-paclitaxel (260 mg/m^2) and carboplatin (AUC 4) every 3 weeks for six cycles, followed by surgery within 4 weeks. Biopsy specimens were collected before treatment for whole-exome sequencing. The primary endpoint was total pathological complete response (tpCR) rate (ypT0/is ypN0). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), disease-free survival (DFS), event-free survival (EFS), overall survival (OS), and safety. **Results:** A total of 29 patients were enrolled from January 31, 2023, to January 20, 2025. The median age was 53 years, and 11 patients (37.9%) were premenopausal. The majority had positive nodal involvement (75.9%) and stage III (51.7%) disease. of the 29 patients, 19 (65.5%, 95% CI: 45.7-82.1) achieved total pathological complete response (tpCR), and 21 (72.4%, 95% CI: 52.8-87.3) achieved breast pCR (bpCR). Tumor downstaging occurred in 89.7% (T) and 62.1% (N) of patients. Radiological assessments showed an objective response rate (ORR) of 93.1% (95% CI: 77.2-99.2) and a disease control rate (DCR) of 100%. All patients experienced at least one treatment-related adverse event (TRAEs), with 51.7% having grade 3/4 events, most commonly neutropenia (37.9%), platelet count decrease (19.2%), and leukopenia (17.2%). Serious TRAEs occurred in 6.9%. Immune-related adverse events (irAEs) of any grade occurred in 14 (48.0%) patients, while those of grade $\geq$ 3 occurred in only one patient (3.4%). The most common irAE was hypothyroidism (44.8%, 13/29), all were grade 1 or 2. Notably, patients with *TASOR2* or *MST1R* mutation demonstrated a significantly lower pCR rate (both P=0.041). Additionally, *CCND1* amplification showed a non-significant negative trend with the pCR rate (P=0.051). **Conclusions:** The combination of cadonilimab, nab-paclitaxel, and carboplatin in neoadjuvant treatment for stage IA-IIIC TNBC showed promising efficacy, with high response rates and significant tumor downstaging, particularly in stage III patients. The regimen was well tolerated with manageable adverse events, supporting its further investigation as a potential neoadjuvant treatment for TNBC. Clinical trial information: ChiCTR2200067005. Research Sponsor: None.

Biomarkers of neoadjuvant dalpiciclib in patients with operable HER2-negative luminal B breast cancer in the DANCER trial.

Yunxiang Zhou, Zhiyun Zhang, Yiding Chen; Department of Breast Surgery and Oncology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: DANCER (NCT05640778) was a circulating tumor DNA (ctDNA)-directed, single-arm, phase II trial investigating the clinical activity of dalpiciclib combined with aromatase inhibitors as a neoadjuvant regimen for operable human epidermal growth factor receptor 2 (HER2)-negative luminal B breast cancer. Although a high complete cell cycle arrest (CCCA) rate (primary endpoint) of 86.7% (26/30) was achieved at 2 weeks (T1), some patients showed suboptimal clinical responses after neoadjuvant therapy. This underscores the importance of identifying biomarkers predictive of response to CDK4/6 inhibitors. **Methods:** Plasma samples collected at baseline (T0), T1, mid-therapy (T2), surgery (S), and postoperatively (PO) underwent ctDNA and Olink proteomic analyses. Tumor tissues obtained at T0, T1, and S were assessed for somatic variation profiling, immunohistochemical markers and MammaPrint index. Patients achieving CCCA at both T1 and S with a concurrent objective response by MRI at S were classified as Good Responders (GRs, n = 15); others were Moderate Responders (MRs, n = 15). **Results:** The baseline clinicopathological features of the patients were balanced between the GR and MR groups. Compared to MRs, the GRs at S exhibited significantly lower residual cancer burden (RCB) scores, preoperative endocrine prognostic index (PEPI) scores, histological tumor grades, Ki67 expressions, and CA153 levels. Additionally, GRs demonstrated significantly higher Miller-Payne grades, tumor-infiltrating lymphocyte levels, and tumor shrinkage rates. In terms of biomarkers, GRs had a higher rate of ctDNA clearance at and prior to T2 (100.0% vs 54.5%; p = 0.045), as well as higher levels of plasma CCL4 (p = 0.029), plasma CCL19 (p = 0.020), immunohistochemical pRb (p = 0.044), and immunohistochemical CDK4 (p = 0.034). Furthermore, *GSTM1* demonstrated a significant shift in its copy number pattern after treatment at S, with five previously detected baseline deletions no longer being identified and five de novo amplifications emerging (p = 0.007). Lack of early ctDNA clearance was also significantly associated with RCB class of III and PEPI score of $\geq$ 4. Besides, MammaPrint high-risk patients showed a significant increase in RCB and PEPI scores vs. low-risk patients. **Conclusions:** Patients with operable HER2-negative luminal B breast cancer who exhibit early ctDNA clearance, MammaPrint low-risk status, *GSTM1* deletion, increased pRb/CDK4 expression, and higher plasma CCL4/CCL19 levels may derive substantial benefit from neoadjuvant dalpiciclib therapy. Clinical trial information: NCT05640778. Research Sponsor: National Natural Science Foundation of China; the Key Research and Development Program of Zhejiang Province.

Patient outcomes in WSG-ADAPT according to NATALEE and MonarchE risk criteria.

Oleg Gluz, Michael Wilhelm Braun, Sherko Kuemmel, Ulrike Nitz, Kerstin Luedtke-Heckenkamp, Maren Darsow, Helmut Forstbauer, Silke Polata, Eva-Maria Grischke, Christoph Uleer, Bahriye Aktas, Claudia Schumacher, Christine zu Eulenburg, Sandy Burmeister, Monika Karla Graeser, Rachel Wuerstlein, Rick Baehner, Matthias Christgen, Hans Heinrich Kreipe, Nadia Harbeck; West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and University Hospital Cologne, Cologne, Germany; Interdisciplinary Breast Center, Rotkreuz-Clinics Munich, Munich, Germany; Breast Unit, Kliniken Essen-Mitte, Essen, and Charité-Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Essen, Germany; West German Study Group, Moenchengladbach, Germany; Department of Oncology and Hematology, Niels-Stensen-Kliniken, Georgsmarienhütte, Germany; Luisenhospital Duesseldorf, Practice for Senologic Oncology, Duesseldorf, Germany; Practice Network Hematology/Oncology, Troisdorf, Germany; Ev. Waldkrankenhaus Spandau, Berlin, Germany; University Women´s Clinic Tuebingen, Eberhard Karls University, Tubingen, Germany; Gynecologists at Bahnhofsplatz, Hildesheim, Germany; Department of Gynecology, University Hospital Leipzig, Leipzig, Germany; St. Elisabeth-Krankenhaus, Köln, Germany; UKE Hamburg, Hamburg, Germany; Institute of Biostatistics and Registry Research, Brandenburg Medical School Theodor Fontane, Neuruppin, Germany; West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and Department of Gynecology, University Medical Center Hamburg, Hamburg, Germany; Breast Center, Dept. OB&GYN, University of Munich (LMU) and CCCLMU, West German Study Group, Munich, Germany; Exact Sciences Corporation, Madison, WI; Hannover Medical School, Institute of Pathology, Hannover, Germany; Hanover Medical School, Institute of Pathology, Hannover, Germany; University Hospital Munich, Munich, Germany

Background: In HR+/HER2- high-risk early breast cancer (eBC), abemaciclib and ribociclib improve the efficacy of standard endocrine treatment (ET), as shown in MonarchE (abemaciclib) and NATALEE (ribociclib). However, the absolute benefit varies according to prognostic factors. We analyzed the outcome of prognostic groups based on MonarchE and/or NATALEE inclusion criteria in the WSG-ADAPT trial considering Recurrence Score (RS, OncotypeDx) and Ki-67 response after preoperative ET. **Methods:** In WSG-ADAPT (NCT01779206), patients (pts) with clinically high-risk HR+/HER2- eBC (cT2-4 or cN+ or G3 or Ki67 $\geq$ 15%) initially received a 3-week standard ET before surgery or sequential biopsy. Pts with c/pN2-3 or G3 with Ki67 $>$ 40% were randomized directly to chemotherapy (CT trial) evaluating (neo)adjuvant 4 $\times$ paclitaxel q2w vs. 8 $\times$ nab-paclitaxel q1w, followed by epirubicin + cyclophosphamide q2w, followed by ET. pN0-1 pts with RS 0-11 or RS 12-25 with ET-response (central $Ki67_{postET} \leq 10\%$) received ET alone (ET trial); RS 12-25 pts without ET-response entered CT trial. Pts with N1-3 or T3 or T2, N0 with either Ki-67 $\geq$ 20% or G3 or RS $>$ 25 were classified as NATALEE high-risk, pts with N2-3 or N1 with either T3-4 or G3 or Ki-67 $\geq$ 20% were classified as MonarchE high-risk. **Results:** In the WSG-ADAPT ET trial, 303 (14.2%) and 784 (36.7%) of 2135 pts were classified as MonarchE and NATALEE high-risk, respectively. In the CT trial, 963 (43.2%) and 1572 (70.5%) of 2230 pts were classified as MonarchE and NATALEE high-risk. After 60 months of median follow-up, both high-risk vs. low-risk classifications were highly prognostic for iDFS and dDFS in ET and CT trials. However, low-risk pts (by both classifications) in the ET trial had 5-y iDFS and dDFS of 94.7% and 96.4%, respectively, vs. 90.1% and 93.6% for high-risk by just NATALEE but not by MonarchE criteria (p = n.s.) and vs. 88.3% and 88.9% in both NATALEE and MonarchE high-risk pts ($p < 0.001$). In the ET-only cohort, survival outcomes were similar between pN0 and pN1 pts at high-risk by NATALEE but not by MonarchE criteria (5-y iDFS of 87.7% vs. 90.2%; p = n.s. and 5-y dDFS of 91.7% vs. 91.9%; p = n.s.). In the CT trial, 5-y iDFS and dDFS rates were 93.9% and 94.9%, respectively, for NATALEE low-risk pts vs. 84.7% and 87.0% for high-risk by NATALEE but not by MonarchE criteria and vs. 77.7% and 79.6% for MonarchE high-risk pts. **Conclusions:** Among 4365 pts in the WSG-ADAPT trial, subgroups classified as high-risk by NATALEE and MonarchE criteria had poor outcomes. However, N0-1 pts who were high-risk by NATALEE but not MonarchE criteria and pts with RS $\leq$ 25 and/or ET response had only slightly inferior outcomes compared to low-risk pts with ET therapy alone. Assuming a hazard ratio of 0.7 for a ribociclib effect, as shown in NATALEE, an absolute benefit of approx. 2% fewer dDFS events after 5 years can be assumed in this group based on the WSG-ADAPT experience. Shared decision-making will be key in this intermediate-risk group. Clinical trial information: NCT01779206. Research Sponsor: Genomic Health (Exact Science); Celgene; Amgen; Allgemeine Ortskrankenkasse.

Racial disparities in clinical outcomes of early-stage triple-negative breast cancer treated with neoadjuvant chemoimmunotherapy: Insights from the NCDB.

Zunairah Shah, Safa Saadat Afridi, Mustafa Ali Samejo, Mrinalini Ramesh, Minaam Abid, Adrienne Groman, Han Yu, Song Yao, Christine B. Ambrosone, Thaer Khoury, Kazuaki Takabe, Chi-Chen Hong, Varsha Gupta, Sheheryar Kairas Kabraji, Ellis Glenn Levine, Shipra Gandhi; Roswell Park Comprehensive Cancer Center, Buffalo, NY; SUNY Upstate Medical University, Syracuse, NY; Advent Health sebring, Sebring, FL; University at Buffalo, Buffalo, NY; Dow University of Health Sciences, Karachi, Pakistan; Roswell Park Cancer Institute, Buffalo, NY; Roswell Park Cancer Institute Department of Cancer Prevention and Population Sciences, Buffalo, NY

Background: Triple-negative breast cancer (TNBC) is an aggressive breast cancer (BC) subtype, and Black patients (pts) with TNBC have worse survival outcomes after neoadjuvant chemotherapy, likely due to biological and socioeconomic factors. Neoadjuvant immune checkpoint inhibitors combined with chemotherapy, i.e. neoadjuvant chemoimmunotherapy (NACI) have improved pCR rates and overall survival (OS), but its efficacy by race is unclear. This study evaluates racial disparities in clinical outcomes for pts with early-stage TNBC treated with NACI, aiming to address this critical gap. **Methods:** We analyzed the National Cancer Database (NCDB) for pts with stage II/III TNBC treated with NACI from 2019 to 2022. Primary outcomes included pCR and OS, which were analyzed with race using univariate and multivariable logistic regression and Cox proportional hazards models, while adjusting for clinicopathologic variables (age, stage, grade, comorbidities (Charlson-Deyo Comorbidity Classification) and socioeconomic factors (residence (rural/urban area), insurance, income). P value ≤ 0.05 was considered statistically significant. **Results:** A total of 5,137 pts were included. Median age was 51 years (range:39-63); 69.9% were White, 20.5% Black, 9.6% Other, 49.3% had stage II and 50.7% had stage III TNBC. Median follow up was 26.6 months (3.3-61.9), pCR was achieved in 76.5% pts, (White: 77%, Black: 74%, Other: 76%; p = 0.113). Pts achieving pCR had significantly higher 3-year OS (92% vs 72%, $p<0.001$) and 5-year OS (84% vs 56%, $p<0.001$) compared to those without pCR. Racial disparities in survival were observed, with 3-year OS of 88%, 84%, and 85% ($p<0.05$) and 5-year OS of 83%, 77%, and 85% for White, Black, and Others, respectively ($p<0.05$). After adjusting for covariates, Black pts had a trend toward lower likelihood of pCR compared to White pts although not statistically significant (odds ratio (OR) 0.76 [95% CI: 0.54–1.07]. The factors independently associated with worse OS were residence in rural areas (HR 1.79 [95% CI: 1.00–3.19], p = 0.05), tumors ≥10 cm (HR 1.92 [95% CI: 1.21–3.06], p = 0.006), stage III disease (HR 1.91[95% CI: 1.47–2.49], $p < 0.001$) and Black vs. White group (HR 1.42 [95% CI: 1.10–1.84], p = 0.007). **Conclusions:** Black pts with TNBC receiving NACI have worse OS than White pts, possibly due in part to social, structural, or biological determinants of health. Further research is needed to investigate personalized treatment strategies that address the unique challenges Black pts face in achieving long-term survival and improving overall prognosis. Research Sponsor: None.

Survival rates and hazard ratios by race.

Race	3-year survival rate (%)	5-year survival rate (%)	Hazard ratio
White	88%	83%	1.00
Black	84%	77%	1.42 [95% CI 1.10–1.84]
Other race	85%	85%	1.19 [95% CI 0.82–1.74]

Outcomes of neoadjuvant endocrine therapy (NAET) versus neoadjuvant chemotherapy (NAC) in stage II-III invasive lobular carcinoma (ILC).

Jason A. Mouabbi, Yara Sakr, Akshara Singareeka Raghavendra, Taiwo Adesoye, Henry Mark Kuerer, Azadeh Nasrazadani, Amy Aida Hassan, Ajit Bisen, Giancarlo Moscol, Vicente Valero, Carlos Hernando Barcenas, Debasish Tripathy, Lavinia P. Middleton, Rachel M. Layman, Paula R. Pohlmann, Funda Meric-Bernstam; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of General Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; Breast Medical Oncology Department, The University of Texas MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ILC is a distinct subtype of breast cancer, accounting for up to 15% of cases, and is characterized by unique clinical and pathological features. ILC often yield poor responses to NAC. Case reports suggest that NAET yields favorable outcomes in ILC. However, no large-scale study has evaluated the impact of NAET in ILC patients. This is the first large study that aims to compare the outcomes of NAC versus NAET in stage II/III ILC. **Methods:** A retrospective analysis was performed on patients treated at MD Anderson Cancer Center with a diagnosis of anatomical stage II-III estrogen receptor-positive (ER+) HER2-ve ILC in our prospectively collected and curated electronic database. Data collected included demographics, receptor status (ER, PR, HER2), treatments received, clinical anatomic and pathologic stage, type of surgery, surgical pathology outcomes, and recurrence. Endpoints included pathologic complete response (pCR), modified Preoperative Endocrine Prognostic Index (mPEPI) score 0, endocrine therapy responsiveness (ETR; Ki67 $\leq$10%), rates of axillary downstaging (from node positive to negative), rate of lumpectomy, rate of axillary lymph node dissection (ALND), and 10-year distant recurrence-free survival (10y DRFS). For DFRS, NAC patients were compared to NAET patients who did not receive adjuvant chemotherapy (ACT). Univariate analysis identified variables associated with outcomes, and multivariate logistic regression was planned for significant factors ($p < 0.05$). **Results:** We analyzed 611 patients among who the median age was 55 (range 30–91), with 77% White, 8.5% Hispanic, and 8.1% Black. 65% were postmenopausal and all patients received adjuvant ET. 509 (80%) received NAC, and 102 (20%) received NAET. Among NAET patients, 83% received a non-steroidal AI, while 98% of NAC patients received anthracycline-containing regimens. pCR was achieved in 13 NAC patients (2.5%) and 2 NAET patients (1.9%). mPEPI score 0 was attained by 10 NAET patients (9.8%), and the ETR rate was 83%. Axillary downstaging occurred in 11% of NAC patients and 5% of NAET patients. Rates of lumpectomy (17.1% in NAC vs. 17.6% in NAET) and axillary lymph node dissection (ALND) (68.6% in NAC vs. 62.6% in NAET) were comparable between the groups. With a median follow-up of 85 months, 10y DRFS was 55% for NAC and 65% for NAET (HR 0.57, 95% CI 0.33–0.98, P = 0.02). Univariate analysis for DRFS revealed no significant associations with age, race, or initial stage (all $p > 0.05$), precluding multivariate analysis. **Conclusions:** This large-scale analysis highlights the limited efficacy of NAC in ILC, with minimal pCR rates. NAET yields promising results, including superior 10y DRFS. These findings underscore the potential of NAET as a viable neoadjuvant option for patients with stage II/III ER+ ILC. Research Sponsor: None.

Serum estradiol (sE2) levels in premenopausal (PreM) women receiving neoadjuvant ovarian function suppression (OFS) with the oral SERD amcenestrant, alone, or in combination with letrozole or abemaciclib in the I-SPY2 Endocrine Optimization Pilot (EOP).

Jo Chien, Peter Norwood, Rita Mukhtar, Karthik Giridhar, Matthew P. Goetz, Christos Vaklavas, Anthony D. Elias, Mei Wei, Hope S. Rugo, Nan Chen, Alexander D. Borowsky, Lamorna Brown Swigart, Rebecca Arielle Shatsky, Laura Ann Huppert, Michelle E. Melisko, Laura Esserman; University of California, San Francisco, San Francisco, CA; Quantum Leap Healthcare Collaborative, San Francisco, CA; Division of Surgical Oncology, Department of Surgery, University of California, San Francisco, San Francisco, CA; Mayo Clinic, Rochester, MN; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; University of Colorado Cancer Center, Aurora, CO; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of Chicago, Chicago, IL; University of California, Davis, Davis, CA; University of California, San Diego Medical Center, La Jolla, CA; University of California San Francisco, San Francisco, CA; Department of Surgery, University of California, San Francisco, San Francisco, CA

Background: The addition of OFS to standard endocrine therapy (ET) improves iDFS for preM women with early-stage hormone receptor positive (HR+) breast cancer (BC). Incomplete OFS occurs in a subset of women, the long-term clinical significance of which is unclear. This study evaluates local sE2 levels in preM women receiving OFS with an oral SERD in the neoadjuvant (NA) setting. **Methods:** The EOP is a I-SPY2 sub-study investigating NA endocrine-based strategies in pts with HR+ HER2- Stage 2/3 BC predicted to have lower benefit from chemotherapy. Pts were randomized to oral amcenestrant 200 mg/d, alone or in combination with either letrozole 2.5 mg/d or abemaciclib 150 mg bid. Additional pts were randomized to a standard of care (SOC) arm consisting of an aromatase inhibitor. All PreM pts received OFS with monthly GnRHa up to 2 wks prior to C1D1 of study therapy. Pts were treated for 6 months prior to surgery. sE2 levels were collected locally prior to each GnRHa injection. Tumor Ki67 was assessed at 3 weeks and surgery, and associated with sE2 level. Statistical significance was determined using a two-sided Student's t-test and a significance level 0.05. **Results:** Between 5/2021-8/2022, 74 pts were enrolled to an amcenestrant containing arm, 40 of whom were preM. 38/40 pts had at least one local sE2 level measured in follow up. Of these 38 pts (median age 45 years), 37 suppressed sE2 into the postmenopausal (postM) range at one or more follow-up timepoints. Of the 37 pts that completely suppressed into the postM range, 6 pts had sE2 levels rebound into the preM range (mean 319 pg/mL, range 20-848 pg/mL) with peak sE2 levels occurring at a median of 12 weeks from C1D1. One pt never suppressed to the postM range (peak sE2 1227 pg/mL) and was found to have an ovarian cyst after 3 months on amcenestrant, requiring surgery. One additional pt had multiple ovarian cysts (sE2 84 pg/mL). Median age of the 7 pts who had sE2 rebound was 43 years. There was no significant difference in Ki67 at 3 weeks and surgery between pts whose sE2 levels remained suppressed (median Ki67 2.0%) compared to those whose estradiol rebounded into the preM range or never suppressed (median Ki67 1.5%). In the 5 pts whose sE2 rebounded to $>$ 200 pg/mL, all pts had tumor Ki67 $<$ 10% at 3 weeks and surgery. Between 12/2022 and 8/2023, 20 pts were enrolled to AI +/- OFS and 11 pts were preM. Of the 11 preM pts, all pts suppressed sE2 to the postM range. No SOC patients had sE2 levels rebound into the preM range. **Conclusions:** In this study of neoadjuvant oral SERD with monthly OFS, 7/38 (18.4%) preM pts had sE2 levels remain or rebound into the preM range. sE2 levels did not appear to impact Ki67 suppression on NA ET. Work up for ovarian cysts should be considered in pts with symptoms, or significantly elevated or persistent sE2 levels. Clinical trial information: NCT01042379. Research Sponsor: Quantum Leap Healthcare Collaborative.

Molecular insights into HR+/HER2+ early-stage breast cancer: Neoadjuvant therapy responses by MammaPrint and BluePrint genomic subtypes.

Laila Samiian, Adam Brufsky, Sahra Uygun, Isha Kapoor, Victoria Poillucci, William Audeh, Joyce O'Shaughnessy; Baptist MD Anderson Cancer Center, Jacksonville, FL; University of Pittsburgh, Pittsburgh, PA; Agendia, Inc., Irvine, CA; Medical Affairs, Agendia, Inc., Irvine, CA; Agendia, Inc, Irvine, CA; Agendia USA, Sherman Oaks, CA; Baylor University Medical Center, Texas Oncology, Dallas, TX and Sarah Cannon Research Institute, Dallas, TX

Background: Clinical HER2+ (cHER2+) early breast cancer (EBC) represents 15-20% of invasive EBC and is typically treated with Neoadjuvant HER2-targeted therapy (NHT) combined with chemotherapy, regardless of ER status. NBRST and I-SPY2 trials showed varied NHT responses in cHER2+ tumors based on genomically-defined molecular subtypes, emphasizing the importance of understanding tumor biology. Genomic assays MammaPrint (MP) and BluePrint (BP) predict therapy response and inform treatment decisions. Here, we explored the biological pathways underlying differential NHT response in triple positive (HR+HER2+) tumors using whole transcriptome analysis (WTA). **Methods:** Patients with HR+/HER2+ early-stage breast cancer treated with NHT (N = 720) were included from FLEX (NCT03053193). MP classified tumors as UltraLow (UL), Low, High 1, or High 2 Risk, while BP categorized them as Luminal A, Luminal B, HER2, or Basal. Differences in clinical characteristics and pathological complete response (pCR) rates were assessed by Chi-Square or Fisher's exact tests and proportional Z-test, respectively. Differential gene expression (DGE) analysis of WT profiles was performed between tumors with and without pCR, using limma package in R, followed by pathway enrichment analysis in Metascape. **Results:** Among 720 HR+/HER2+ EBCs, MP classified 19 (2.6%) as UL, 107 (14.9%) as Low, 385 (53.5%) as High 1, and 209 (29.0%) as High 2. BP classified 120 (16.7%) as Luminal A, 307 (42.6%) as Luminal B, 278 (38.6%) as HER2, and 15 (2.1%) as Basal. Compared to other BP subtypes (Luminal A/B), BP HER2 tumors were associated with younger age (54 vs 60, $p < 0.001$), premenopausal status ($p = 0.002$), higher grade (G3: 54.7%, $p < 0.001$), and T3 tumors (10.7% vs 3-4%, $p < 0.001$). pCR rates with NHT were higher in BP HER2 tumors compared to Luminal A/B tumors (n = 41, 61.2% vs n = 18, 26.5%, respectively, $p < 0.001$). WTA of BP HER2 tumors with pCR showed 23 genes with 2-fold change (not statistically significant after correction), 20 of which were upregulated and associated with regulation of bone morphogenic protein encoding genes and increased cell-substrate/cell matrix adhesion, compared to tumors that had residual disease. **Conclusions:** These data show heterogeneity within HR+/HER2+ tumors, with approximately 60% genomically reclassified as non-HER2-type by BP. Consistent with I-SPY2, BP HER2 cancers showed higher pCR rates than Luminal A/B, suggesting that additional therapeutic strategies are needed to increase the pCR rates in these cancers. Although WTA in BP HER2 tumors with and without pCR identified DGE, the findings were not statistically significant. Future analyses of WTA in larger numbers of BP subtypes within the HR+ HER2+ EBC patients who are being enrolled on the FLEX trial may elucidate the biology of the cancers with pCR vs non-pCR. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

Results of the prospective randomized controlled trial VOG-01: Neoadjuvant endocrine therapy ribociclib + fulvestrant + GnRH-a versus chemotherapy 4 AC + 4 T for early HR+/HER2-negative breast cancer in premenopausal patients.

Rashida Orlova, Almira Vakhitova, Mark Gluzman, Eldar Topuzov, Petr Krivorotko, Alexandra Androsova, Ekaterina Serikova, Vitaly Skvortsov; Saint Petersburg State University, Saint Petersburg, Russian Federation; SPbGU, Saint Petersburg, Russian Federation; St. Petersburg City Clinical Oncology Dispensary, Saint Petersburg, Russian Federation; N.N. Petrov National Medical Research Center of Oncology, Saint Petersburg, Russian Federation; City Clinical Oncology Dispensary, Saint Petersburg, Russian Federation; Saint-Petersburg State University, Saint-Petersburg, Russian Federation

Background: CDK4/6 inhibitors are used to treat HR+/HER2- metastatic breast cancer in combination with endocrine therapy. However, there is still a lack of evidence about combined endocrine therapy in neoadjuvant setting. VOG-01 is a phase II randomized trial that evaluated the effects of combination ribociclib plus fulvestrant and GnRH-a as neoadjuvant therapy in premenopausal patients. **Methods:** Premenopausal women with HR+/HER2-negative stage II-III were randomly assigned to Fulvestrant (500 mg on the 1st, 15th, 28th days of the first cycle, then once every 28 days), Triptorelin (3.75 mg every 28 days) and Ribociclib (600 mg daily, 3 weeks/4) during 16-24 weeks (NET), or Doxorubicin 60 mg/m2 + Cyclophosphamide 600 mg/m2 x4 21-day courses followed by Docetaxel 75 mg/m2 x4 21-day courses (NCT). Primary endpoint was objective response rate. Secondary endpoints were pathological response rate (RCB), frequency of breast-conserving surgery, severity of adverse events and the quality of life (EORTC QLQ-C30). **Results:** Eighty two patients were recruited. The objective response rate was 83% in the NET and 71% in the NCT ($p = 0.2$). Complete pathological response (RCB 0) was in 2 cases (5%) in the NET and in 4 cases (10%) in the NCT; RCB I was in 1 case (2.6%) in the NCT and did not occur in the NET; RCB II - 55% in the NET and 62% in the NCT, RCB III was in 40% and 26% respectively. Breast-conserving surgery were not so common in both groups: 37% in the NET and 32% in the NCT ($p=0.5$). Severe adverse events (CTCAE ver 5 G3-4) were 66% in the NET and 87% in NCT ($p < 0.019$). Quality of life significantly decreased during NCT compared with NET: the total score was 75.7 ± 22.2, 42.0 ± 19.7, 66.3 ± 12.9 in NCT at visits on 1-12-24-weeks and 76.4 ± 20, 70.7 ± 25.4, 76.1 ± 20.5 in NET at the same visits ($p < 0.05$). **Conclusions:** For the first time randomised trial comparing NET and NCT was conducted in premenopausal women with HR+/HER2- early breast cancer. NET was not inferior to standard NCT in terms of objective response rate, complete or pronounced pathological response rate and breast-conserving surgery. At the same time it was associated with a lower severity of adverse events and increased quality of life. Nevertheless new treatment approach requires confirmation of its effectiveness in large studies. Clinical trial information: NCT04753177. Research Sponsor: None.

HER2DX genomic test in HER2-positive breast cancer treated with 15 weeks of neoadjuvant paclitaxel, trastuzumab, and pertuzumab (THP): Final analysis from the BiOnHER clinical trial.

Bartomeu Fullana Grimalt, Fara Brasó-Maristany, Anna Petit, Ortega Raúl, Nadia Gómez, María Vicente, Catalina Falo, Silvia Vazquez, Agostina Stradella, Rafael Villanueva-Vázquez, María Jesús Pla, David Cordero, Teresa Soler Monso, Sandra Cobo, Laia Pare, Patricia Galván, Charles Perou, Patricia Villagrasa, Aleix Prat, Sonia Pernas; Avinguda de la Granvia de l'Hospitalet, 199-203, L'hospitalet De Llobregat, Barcelona, Spain; Hospital Clínic de Barcelona, Barcelona, Spain; August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain; Pathology, Hospital Universitari de Bellvitge, Hospitalet De Llobregat, Barcelona, Spain; Hospital Universitari de Bellvitge, Hospitalet De Llobregat, Spain,, L'hospitalet De Llobregat, Barcelona, Spain; Catalan Institute of Oncology, L'hospitalet De Llobregat, Barcelona, Spain; ICO Hospitalet; GEICAM Spanish Breast Cancer Group, L'hospitalet De Llobregat, Spain; ICO - Institut Català d'Oncologia - Hospital Duran i Reynals, Hospitalet De Llobregat, Spain, L'hospitalet De Llobregat, Barcelona, Spain; Institut Català d'Oncologia L'Hospitalet, Medical Oncology Department, Hospitalet de Llobregat, Barcelona, Spain; Institut Català d'Oncologia, ICO Hospitalet, l'Hospitalet de Llobregat, Barcelona, Spain; Hospital Universitari de Bellvitge, Hospitalet De Llobregat, Spain,, L'hospitalet De Llobregat, Barcelona, ES51, Spain; Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; Reveal Genomics Srl, Barcelona, Spain; Hospital Clinic Barcelona / IDIBAPS, Barcelona, Spain; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Reveal Genomics, Barcelona, Spain; Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Hospital Clinic of Barcelona, Barcelona, Spain; Institut Català d'Oncologia, IDIBELL, L'Hospitalet, L'hospitalet, Barcelona, Spain

Background: HER2DX is a 27-gene genomic assay providing prognostic and predictive insights in early-stage HER2-positive (HER2+) breast cancer. Although widely validated, less data exists for its performance in THP beyond the DAPHNe trial (JAMA Oncol 2023), which included 80 patients (pts). This study aimed to validate HER2DX for predicting pathological complete response (pCR) with THP and compare its performance to hormone receptor (HR) status. **Methods:** HER2DX (Reveal Genomics) was centrally evaluated on all tumor biopsies from the BiOnHER trial (NCT05912062), where pts with stage I-III HER2-positive breast cancer received 15 weeks of neoadjuvant THP at the Catalan Institute of Oncology. Biopsies were collected at pre-treatment baseline (D1) and day 8 (D8) after an HP loading dose but before initiating paclitaxel. HER2DX pCR group cutoffs were based on predefined thresholds for HER2DX low-, medium-, and high groups. Logistic regression and receiver-operating characteristic (ROC) curve analyses were used for statistical evaluation. The primary objective was to assess HER2DX pCR score for predicting pCR (ypT0/isN0). Secondary objectives included evaluating HER2DX performance by HR status, baseline TILs/Ki67, and additional insights from D8 data. **Results:** HER2DX was successfully evaluated in all 83 enrolled patients. The cohort included 65.1% T2 tumors, 62.7% cN0 status, 69.9% stage II disease, and 67.5% HR-positive tumors. The overall pCR rate was 45.8% (95% CI, 34.9–57.0%), and the ypT1miN0 rate was 54.2%. HER2DX pCR score was significantly associated with pCR (odds ratio [OR] = 5.26, $P < 0.001$), with an AUC of 0.835. Patients were categorized into 35.0% low, 37.5% medium, and 27.5% high HER2DX pCR score groups, with pCR rates of 13.3% (95% CI, 4.4–31.6%), 51.6% (95% CI, 33.4–69.4%), and 81.8% (95% CI, 59.0–94.0%), respectively. Among HR-negative tumors, pCR rates were 78.6% for high-pCR and 0.0% for low-pCR groups, while in HR-positive tumors, pCR rates were 87.5% and 13.8%, respectively. HR status alone was associated with pCR (OR = 0.125, $P = 0.006$) but lost significance in multivariable analysis including HER2DX. Baseline Ki67 (median: 35.0%) and TILs (median: 8.0%) were not associated with pCR. While D8 data offered biological insights, it did not improve predictive performance beyond baseline HER2DX. **Conclusions:** HER2DX is a robust predictor of pCR following neoadjuvant THP in stage I-III HER2-positive breast cancer, outperforming HR status. Baseline TILs and Ki67 were not predictive of pCR, and HER2DX D8 data did not improve predictive performance. Clinical trial information: NCT05912062. Research Sponsor: Instituto de Salud Carlos III (ISCIII); FIS PI20/00544.

Outcomes of elderly patients with early-stage triple-negative breast cancer treated with the KEYNOTE-522 regimen.

Renata Colombo Bonadio, Flavia Balint, Isadora Martins de Sousa, Monique Celeste Tavares, Fernanda Madasi Pinheiro, Jose Bines, Rafael Dal Ponte Ferreira, Daniela Dornelles Rosa, Zenaide Silva de Souza, Daniele Assad Suzuki, Debora De Melo Gagliato, Carlos Henrique dos Anjos, Bruna M. Zucchetti, Anezka Carvalho Rubin de Celis Ferrari, Mayana Lopes De Brito, Maria Marcela F. Monteiro, Paulo Marcelo Hoff, Laura Testa, Maria Del Pilar Estevez-Diz, Romualdo Barroso-Sousa; Instituto D'Or de Pesquisa e Ensino (IDOR), São Paulo, Brazil; A.C. Camargo Cancer Center, São Paulo, Brazil; Instituto D'Or de Pesquisa e Ensino (IDOR), Rio De Janeiro, Brazil; Hospital Moinhos de Vento, Porto Alegre, Brazil; Hospital Sírio-Libanês, Brasília, Brazil; Hospital Beneficência Portuguesa, São Paulo, Brazil; Hospital Sírio-Libanês, São Paulo, Brazil; DASA Oncology, Hospital 9 De Julho, São Paulo, Brazil; DASA Oncologia - Hospital Santa Paula, São Paulo, Brazil; DASA Oncology - Clínica AMO, Salvador, Brazil; Instituto do Câncer do Ceara, Fortaleza, Brazil; Instituto do Câncer do Estado de São Paulo, University of São Paulo and Instituto D'Or de Pesquisa e Ensino, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; DASA Oncology, Brasilia Hospital, Brasília, Brazil

Background: The KEYNOTE-522 regimen (neoadjuvant pembrolizumab combined with a four-drug chemotherapy backbone, followed by adjuvant pembrolizumab) is a standard of care for stage II-III triple-negative breast cancer (TNBC). However, the median age of TNBC diagnosis is 40–50 years, and elderly patients (pts) are underrepresented in clinical trials. **Methods:** The effectiveness and safety of the KEYNOTE-522 regimen were evaluated in patients aged ≥65 years (y) in the Neo-Real/GBECAM-0123 trial, a real-world, multicenter study conducted across ten institutions since July 2020. Pathological complete response (pCR) was assessed as the primary endpoint. Patients < 65y served as the control group. **Results:** Of the 413 pts included in the study, 45 (10.9%) were aged ≥65y. Compared to younger patients, elderly pts exhibited a higher proportion of special histological types (15.6% vs 6.8%, P = 0.055), lower-grade tumors (grade 1–2: 35.5% vs 13.6%, P = 0.001), lower Ki-67 index (< 50%: 46.7% vs 16.6%, P < 0.001), and fewer germline BRCA1/2 mutations (2.2% vs 13%, P = 0.039). The majority of patients in both groups had stage II disease (77.8% vs 69.3%, P = 0.574). Elderly pts were less likely to receive dose-dense anthracycline and cyclophosphamide (AC) (44.4% vs 55.4%, P = 0.027). Patients aged ≥ 65y had lower pCR rates compared to those < 65y (46.3% vs 64%; univariate logistic regression: OR 0.48, 95%CI 0.25–0.93, P = 0.030). However, this difference was not significant in multivariable analysis adjusted for histological type, tumor grade, Ki-67 index, BRCA status, and AC schedule (OR 1.80, 95% CI 0.74–4.37, P = 0.188). Elderly pts experienced significantly higher rates of safety concerns (Table 1). **Conclusions:** TNBC in elderly pts appears to have distinct biological characteristics, which may contribute to lower pCR rates with the KEYNOTE-522 regimen. Additionally, the higher incidence of safety issues in this population underscores the importance of personalized treatment strategies and careful patient selection. Further studies focused on elderly pts with TNBC are needed. Research Sponsor: None.

Safety outcomes of elderly patients treated with KN522 regimen.

	≥ 65y	< 65y	P
Drug discontinuation due to AE	33.3%	21.7%	0.140
AC discontinuation	17.8%	3.8%	0.001
Dose reduction	27.2%	12.2%	0.010
Delay for neoadjuvant treatment conclusion	42.2%	22.3%	0.006
Hospitalization due to AE	33.3%	15.2%	0.011
Antibiotics use	44.4%	25.5%	0.019
Grade ≥ 3 AE	48.9%	34.2%	0.137
Anemia	8.9%	2.4%	0.042
Neutropenia	35.5%	19.6%	0.020
Febrile neutropenia	22.2%	10.3%	0.026
Fatigue	6.7%	1.4%	0.046

Early adverse symptoms to predict response to treatment among patients in the I-SPY trial.

Amrita Basu, Saumya Umashankar, Denise M. Wolf, Christina Yau, Ritu Roy, Kathryn Jean Ruddy, Anne Hudson Blaes, Adam B. Olshen, Angela DeMichele, Jane Perlmutter, Douglas Yee, Nola Hylton, Laura van t Veer, Rebecca Arielle Shatsky, Claudine Isaacs, Hope S. Rugo, Laura Esserman, Michelle E. Melisko, Dawn L. Hershman, I-SPY Trial Investigators and Patient Advocates; University of California, San Francisco, San Francisco, CA; Mayo Clinic, Rochester, MN; University of Minnesota, Minneapolis, MN; University of Pennsylvania, Philadelphia, PA; Gemini Group, Ann Arbor, MI; Masonic Cancer Center, University of Minnesota, Minneapolis, MN; University of California-San Francisco, San Francisco, CA; University of California, San Diego Medical Center, La Jolla, CA; Lombardi Cancer Center, Georgetown University, Washington, DC; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Department of Surgery, University of California, San Francisco, San Francisco, CA; Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY

Background: The adverse event (AE) landscape in oncology is changing due to the introduction of immunotherapy and antibody drug conjugates. These AEs come with both short and long-term symptoms that significantly impact patient quality of life. Monitoring for early onset of symptoms could optimize therapy for a particular patient, maximizing potential efficacy while mitigating toxicity. It is also possible that some toxicities are directly associated with drug sensitivity. We sought to identify symptoms associated with pathologic complete response (pCR) using patient-reported outcomes (PROs) in early-stage high-risk breast cancer patients. **Methods:** Our study population included 288 stage II/III high-risk breast cancer patients enrolled on the I-SPY2 trial from 2021-2024, who received novel neoadjuvant therapies ± standard paclitaxel. pCR was assigned if tumor was absent in breast and nodes at surgery following neoadjuvant treatment. Patients (n = 288, pCR rate = 29%, 89% administered immunotherapy) were sent electronic PROs. 33 patient-reported AEs were measured using NCI's Patient Reported Outcomes - Common Terminology Criteria for Adverse Events (PRO-CTCAE). Each symptom was evaluated using severity, frequency, and interference on a Likert Scale. Presence of early PRO symptoms (cycles 1-3 of treatment) were binarized (at least one of moderate or greater), and odds ratios were computed with pCR as outcome. To assess whether higher grade AEs were enriched in patients that achieved a pCR, we also performed the Wilcoxan rank sum test using maximum (worst) symptom severity. **Results:** Of 288 patients included in our analysis (median age = 48 years, range = 20-78), 203 (70.5%) were White, 17 (5.9%) were Asian, 33 (11.5%) were Black or African American, and 35 (12.2%) were Hispanic. PRO analysis revealed that patients that had moderate to severe muscle pain (27% vs 10% OR = 3.15, $p < 0.05$), joint pain (22% vs 8% OR = 3.23, $p < 0.05$), headache (27% vs 12.5% OR = 2.59, $p < 0.05$), or mouth/throat sores (16% vs 5% OR = 3.56, $p < 0.05$) within weeks 1-3 had higher odds of achieving a pCR. When we looked at maximum severity between weeks 1-3, patients that achieved a PCR had higher grade muscle pain ($p = 0.04$), heart palpitations ($p = 0.035$), and significantly lower grade numbness and tingling ($p = 0.002$). Beyond 6 weeks, associations were weaker or insignificant. **Conclusions:** Our study utilizes an analysis framework that was able to determine sentinel symptoms such as muscle and joint pain, mouth/throat sores and palpitations as early as weeks 1-3 associated with increased efficacy. This may suggest an early immune reaction in patients that eventually respond favorably to treatment. Our work can help provide earlier proactive monitoring to mitigate toxicities, treatment redirection if needed, and a potential symptom-based early understanding to personalize treatment efficacy. A similar analysis is underway to predict immune related AEs. Clinical trial information: NCT01042379. Research Sponsor: National Cancer Institute.

Automated prediction of response to neoadjuvant chemotherapy from digitized H&E slides of pre-treatment core needle biopsies in INFORM (TBCRC 031) patients with low stromal TILs.

Stuart J. Schnitt, Nadine M. Tung, Judy Ellen Garber, Satabhisa Mukhopadhyay, Tathagata Dasgupta, Craig A. Bunnell; Brigham and Women's Hospital, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; 4D Path Inc., Newton, MA

Background: We previously performed anautomated analysis of whole slide images (WSI) of H&E-stained pre-treatment core needle biopsies (CNBs) from patients (pts) enrolled in the INFORM phase II trial of neoadjuvant cisplatin vs doxorubicin-cyclophosphamide in HER2-negative germline *BRCA* carriers. That analysis demonstrated that a digital biomarker of complex immune response (CmbI) which combines immune heterogeneity index (IHI), proliferative, and cell cycle G1/S deregulation signatures, was significantly predictive of response (RCB 0,1) to neoadjuvant chemotherapy (NAC) in all pts, in sub-cohorts including TNBC, and in both therapy arms. Further, a lower IHI, indicating less heterogeneity of stromal tumor infiltrating lymphocytes (sTIL), was predictive of a better response to NAC (RCB 0,1), whereas a higher IHI, indicating greater heterogeneity of sTIL was associated with a worse response (RCB 2,3). The predictive performance of IHI alone was modest compared to CmbI but superior to sTIL. High sTIL is associated with favorable prognosis for NAC, especially in TNBC. However, the impact of heterogeneity of immune cell distribution on NAC response, particularly in those with low sTIL is unknown. The current study evaluated if IHI could augment sTIL assessment by identifying NAC responders in patients with tumors demonstrating low sTIL. **Methods:** CNBs scanned at 40x on a Hamamatsu Nanozoomer scanner were evaluated using the 4D QPOR platform to generate IHI as a continuous index. Among 88 QPOR analyzable pts, 85 had sTIL scores available from prior visual pathologic review. Tumors with low sTIL ($<$ 30%, a previously documented clinically significant cut-off),were further stratified into low vs high IHI using median IHI for the population as the cut-off. We then determined the relationship between IHI and likelihood of response to NAC (RCB 0,1) in the overall cohort, and in the TNBC and ER low ($<$ 10%) sub cohorts. The analysis was also performed using the median sTIL cut-off $<$ 20% previously used in INFORM. **Results:** Low IHI was significantly predictive of NAC response (RCB 0,1) in low sTIL pts in the overall cohort (N = 64, OR = 4.75; 95% CI1.50, 16.21), p = 0.005, PPV = 70%) and in the ER low sub cohort (N = 46, OR = 4.04;95% CI 1.04-17.38, p = 0.04, PPV = 72%). IHI was modestly predictive in the low sTIL pts in TNBC sub cohort (N = 41, OR = 4.28 (0.99, 20.77), p = 0.03, PPV = 71%) but not predictive in high sTIL pts ($<$ 1/3 pts in each subgroup). For sTIL $<$ 20%, IHI had stronger predictive ability in all pts (N = 64, OR = 7.63 (1.83, 40.09), p = 0.0016, PPV = 80%). **Conclusions:** Heterogeneity of immune cell distribution determined by computational analysis of WSI of pre-treatment CNB of patients with germline BRCA mutations and HER2-negative cancers in the INFORM trial improves response prediction to NAC in patients with low baseline sTIL as determined by visual analysis. Research Sponsor: None.

I-SPY2 endocrine optimization pilot (EOP): Neoadjuvant lasofoxifene (Laso) in molecularly selected patients with hormone receptor positive (HR+)/HER2 negative (HER2-) stage 2/3 breast cancer (BC).

Mei Wei, Anthony D. Elias, Karthik Giridhar, Matthew P. Goetz, Rita Mukhtar, Christos Vaklavas, Laura van t Veer, Silver Alkhafaji, Gillian L. Hirst, Hope S. Rugo, Nan Chen, W. Fraser Fraser Symmans, Alexander D. Borowsky, Lamorna Brown Swigart, Natsuko Onishi, Douglas Yee, Nola Hylton, Laura Esserman, Jo Chien; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; University of Colorado Cancer Center, Aurora, CO; Mayo Clinic, Rochester, MN; Division of Surgical Oncology, Department of Surgery, University of California, San Francisco, San Francisco, CA; Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT; Department of Laboratory Medicine, University of California, San Francisco, San Francisco, CA; University of California, San Francisco, San Francisco, CA; UCSF Comprehensive Cancer Center, San Francisco, CA; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; University of Chicago, Chicago, IL; The University of Texas MD Anderson Cancer Center, Alliance for Clinical Trials in Oncology, Houston, TX; University of California, Davis, Davis, CA; Masonic Cancer Center, University of Minnesota, Minneapolis, MN; Department of Surgery, University of California, San Francisco, San Francisco, CA

Background: EOP, an I-SPY2 sub-study, evaluates the tolerability and activity of novel endocrine strategies in stage 2/3 breast cancer (BC) patients (pts) predicted to have lower chemotherapy benefit. Laso, a selective estrogen receptor modulator (SERM), has shown favorable toxicity profile and activity in HR+/HER2- endocrine-resistant metastatic BC. **Methods:** Pts with Stage 2/3 HR+/HER2-, MammaPrint (MP) low risk BC were enrolled. Pts with MP High1 BC were included if clinically node-negative. Pts received oral laso 5 mg daily for six 28-day cycles. Laso was continued until the day prior to surgery. Premenopausal pts received ovarian function suppression (OFS) starting C2D1. The primary endpoint was feasibility (>75% of patients completing >75% study therapy). Baseline (T0), 3-wk (T1) biopsies, and the surgical specimen (T3) was assessed centrally for Ki-67. Breast MRI functional tumor volume (FTV) was performed at T0, T1, 12 weeks (T2), and pre-operatively (T3). Blood was collected for tumor informed ctDNA at T0, T1, T2, T3. Advance event (AE) was assessed using CTCAE V5. **Results:** From 3/2023 to 5/2024, 20 pts were enrolled. Median age 50.5 years, 50% premenopausal, and 1 male pt. 60% cN0, 80% MP low-risk signature. 18 (90%) pts completed >75% study therapy. Two pts discontinued treatment due to pt preference. Median Ki67 at T0 was 14.7%. At T1, 87.5% of pts remained or suppressed Ki67 to <10% and 37.5% suppressed to <2.7%. Ki67 at T1 was similar between pre-and postmenopausal pts despite OFS (Table). The median MRI FTV was 8.4 cc at T0, and 3.4 cc at T3. Median % FTV reduction from T0 to T3 was -47.5%. 2/20 pts (10%) achieved a modified PEPI score of 0. No patients achieved completed pathological response. Of the 16 pts with RCB results, 2 (12.5%) RCB-1, 6 (37.5%) RCB-2, 8 (50%) RCB-3 disease. 14 pts had ctDNA available at T0. 4/14 were ctDNA+ at T0, 2 of whom became ctDNA negative, and 2 remained ctDNA+. 10/14 pts were ctDNA negative at T0, 8 of whom remained negative, 2 became positive at T1 then cleared. All AEs were grade(G) 1 except 1 pt with G2 hot flashes. Most common AEs include hot flashes (85%), constipation (50%), fatigue (50%), and nausea (35%). One pt had G3 hypersensitivity and hypertension, both unrelated to therapy. **Conclusions:** Neoadjuvant laso demonstrates a favorable AE profile and promising anti-tumor activity in suppressing 3-wk Ki67 and MRI FTV change in pts with HR+ HER2-negative early BC. Ki67 suppression in premenopausal pts was seen in the absence of OFS. Clinical trial information: NCT01042379. Research Sponsor: NIH PO1-CA210961.

Ki67 expression at pre-treatment, and 3-wk time point.

	All Patients (n=20)	Premenopausal (n=10)	Postmenopausal (n=9)
Median Ki67 expression			
Baseline	10.0%	12.5%	10.0%
3-wk	5.1%	3.0%	6.0%
Number of pts with Ki67 expression <10% at 3-wk	87.5%[1]	87.5%	85.7%
Number of pts with Ki67 expression <2.7% at 3-wk	37.5%	50%	28.6%

[1]Include the one male pt.

Verification of the BREASTEST assay in an Australian population: A novel liquid biopsy assay measuring lipid biomarkers for early-stage breast cancer screening.

David Speakman, Klaus-Peter Adam, Tim Huang, Sanjay Warrier, Corinne Ooi, James French, Elisabeth Elder, Cindy Mak, Mary Rickard, Wendy Vincent, Catherine Poliness, Kuan-Chi Wang, Nirmala Pathmanathan, Bruce Mann, Amani Batarseh, John Hurrell, Fatemeh Vafaee, Simon Preston; BreastScreen Victoria, Melbourne, VIC, Australia; BCAL Diagnostics Inc., Raleigh, NC; OmniOmics.ai, Sydney, NSW, Australia; Chris O'Brien Lifehouse, Sydney, NSW, Australia; Southern Breast Oncology, Melbourne, VIC, Australia; Lakeview Private Hospital, Sydney, NSW, Australia; Sydney Breast Clinic, Sydney, NSW, Australia; BreastScreen NSW (SLHD), Royal Prince Alfred Hospital, Sydney, NSW, Australia; The Royal Melbourne Hospital, Melbourne, VIC, Australia; St Vincents Private Hospital, Sydney, NSW, Australia; Westmead Hospital, Sydney, NSW, Australia; BCAL Diagnostics, Sydney, NSW, Australia

Background: Women with dense breasts are at higher risk of developing breast cancer however there is no agreement on how to screen these women, despite mandatory density reporting becoming more prevalent. Currently available image-based, population level breast screening modalities have poor sensitivity in these women. Likewise, the positive predictive value of imaging is reduced due to a higher false positive rate/recall rate compared to that of women with less dense breasts. Liquid biopsy approaches do not suffer from imaging-dependent challenges with density and provide a promising option in this population. We have discovered a novel liquid biopsy assay using a lipidomic discovery platform by combining liquid chromatography tandem mass spectrometry (LC-MS/MS) and machine learning. The BREASTEST assay is intended to complement standard of care screening and address gaps in the current screening paradigm. **Methods:** This study was conducted to verify the performance of the BREASTEST assay in an Australian population (n = 720). This verification study was an observational case-control study that prospectively recruited women with breast cancer (n = 275) or without (n = 446) across 10 clinical sites over a 34-month period. A primary imaging modality was identified for each subject and a binary classification was assigned to the outcome of this imaging (normal/suspicious) to enable comparison to, and combination with, the BREASTEST assay. An assay with a high sensitivity has utility as a rule-out test and would complement population-based imaging (high specificity). Therefore, the assay was designed to achieve a sensitivity of 0.90. The combined specificity of imaging with the assay was calculated to estimate the clinical benefit BREASTEST could bring in ruling-out women without breast cancer. A safe de-escalation rate was also calculated in this study to assess the potential reduction in unnecessary further assessment if this assay was added to standard imaging. **Results:** The utility of the BREASTEST assay was observed when results were combined with primary imaging data in the study cohort. Across all imaging modalities and breast densities, the assay improved the combined specificity in 45–75-year-old women by +6.1% (0.712, 0.773) and had a safe de-escalation rate of 21.0%. Highlighting the potential benefit to women with dense breasts, in women aged 30-49 years with breast density category D the combined specificity was +14.7% (0.585, 0.732) and safe de-escalation rate of 37.5%. The BREASTEST assay alone obtained a sensitivity of 0.90, specificity of 0.369 with an AUC of 0.743. **Conclusions:** The performance and utility of the BREASTEST assay was verified in this study in an Australian population. It has highlighted the potential of this assay in the workup of women with breast conditions, in particular women with dense breasts. Research Sponsor: BCAL Diagnostics.

TPS615 Poster Session

A phase III trial evaluating addition of adjuvant chemotherapy to ovarian function suppression + endocrine therapy in premenopausal women with pN0-1, HR+/HER2- breast cancer (BC) and oncotype recurrence score (RS) ≤25 (OFSET): NRG-BR009.

Eleftherios P. Mamounas, Gong Tang, Shannon L. Puhalla, Sandra M. Swain, Patricia A. Ganz, Norah Lynn Henry, Reena S. Cecchini, Sonya A. Reid, Priya Rastogi, Charles E. Geyer Jr., Julia R. White, Amy Sanders Clark, Tufia C. Haddad, Gregory A. Vidal, Norman Wolmark; NSABP and AdventHealth Cancer Institute, Orlando, FL; NRG Oncology SDMC; Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA; NSABP Foundation, Inc.; UPMC Hillman Cancer Center; University of Pittsburgh School of Medicine, Pittsburgh, PA; Georgetown Lombardi Comprehensive Cancer Center; Georgetown University Medical Center; and MedStar Health, Washington, DC; David Geffen School of Medicine at UCLA, UCLA Fielding School of Public Health, UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; University of Michigan Medical School, Ann Arbor, MI; Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN; NSABP Foundation, Inc.; UPMC Hillman Cancer Center; and University of Pittsburgh School of Medicine, Pittsburgh, PA; University of Kansas Medical Center Comprehensive Cancer Center, Kansas City, KS; Perelman School of Medicine at the University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; Mayo Clinic, Rochester, MN; West Cancer Center & Research Institute, Germantown, TN

Background: The TAILORx and RxPONDER trials demonstrated that RS identifies many postmenopausal pts with node-neg and node-pos BC and RS ≤25, who do not benefit from addition of ACT to endocrine therapy (ET). Both trials also showed that certain subsets of premenopausal pts (node-neg/high clinical risk/RS 16-20, node-neg/RS 21-25, and node-pos/RS ≤25) benefited from adding ACT to ET. Most premenopausal pts in these trials did not receive ovarian function suppression (OFS) as part of their ET regimen. Given the observed benefit from OFS in high-risk premenopausal pts with HR+/HER2- BC in the SOFT/TEXT trials, many questioned whether all or part of the observed ACT benefit in the TAILORx/RxPONDER trials may have been the result of chemotherapy-induced OFS. To address this question, we developed OFSET, a phase III, multicenter clinical trial comparing OFS+ET *v* ACT+OFS+ET. **Methods:** We hypothesize that addition of ACT to OFS+ET is superior to OFS+ET in improving invasive breast cancer-free survival (IBCFS) among premenopausal, early-stage BC pts with HR+/HER2- tumors, and a 21-gene RS between 16-25 (for pN0 pts) and 0-25 (for pN1 pts). Secondary objectives include invasive disease-free survival, overall survival, distant recurrence-free interval, breast cancer-free interval, and health-related quality of life (HRQOL). Pts must be node-neg with RS 16-20 (plus high clinical risk), or RS 21-25, or have 1-3 positive nodes with RS ≤25. Stratification is by nodal status/RS status (pN0 RS 16-25 *v* pN1 RS 0-15 and pN1 RS 16-25), intent to receive CDK4/6 inhibitor (yes; no), and age (18-39 *v* ≥40). Pts are randomized after surgery to either OFS+ET or ACT+OFS+ET*v* ET is an aromatase inhibitor (AI). Choice is per investigator discretion; tamoxifen is allowed if AI is not tolerated or if OFS is incomplete. Radiotherapy will be administered per investigator discretion per protocol guidelines. The HRQOL sub-study will assess differences in severe menopausal symptoms, measured by the FACT ESS-19 score between arms, as well as increased pain severity (PROMIS). Blood and tumor specimens will be collected for future research. Accrual of 3,960 pts is anticipated to be completed in 7 yrs, 7 mos. Per NSABP B-28 and RxPONDER data, 5yr IBCFS of pN1 pts on the ACT+OFS+ET arm is estimated at 92.3%. Based on TAILORx data, 5yr IBCFS of pN0 pts on the ACT arm is ~95%. Assuming 56% of pts to be pN0 and 44% pN1, and a 0.5% annual loss-to-follow-up rate, the definitive analyses to detect a hazard ratio: 0.75 with ACT+OFS+ET *v* OFS+ET, with one-sided α of 0.025 and 80% power, will require 380 IBCFS events, expected to occur~11 yrs after study initiation. OFSETwas activated Aug 2023. As of 1-6-25, accrual is: 188/3,960. NCT #: NCT05879926. Support: U10CA180868, -80822, UG1CA189867, U24CA196067. Clinical trial information: NCT05879926. Research Sponsor: National Cancer Institute; U10CA180868; National Cancer Institute; U10CA180822; National Cancer Institute; UG1CA189867; National Cancer Institute; U24CA196067.

A phase 3, randomized study of adjuvant sacituzumab tirumotecan plus pembrolizumab vs treatment of physician's choice in participants with triple-negative breast cancer who received neoadjuvant therapy and did not achieve a pathologic complete response at surgery.

Heather L. McArthur, Rebecca Alexandra Dent, Rina Hui, Yeon Hee Park, Peter Schmid, Jing Wei, Jaime A. Mejia, Wilbur Pan, Javier Cortes; UT Southwestern Medical Center, Dallas, TX; National Cancer Center Singapore and Duke-National University of Singapore (NUS) Medical School, Singapore, Singapore; Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; and Centre of Cancer Medicine, School of Clinical Medicine, University of Hong Kong, Hong Kong SAR, China; Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Merck & Co., Inc., Rahway, NJ; Merck & Co, Inc., Rahway, NJ; Medica Scientia Innovation Research (MEDSIR), International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Universidad Europea De Madrid, Madrid, Spain

Background: Trophoblast cell surface antigen 2 (TROP2) expression is higher in triple-negative breast cancer (TNBC) vs other breast cancer subtypes, and high expression is associated with poor prognosis. Sacituzumab tirumotecan (sac-TMT; also known as MK-2870/SKB264) is a novel antibody-drug conjugate composed of anti-TROP2 antibody coupled to a cytotoxic belotecan derivative via a novel linker (average drug/antibody ratio, 7.4). In a prior phase 3 study (OptiTROP-Breast01), sac-TMT alone improved PFS (HR, 0.31; 95% CI, 0.22-0.45; $P < 0.00001$) and OS (HR, 0.53; 95% CI, 0.36-0.78; $P = 0.0005$) vs chemotherapy in participants with heavily pretreated advanced TNBC. The current standard of care (SOC) for patients with newly diagnosed, high-risk, early-stage TNBC is neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab after surgery. Patients who do not achieve a pathologic complete response (pCR) with the current SOC have higher rates of recurrence and mortality vs patients who achieve pCR. This study (NCT06393374) evaluates adjuvant sac-TMT + pembrolizumab vs treatment of physician's choice (TPC; pembrolizumab ± capecitabine) in participants with TNBC who received neoadjuvant therapy and did not achieve pCR at surgery.
Methods: This phase 3, multicenter, open-label study is enrolling participants ≥18 years old with centrally confirmed TNBC per most recent American Society of Clinical Oncology/College of American Pathologists guidelines. Participants have non-pCR after ≥5 cycles of neoadjuvant pembrolizumab + chemotherapy, including ≥1 cycle of anthracycline-based neoadjuvant therapy. Participants must provide tissue from the surgical specimen for central TROP2 assessment and be able to continue on adjuvant pembrolizumab. Randomization must be conducted ≤12 weeks from surgical resection (window may be extended in consult with sponsor). Participants are randomized 1:1 to pembrolizumab 400 mg Q6W for 5 doses + sac-TMT 4 mg/kg Q2W for 12 doses or TPC with pembrolizumab 400 mg Q6W for 5 doses ± capecitabine 1000-1250 mg/m^2 BID on days 1-14 and days 22-35 every 42 days for 4 cycles until completion of therapy or disease recurrence, unacceptable toxicity, or withdrawal. Randomization is stratified by residual tumor and lymph node status, TROP2 expression, and intention to use capecitabine. Primary endpoint is invasive disease-free survival. Secondary endpoints are OS, distant recurrence-free survival, patient-reported outcomes, and safety. Enrollment began Q2 2024. Clinical trial information: NCT06393374. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS617 **Poster Session**

Adjuvant WIDER: A phase 3b trial of ribociclib (RIB) + endocrine therapy (ET) as adjuvant treatment (tx) in a close-to-clinical-practice patient (pt) population with HR+/HER2− early breast cancer (EBC).

Stephanie L. Graff, Fatima Cardoso, Hope S. Rugo, Christine Brezden-Masley, Gustavo Werustsky, Debasish Tripathy, Joyce O'Shaughnessy, Cynthia X. Ma, Michael A. Danso, Yen-Shen Lu, Gul Basaran, Mario Campone, Michelino De Laurentiis, Javier Cortes, Valarie Worthy, Melissa Gao, Benoit Musel, Fen Ye, Kristyn Pantoja, Peter A. Fasching; Brown University Health Cancer Institute, The Warren Alpert Medical School of Brown University, Providence, RI; ABC Global Alliance, Lisbon, Portugal; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; Division of Medical Oncology and Hematology, Faculty of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; Latin American Cooperative Oncology Group, and Hospital São Lucas, PUCRS University, Porto Alegre, Brazil; The University of Texas MD Anderson Cancer Center, Houston, TX; Baylor University Medical Center, Texas Oncology, Dallas, TX and Sarah Cannon Research Institute, Dallas, TX; Division of Oncology, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO; Brock Cancer Center, Virginia Oncology Associates and Sarah Cannon Research Institute, Norfolk, VA; National Taiwan University Hospital, Taipei, Taiwan; Department of Oncology, Acıbadem Altunizade Hospital, Istanbul, Turkey; Institut de Cancérologie de l'Ouest-René Gaudducheau, Centre de Recherche en Cancérologie, Saint-Herblain, France; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; MEDSIR, IBCC, Pangaea Oncology, Quiron Group, Universidad Europea de Madrid, IOB Madrid, Institute of Oncology, Hospital Beata Maria Ana; Hospital Universitario Torrejón, Ribera Group, Madrid, Spain; TOUCH, The Black Breast Cancer Alliance, Annapolis, MD; Novartis Pharma AG, Basel, Switzerland; Novartis Pharmaceuticals Corporation, East Hanover, NJ; Novartis Pharmaceuticals Corporation, Cambridge, MA; University Hospital Erlangen Comprehensive Cancer Center Erlangen-EMN, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany

Background: The phase 3 NATALEE trial met its primary endpoint with significant invasive disease–free survival benefit with RIB + ET vs ET alone in a broad pt population with stage II/III HR+/HER2− EBC, sustained with additional follow-up at 44.2 months (hazard ratio, 0.715). The Adjuvant WIDER trial will evaluate RIB + ET in an HR+/HER2− EBC pt population that reflects pts seen in clinical practice as it has wider eligibility criteria, including an additional focus on enrolling minority pts underrepresented in NATALEE. Given the unmet need in pts with Stage II/III EBC, the results of this trial will complement existing data on benefits of RIB + ET. **Methods:** This phase 3b, multicenter, open-label, single-arm trial will evaluate, with early involvement of key pt advocacy groups, the efficacy and safety of adjuvant RIB + ET in a close-to-clinical-practice pt population with HR+/HER2− EBC. Eligible women and men aged ≥18 years with an ECOG PS of 0 to 2 and anatomic stage II/III disease (AJCC 8th ed), with additional criteria for stage IIA disease (N1 or N0 with grade 3, or grade 2 with Ki-67 ≥20% or high genomic risk), will be included. Pts will receive RIB (400 mg/d; 3 wk on/1 wk off) + ET (letrozole 2.5 mg/d, anastrozole 1 mg/d, or exemestane 25 mg/d) for 36 months, followed by ET alone as SOC per investigator's clinical judgment. Pre/peri-menopausal women and men will receive goserelin 3.6 mg or leuprolide 3.75 mg/4 wk. Switching between ETs during study tx will be allowed in cases of unmanageable toxicity. Pts may have received (neo)adjuvant ET if initiated ≤36 months prior to enrollment. The number of pts with prior ET between 12 and 36 months will be capped at ≈30%; this cap will not be applicable to Black or African American pts. For pts with prior ET >12 months, restaging is recommended. Pts with prior CDK4/6i tx (except RIB) in the adjuvant setting for ≤6 months who discontinued due to toxicity can be included. Study tx may be held ≤28 days (or longer on agreement) to recover from RIB-related toxicity before restarting. If indicated, pts must have completed radiotherapy or chemotherapy before screening. Key exclusion criteria are distant metastases and/or recurrence and clinically significant, uncontrolled heart disease at screening. The primary endpoint is investigator-assessed invasive breast cancer–free survival rate at 3 years per STEEP v2.0 criteria. Secondary endpoints include invasive disease–free survival, distant disease–free survival, distant relapse–free survival, recurrence–free interval, overall survival, quality of life, and safety. Exploratory endpoints will assess subsequent antineoplastic tx, potential mechanisms of RIB benefit/resistance to RIB + ET, and RIB efficacy/safety in Black pts. Estimated enrollment is 1400 pts globally. Recruitment is ongoing. Clinical trial information: NCT05827081. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS618 **Poster Session**

Phase III study to evaluate the efficacy and safety of GLSI-100 (GP2 + GM-CSF) in breast cancer patients with residual disease or high-risk PCR after both neo-adjuvant and postoperative adjuvant anti-HER2 therapy: Flamingo-01.

Snehal Patel, Jaye Thompson, Mira Patel, F. Joseph Daugherty, Mothaffar F. Rimawi; Greenwich LifeSciences, Stafford, TX; Lester and Sue Smith Breast Center, Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX

Background: GP2 is a biologic nine amino acid peptide of the HER2/*neu* protein delivered in combination with Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) that stimulates an immune response targeting HER2/neu expressing cancers, the combination known as GLSI-100. Of the 146 patients that have been treated with GLSI-100 over 4 clinical trials, GLSI-100 was well-tolerated and no serious adverse events observed were considered related to the immunotherapy. **Methods:** This Phase III trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy, 6 intradermal injections of GLSI-100 or placebo will be administered over the first 6 months and 5 subsequent boosters will be administered over the next 2.5 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up. Study Size – Interim Analysis: Approximately 498 patients will be enrolled. To detect a hazard ratio of 0.3 in invasive breast cancer free survival (IBCFS), 28 events will be required. An interim analysis for superiority and futility will be conducted when at least 14 events have occurred. This sample size provides 80% power if the annual rate of events in placebo patients is 2.4% or greater. Up to 250 non-HLA-A*02 subjects will be enrolled in an open-label arm. Eligibility Criteria: The patient population is defined by these key eligibility criteria: 1) HER2/neu positive and HLA-A*02, 2) Residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy, 3) Exclude Stage IV, and 4) Completed at least 90% of planned trastuzumab-based therapy. Trial Objectives: The trial objectives are to: 1) Determine if GP2 therapy increases IBCFS, 2) Assess the safety profile of GP2, and 3) Monitor immunologic responses to treatment and assess relationship to efficacy and safety. Study Status: The study is actively recruiting and enrolling patients in the US and Europe at up to 150 sites. Contact Information: Greenwich LifeSciences, Inc., Stafford, TX; Email: Flamingo-01@greenwichlifesciences.com; Website: greenwichlifesciences.com Funding: This trial is supported by Greenwich LifeSciences. Clinical trial information: NCT05232916. Research Sponsor: None.

TPS619 Poster Session

ELEGANT: Elacestrant versus standard endocrine therapy (ET) in women and men with node-positive, estrogen receptor-positive (ER+), HER2-negative (HER2-), early breast cancer (eBC) with high risk of recurrence in a global, multicenter, randomized, open-label phase 3 study.

Aditya Bardia, Virginia G. Kaklamani, Joyce O'Shaughnessy, Peter Schmid, J. Thaddeus Beck, Michelino De Laurentiis, Giuseppe Curigliano, Hope S. Rugo, Carlos Hernando Barcenas, William John Gradishar, Michail Ignatiadis, David A. Cameron, Giulia Tonini, Simona Scartoni, Jennifer A. Crozier, Leonardo Viana Nicacio, Tomer Wasserman, Sara M. Tolaney; UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA; University of Texas Health Science Center at San Antonio, San Antonio, TX; Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Highlands Oncology, Springdale, AR; Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; Istituto Europeo di Oncologia, IRCCS, University of Milano, Milano, Italy; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Medicine, Division of Hematology and Oncology, CTC Core Facility, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; Breast Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Brussels, Belgium; Institute of Genetics and Cancer and Usher Institute, University of Edinburgh, Edinburgh, Scotland, United Kingdom; Menarini Group, Florence, Italy; Menarini Group, New York, NY; Dana-Farber Cancer Institute, Boston, MA

Background: Adjuvant ET is the standard of care (SOC) for treating ER+/HER2- eBC. Despite advances to optimize adjuvant treatment in high-risk ER+/HER2- eBC, there continues to be a risk of local and metastatic (incurable) recurrence that persists, and new therapies with desirable safety profiles are warranted. Elacestrant is a next-generation oral SERD that provides a novel mechanism of action that has shown both SERD (degradative) and SERM (partial agonist) activity that differs from currently available adjuvant ET (Wardell, ERC 2015). In the EMERALD trial, elacestrant significantly prolonged PFS vs SOC ET in the overall population (HR 0.70; 95% CI 0.55-0.88; P=0.0018) and in patients with *ESR1*-mut tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) (Bidard, JCO 2022). In patients with *ESR1*-mut tumors who received prior ET+CDK4/6i ≥12 mo, mPFS with elacestrant was 8.6 vs 1.9 mo with SOC ET (Bardia, CCR 2024). In a preoperative, window of opportunity ER+/HER2- eBC trial (SOLTI-1905-ELIPSE), elacestrant was associated with complete cell cycle arrest (defined as Ki67<2.7%) rate of 27% and a statistically significant mean change from baseline, shifting tumor biology toward a more endocrine-sensitive and less proliferative tumor phenotype (Vidal, CCR 2025). Given that elacestrant demonstrated efficacy in mBC regardless of *ESR1*-mut status relative to SOC ET and has shown biologic activity in eBC, it is hypothesized that elacestrant can prolong invasive breast cancer-free survival (IBCFS) in patients with high-risk eBC who received prior adjuvant ET±CDK4/6i. **Methods:** ELEGANT (NCT06492616) is a global, multicenter, open-label phase 3 study designed to evaluate elacestrant vs SOC ET (AI or tamoxifen) in patients with eBC and a high risk of recurrence. Patients will be randomized 1:1 to continue SOC ET or to elacestrant for a duration of 5 yrs. Eligible patients are women or men with ER+/HER2− node-positive eBC who have completed 24-60 mo of adjuvant ET±CDK4/6i and have ECOG PS ≤1. Patients who received a prior CDK4/6i or a PARP inhibitor must have already completed or discontinued these treatments. Pre/perimenopausal women and men will be administered a LHRH agonist. Exclusion criteria include inflammatory breast cancer, history of prior invasive breast cancer, and >6 mo continuous interruption of prior SOC adjuvant ET or discontinuation of adjuvant ET >6 mo prior to randomization. The primary endpoint is IBCFS. Key secondary endpoints include distant relapse-free survival, overall survival, invasive disease-free survival, safety, patient-reported outcomes-quality of life, and pharmacokinetics. Status: Planned enrollment is 4,220 patients; recruitment is ongoing. Clinical trial information: NCT06492616. Research Sponsor: Menarini Group.

TPS620 **Poster Session**

EORTC-2129-BCG: Elacestrant for treating ER+/HER2- breast cancer patients with ctDNA relapse (TREAT ctDNA).

Michail Ignatiadis, Emmanouil S. Saloustros, Ana Joaquim, Fanny Grillet, Yiola Marcou, Sonia Pernas, Patrick Neven, Sonia Del Barco Berron, Jose Juan Ponce-Lorenzo, Catharina Willemien Menke-van Der Houven Van Oordt, Catherine Margaret Kelly, Mathias Konrad Fehr, Evangelia Razis, Theodoros Foukakis, Matteo Lambertini, Francois Clement Bidard, Coralie Poncet, Wolfgang Janni; Breast Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (HUB), Brussels, Belgium; Department of Medical Oncology, University Hospital of Larissa, Larissa, Greece; EORTC, Brussels, Belgium; European Organization for Research and Cancer (EORTC) Headquarters, Brussels, Belgium; BOCOC, Nicosia, Cyprus; Institut Català d'Oncologia, IDIBELL, L'Hospitalet, L'hospitalet, Barcelona, Spain; UZ Gasthuisberg - Leuven Cancer Institute, Leuven, Belgium; Instituto Catalán de Oncología de Girona; GEICAM Spanish Breast Cancer Group, Girona, Spain; Oncology Department, Dr. Balmis General University Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain; Department of Medical Oncology, Amsterdam University Medical Center; Cancer Centre Amsterdam, Amsterdam, Netherlands; Trinity St James's Cancer Institute, Dublin, Ireland; Kantonsspital Frauenfeld, Frauenfeld, Switzerland; Hygeia Hospital, Athens, Greece; Karolinska Institute, Solna, Sweden; U.O. Clinical Oncology, IRCCS Ospedale Policlinico San Martino, University of Genova, Genova, Italy; Institut Curie and University of Versailles Saint-Quentin-en-Yvelines-Paris-Saclay University, Paris, France; EORTC, Woluwe-Saint-Lambert, Belgium; University Hospital Ulm, Ulm, Germany

Background: (Neo)adjuvant systemic treatment, with chemotherapy and/or endocrine therapy (ET), substantially reduces the recurrence rates of estrogen receptor positive (ER+) human epidermal growth factor receptor 2 negative (HER2-) early-stage breast cancer (BC). However, recurrences still occur up to 20 years after diagnosis. Circulating tumor DNA (ctDNA) has emerged as a useful biomarker for surveillance in several solid tumors. ctDNA-based detection of molecular recurrence could allow the start of effective therapies before the clinical evidence of metastases. Elacestrant, a selective ER degrader, approved in the advanced setting of ER+/HER2- ESR1-mutated BC following progression on a CDK4/6-inhibitor, could be used at the time of ctDNA-based molecular relapse to delay or prevent the clinical manifestation of distant metastasis. **Methods:** TREAT ctDNA is an European Organisation for Research and Treatment of Cancer (EORTC)-led intergroup international, multicentre, randomised, open label, superiority phase III trial to evaluate adjuvant elacestrant vs standard ET in patients with ER+/HER2- BC. The study comprises a screening and a randomised phase based on ctDNA status using a clinically-validated, tumor-informed molecular residual disease ctDNA assay (Signatera). Screening phase: 1960 patients with intermediate to high-risk stage II or III ER+/HER2- BC on medium to long duration ET will be screened for a ctDNA-based molecular relapse every 6 months. Randomised phase: 220 ctDNA-positive patients without imaging evidence of recurrence will be randomised 1:1 between continuing current ET versus switching to elacestrant for a duration of at least 7 years of ET in total. Participants will undergo intensive follow-up for 3 years with computed tomography and bone scans, in addition to the standard annual breast imaging. The primary endpoint of the study is distant metastasis free survival and secondary endpoints are invasive disease-free survival, relapse-free survival, overall survival, safety and quality of life. Recruitment started in December 2023 in Belgium, is open in 12 countries at 74 sites and anticipates up to 120 enrolling sites in 2025. Overall study status and databases status will be periodically reviewed by the IDMC. Clinical trial identification: EU trial number 2022-501453-36-00. NCT05512364. Study conducted under the Breast International Group (BIG) umbrella. Collaborative groups: GIM, CTI, SUCCESS, SOLTI, HeCOG, HORG, BOOG, SweBCG and ETOP-IBCSG. Clinical trial information: 2022-501453-36-00. Research Sponsor: BERLIN-CHEMIEAG MENARINI from Germany.

TPS621 Poster Session

The SURVIVE study: Standard surveillance vs. intensified liquid biopsy-based surveillance in early breast cancer survivors.

Henning Schäffler, Sophia Huesmann, Thomas W. P. Friedl, Kerstin Pfister, Angelina Fink, Franziska Mergel, Tatjana Braun, Forca Mehmeti, Natalie Uhl, Sabine Heublein, Andreas D. Hartkopf, Volkmar Mueller, Lisa Maria Wiesmueller, Tanja N. Fehm, Brigitte Rack, Peter A. Fasching, Wolfgang Janni; Department of Gynecology and Obstetrics, University Hospital Ulm, Ulm, Germany; Department of Gynecology and Obstetrics, SLK Klinikum Heilbronn, Heilbronn, Germany; Department of Obstetrics and Gynecology, University of Tuebingen, Tuebingen, Germany; Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany; Department of Gynecology and Obstetrics, University Hospital Düsseldorf, Düsseldorf, Germany; University Hospital Erlangen, Comprehensive Cancer Center (CCC) Erlangen-EMN, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany; University Hospital Ulm, Ulm, Germany

Background: Current breast cancer (BC) follow-up relies on clinical examinations and breast imaging, as studies from the 1980s demonstrated no survival benefit from distant metastasis screening. However, with advancements in treatment strategies and the diagnostic potential of liquid biopsies, this approach warrants re-evaluation. To enable pre-symptomatic detection of distant relapse, we propose assessing a liquid biopsy-guided surveillance strategy incorporating tumor markers (CA 27.29, CA 125, CEA), circulating tumor cells (CTCs), and circulating tumor DNA (ctDNA). **Methods:** The SURVIVE study (NCT05658172) is the first large-scale, multicenter, partially double-blinded randomized controlled trial comparing intensified and standard surveillance in 3,500 survivors of medium- to high-risk early breast cancer (eBC). All subtypes are eligible. High risk includes (neo-)adjuvant chemotherapy, tumor size >50 mm, positive lymph nodes (≥pN1mi), or high grade (≥G3). Patients are randomized 1:1 to standard or liquid biopsy-guided intensified follow-up. Primary therapy (surgery, adjuvant chemo- or radiotherapy) completion is required, while adjuvant endocrine, antibody, or targeted therapy is permitted. Enrollment is allowed up to 24 months post-primary therapy for TNBC/HER2+ eBC and 60 months for HR+/HER2- eBC. In both arms, guideline-based follow-up is performed, with additional blood samples collected longitudinally (years 1–3 every 3 months; years 4–5 every 6 months). In the intervention arm, these samples are analyzed for tumor markers, CTCs, and ctDNA (RaDaR assay). Abnormal findings indicating minimal residual disease (MRD) trigger full staging. Recurrence is treated per national guidelines. In the case of M0 status, liquid biopsy testing and staging continue, with the option for inclusion in interventional trials, if applicable. The study is recruiting, with the first patient enrolled in December 2022. By January 2025, 812 patients were randomized across 78 centers. Final enrollment is scheduled for 2026 but may occur earlier due to accelerated recruitment. Statistics: The two primary objectives are to evaluate the lead time effect obtained by liquid biopsy marker testing in the intensified follow-up arm and to test whether intensified, liquid biopsy-guided surveillance improves overall survival (OS) compared to standard follow-up. OS will be analyzed in the ITT population using Kaplan-Meier and Cox regression, while the lead-time effect is assessed descriptively. Secondary endpoints include IDFS, DDFS, DRFS, BCSS, and QoL as well as biomarker sensitivities and specificities obtained in the intensified follow-up arm. Aims: We aim to determine whether liquid biopsy-guided follow-up enables earlier, sensitive, and specific detection of distant (oligo-)metastases, facilitating timely intervention and improving OS. Clinical trial information: NCT05658172. Research Sponsor: German Federal Ministry of Education and Research.

TPS622 Poster Session

The SURVIVE HERoes study: Targeting molecular relapse in breast cancer—A secondary adjuvant intervention study of trastuzumab deruxtecan versus SOC treatment in patients with HER2-positive or HER2-low early breast cancer and ctDNA positivity after primary therapy.

Kerstin Pfister, Thomas W. P. Friedl, Henning Schäffler, Franziska Mergel, Sophia Huesmann, Forca Mehmeti, Natalie Uhl, Angelina Fink, Tatjana Braun, Tanja N. Fehm, Volkmar Mueller, Sabine Heublein, Lisa Maria Wiesmueller, Klaus Pantel, Brigitte Rack, Andreas D. Hartkopf, Peter A. Fasching, Wolfgang Janni; Department of Gynecology and Obstetrics, University Hospital Ulm, Ulm, Germany; Department of Gynecology and Obstetrics, SLK Kliniken Heilbronn, Heilbronn, Germany; Department of Gynecology and Obstetrics, University Hospital Düsseldorf, Düsseldorf, Germany; Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany; Institute of Tumor Biology, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany; Department of Gynecology and Obstetrics, University of Tuebingen and University of Ulm, Tuebingen and Ulm, Germany; University Hospital Erlangen Comprehensive Cancer Center Erlangen-EMN, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany; University Hospital Ulm, Ulm, Germany

Background: Current research on circulating tumor DNA (ctDNA) in the adjuvant setting of early breast cancer (eBC) underscores its strong prognostic significance. Patients who are ctDNA-positive but show no radiological signs of relapse (i.e., molecular relapse) exhibit reduced disease-free and overall survival. Secondary adjuvant intervention studies represent an innovative and promising therapeutic approach. **Methods:** We introduce SURVIVE HERoes (NCT06643585), a phase III randomized clinical trial comparing the potent antibody-drug conjugate trastuzumab deruxtecan to standard of care (SoC) in patients with HER2-positive or HER2-low eBC and molecular residual or recurrent disease (ctDNA-positive, cM0) following primary therapy. Patients tested positive for ctDNA in a tumor-informed approach are eligible, if staging examinations do not show any residual or recurrent cancer. Participants are randomized in a 2:1 ratio to receive trastuzumab deruxtecan (+ endocrine therapy for HR+ patients) or SoC therapy. Stratification factors include hormonal receptor status (positive versus negative) and HER2 status (positive versus low). The primary endpoint is ctDNA clearance rate after 12 months of therapeutic intervention. Secondary endpoints include relapse-free survival, overall survival, safety, and quality of life (QoL). The trial will enroll a total of 180 participants across 50 centers in Germany. Staging examinations and ctDNA assessments will be performed at regular intervals. The study is accompanied by a comprehensive translational research program. Recruitment began in January 2025 and is anticipated to continue until 2030. Discussion: Treating ctDNA-positive patients without radiographic evidence of recurrence is a novel therapeutic strategy. If SURVIVE HERoes and similar studies targeting minimal residual disease (MRD) yield positive results, they could pave the way for a new molecularly driven individualized treatment approach aimed at achieving cure by liquid biopsy triggered early intervention in this new therapeutic window of pre-symptomatic MRD. Clinical trial information: NCT06643585. Research Sponsor: Astra Zeneca.

TPS623 **Poster Session**

Short-term pre-operative durvalumab (MEDI 4736) in early small triple-negative breast cancer patients (POP-Durva).

Joana M. Ribeiro, Julia Dixon-Douglas, Isabelle Pic, Quentin Blampey, Elie Rassy, Nusaibah Ibrahimi, Marie-Ange Mouret-Reynier, Monica Arnedos, Olivier Tredan, Kamar Serhal, Alessandro A. Viansone, Fernando Bazan, Salim Laghouati, Barbara Pistilli, Magali Lacroix-Triki, Corinne Balleyguier, Maud Kamal, Nadege Bercovici, Paul-Henri Cournede, Fabrice Andre; Gustave Roussy, Department of Medical Oncology, IHU-National PRecISion Medicine Center in Oncology, France, Villejuif, France; Peter MacCallum Cancer Centre, Hobart, Australia; Institute Gustave Roussy, Villejuif, Val-de-Marne, France; Paris-Saclay University, Centrale Supelec, Laboratory of Mathematics and Computer Science ´6 (MICS), Gif-Sur-Yvette, France; Gustave Roussy, Villejuif, France; Centre Jean Perrin, Clermont-Ferrand, France; Institut Bergonie, Bordeaux, France; Medical Oncology, Centre Léon Bérard, Lyon, France; Gustave Roussy, Direction de la Recherche Clinique, Bureau Projets et Promotion, Villejuif, Val-de-Marne, France; Gustave Roussy, Département de médecine oncologique, F-94805, VILLEJUIF France, Villejuif, France; Department of Medical Oncology, Centre Jean Perrin, Clermont-Ferrand, France; Pharmacovigilance Unit, Clinical Research Direction, Gustave Roussy Cancer Campus, Université Paris-Saclay, Villejuif, France; Breast Cancer Unit, Gustave Roussy, Villejuif, France; Gustave Roussy, Department of Medical Biology and Pathology, IHU-National PRecISion Medicine Center in Oncology, Villejuif, France; Gustave Roussy, Université Paris-Saclay, Department of Radiology, Villejuif, France; Université Paris Cité, Institut Cochin, INSERM, CNRS, Paris, France; Centrale Supelec, Gif-Sur-Yvette, France; Gustave Roussy, INSERM U981, Université Paris-Saclay, IHU-National PRecISion Medicine Center in Oncology, Villejuif, France

Background: Pathological response to neoadjuvant immune checkpoint inhibitors (ICI) is associated with excellent survival in several tumor types. In Stage II-III triple negative breast cancer (TNBC), neoadjuvant anti-PD-(L)1 with chemotherapy improves pathological complete response (pCR) and reduces recurrence. In Stage I TNBC, (neo)adjuvant chemotherapy remains standard of care. Exceptional responses to ICI in TNBC have been observed, suggesting a subgroup of Stage I TNBC could be treated with ICI alone; however, biomarkers to select patients are lacking. **Methods:** Trial Design: POP-Durva (NCT05215106) is a prospective, single-arm phase II trial evaluating pCR after two doses of durvalumab in Stage I TNBC. Patients with untreated clinical stage I ($\leq$2cm, N0) TNBC (ER $<$ 10%, PR $<$ 10%, HER-2 non-amplified) with sTIL of $\geq$ 5% will be included. Study treatment consists of two doses of durvalumab 10mg/kg IV, on D1 and D15. On completion of study treatment, patients will undergo breast US and will proceed to surgery, or standard neoadjuvant treatment, per physician preference. Fresh tissue biopsy and Formalin-Fixed Paraffin-Embedded (FFPE) will be collected at screening, on D22 or at surgery; blood will be collected for PBMC and ctDNA at screening, D1, D15 and on D22; faecal specimen collection will occur at baseline and at end of treatment (for microbiota analysis). Trial Endpoints: The primary endpoint is pCR (ypT0/is ypN0). In patients who proceed directly to surgery following durvalumab, pCR will be assessed at surgery. Patients with residual invasive disease at the D22 biopsy who receive further neoadjuvant therapy will be considered non-pCR for the primary endpoint. With an expected pCR rate of 20%, a sample size of 195 patients provides a 95% confidence interval of a precision of 6.2%. The secondary objectives are ORR and safety. The key exploratory objective is to identify biomarkers of response to ICI. Spectral cytometry, single-cell RNA and TCR sequencing will be performed to describe on-treatment immune cell dynamics and to identify mechanisms of response to ICI monotherapy. Imaging-mass cytometry will characterise tumour-immune cell spatial interactions. Microbiome profiles will be correlated with response. 4 sites in France are actively recruiting; as of 27/01/2025, 35 patients have been treated. Clinical trial information: NCT05215106. Research Sponsor: None.

TPS624 Poster Session

RECAST (Re-Evaluating Conditions for Active Surveillance Suitability as Treatment) for DCIS: Clinical trial in progress.

Ruolin Lorraine Jiang, Heather Greenwood, Cristian Maldonado Rodas, Hannah Chay, Kelly Hewitt, Laura Esserman; University of California, San Francisco, San Francisco, CA; University of Utah Health and Huntsman Cancer Institute, Salt Lake City, UT; Department of Surgery, University of California, San Francisco, San Francisco, CA

Background: Ductal Carcinoma In Situ (DCIS) is a condition where cancerous cells are confined to the breast ducts. The standard of care is surgery, either breast conservation and radiation or mastectomy. Data from the COMET study in hormone receptor-positive (HR+) DCIS demonstrates that active surveillance (AS) is a safe alternative for initial treatment. Starting with endocrine risk-reducing therapy first may assist in identifying candidates for risk reduction vs. focal surgical removal. The RECAST (Re-Evaluating Conditions for Active Surveillance Suitability as Treatment) study re-orders the treatment, starting with endocrine risk reduction, and uses serial imaging to assess treatment response to predict who can safely proceed with AS and endocrine therapy. Imaging response markers are tested to predict the success of endocrine therapy. Several novel endocrine treatments are tested. The trial gives patients a window of opportunity to evaluate the impact of endocrine therapy based on their imaging characteristics to explore alternatives to surgery. Rather than being randomly assigned to surgery or AS, all patients start with AS and serve as their own control. **Methods:** Women are screened for and randomized to 1 of 4 endocrine treatments, one of which is the standard of care endocrine therapy (choice of tamoxifen, baby tamoxifen, or an aromatase inhibitor is left to patient and physician discretion); MRIs are conducted at baseline, 3 and 6 months and semiquantitative imaging determines suitability for AS. Patients on AS are eligible to continue treatment for 3 years. Follow-up consists of an MRI alternating with a mammogram every 6 months. Quality of life (QOL) is measured using PROMIS and the FACT-ES composite scores. *Eligibility:* All patients with a diagnosis of HR+ DCIS (any grade), defined as $>$ 50% ER+ or PR+ on immunohistochemistry *Exclusion*: Presence of invasive disease, pregnancy or active breastfeeding, history of deep vein thrombosis. Patients with a solid mass on MRI must have a repeated biopsy *Primary objectives:* To determine whether novel endocrine therapy increases the fraction of patients who are suitable for long-term AS and how medications are tolerated compared to standard endocrine treatment *Primary endpoints:* QOL and fraction of patients who meet criteria for remaining on AS after 6 months based on MRI *Secondary endpoints:* Biomarkers of response and resistance *Progress to date:* RECAST activated on 01/22/2024. Currently,12 sites in the US are open to enrollment. 28 are in the process of activation. There are 22 patients accrued with 6 in screening. RECAST is an important next step in elucidating the factors that predict the success of AS and provide a framework for understanding endocrine resistance in the HR+ DCIS population. Clinical trial information: NCT06075953. Research Sponsor: Quantum Leap Healthcare Collaborative.

TPS625 **Poster Session**

NRG-BR007: A phase III trial evaluating de-escalation of breast radiation (DEBRA) following breast-conserving surgery of stage 1, HR+, HER2-, RS ≤18 breast cancer.

Julia R. White, Reena S. Cecchini, Eleanor Elizabeth Harris, Eleftherios P. Mamounas, Jose G. Bazan, Daniel G. Stover, Patricia A. Ganz, Reshma Jagsi, Stewart J. Anderson, Carmen Bergom, Valérie Théberge, Mahmoud El-Tamer, Richard C. Zellars, Dean Shumway, Guang-Pei Chen, Thomas B. Julian, Norman Wolmark; University of Kansas Medical Center Comprehensive Cancer Center, Kansas City, KS; NRG Oncology SDMC; Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA; St. Luke's University Health Network Cancer Center, Easton, PA; NSABP and AdventHealth Cancer Institute, Orlando, FL; City of Hope Comprehensive Cancer Center, Duarte, CA; The Ohio State University - James Comprehensive Cancer Center, Columbus, OH; David Geffen School of Medicine at UCLA, UCLA Fielding School of Public Health, UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA; Emory University School of Medicine, Atlanta, GA; NSABP Foundation, Inc.; NRG Oncology SDMC; Department of Biostatistics and Health Data Science, University of Pittsburgh, Pittsburgh, PA; Washington University School of Medicine, St. Louis, MO; CHU de Québec-Université Laval, Quebec City, QC, Canada; Memorial Sloan Kettering Cancer Center; Weill Cornell Medical School, New York, NY; Indiana University Simon Comprehensive Cancer Center, Indianapolis, IN; Department of Radiation Oncology, Mayo Clinic, Rochester, MN; Medical College of Wisconsin, Milwaukee, WI; Allegheny Health Network Cancer Institute, Pittsburgh, PA; NSABP Foundation, Inc.; UPMC Hillman Cancer Center; University of Pittsburgh School of Medicine, Pittsburgh, PA

Background: Approximately 50% of newly diagnosed invasive breast cancers are stage 1, with the majority being ER/PR-positive, HER2-negative. Genomic assays such as the Oncotype DX have identified patients (pts) with reduced risk of distant metastasis and without benefit from chemotherapy added to endocrine therapy (ET), freeing them from excess toxicity. Genomic assays are also recognized as prognostic for in-breast recurrence (IBR) after breast-conserving surgery (BCS) and could similarly allow de-escalation of adjuvant radiotherapy (RT). Reducing overtreatment is of interest to pts, providers, and payers. **Methods:** We hypothesize that BCS alone is non-inferior to BCS plus RT for IBR and breast preservation in women intending ET for stage 1 invasive breast cancer (ER and/or PR-positive, HER2-negative with an Oncotype DX Recurrence Score [RS] of ≤18). Stratification is by age (<60; ≥60), tumor size (≤1 cm; >1-2cm), and RS (≤11, >11-18/MammaPrint Low). Pts are randomized post-BCS to Arm 1 with breast RT using standard methods (moderate or ultra hypo- or conventional-fractionated whole breast RT with/without boost, or APBI) with ≥5 yrs of ET (tamoxifen or AI) or Arm 2 with ≥5 yrs of ET (tamoxifen or AI) alone. The specific regimen of ET in both arms is at the treating physician's discretion. Eligible pts are stage 1: pT1 (≤2 cm), pN0, age ≥50 to <70 yrs, s/p BCS with negative margins (no ink on tumor), s/p axillary nodal staging (SNB or ALND), ER and/or PR-positive (ASCO/CAP), HER2-negative (ASCO/CAP), and Oncotype DX RS ≤18 (diagnostic core biopsy or resected specimen). A "low risk" MammaPrint is permissible if completed as part of usual care prior to screening. Primary endpoint is IBR (invasive breast cancer or DCIS). Secondary endpoints are breast conservation rate, invasive in-breast recurrence, relapse-free interval, distant disease-free survival, overall survival, patient-reported breast pain, patient-reported worry about recurrence, and adherence to ET. We assume a clinically acceptable difference in IBR of 4% at 10 yrs to judge omission of RT as non-inferior (10-yr event-free survival for RT group is 95.6% *v* 91.6% for the omission-of-RT group). BR007 is powered to detect non-inferiority with 80% power and a one-sided α=0.025, assuming that there would be a ramp-up in accrual in the first two years (leveling off in Yrs 3-5); 1,670 pts (835 per arm) are required for randomization. Conservative loss to follow-up is 1%/yr. Some T1a pts screened may have Oncotype DX scores >18, making them ineligible for the study. In the accrual process, 1,714 pts will be required to register to ensure that our final randomized cohort is 1,670 pts. As of 1-6-2025: 1,168/1,670 pts have been randomly assigned, and 1,294 screened. Support: U10 CA180868, -180822, UG1 CA189867. Clinical trial information: NCT04852887. Research Sponsor: National Cancer Institute; U10 CA180868; National Cancer Institute; UG1CA189867; National Cancer Institute; UG1 CA189867.

TPS627 Poster Session

MELODY: A prospective non-interventional multicenter cohort study to evaluate different imaging-guided methods for localization of malignant breast lesions (EUBREAST-4/iBRA-NET/AGO-B-062, NCT 05559411).

Maggie Banys-Paluchowski, Nina Ditsch, Jai Min Ryu, Neslihan Cabioglu, Guldeniz Karadeniz Cakmak, Tove Filtenborg Tvedskov, Dawid Murawa, Severine Alran, Oreste Davide Gentilini, Rosa Di Micco, James Harvey, Yazan Masannat, Lina Pankratjevaite, Maria Luisa Gasparri, Jana de Boniface, Andreas Karakatsanis, Walter Weber, Natalia Krawczyk, Steffi Hartmann, Thorsten Kühn, MELODY Study Group; Department of Obstetrics and Gynecology, University Hospital of Schleswig Holstein, Campus Lübeck, Lübeck, Germany; Department of Gynecology and Obstetrics, University Hospital Augsburg, Augsburg, Germany; Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Istanbul University Faculty of Medicine, Department of Surgery, Istanbul, Turkey; Zonguldak BEUN The School of Medicine, Breast and Endocrine Unit, General Surgery Department, Kozlu/Zonguldak, Turkey; Faculty of Health and Medical Sciences, University of Copenhagen, Dept of Breast Surgery, Herlev & Gentofte University Hospital, Copenhagen, Denmark; General Surgery and Surgical Oncology Department, Collegium Medicum, University in Zielona Gora, Zielona Gora, Poland; Breast & Gynecologic Surgery Service Groupe Hospitalier Paris Saint Joseph, Paris, France; Breast Unit, IRCCS San Raffaele Scientific Institute/Università Vita-Salute San Raffaele, Milan, Italy; Breast Surgery Unit, IRCCS Ospedale San Raffaele, Milan, Italy; The Nightingale and PREVENT Breast Cancer Centre, Manchester University NHS Foundation Trust & Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom; Aberdeen Breast Unit, Aberdeen Royal Infirmary, Aberdeen, United Kingdom; Ospedale Regionale di Lugano EOC; Centro di Senologia della Svizzera Italiana (CSSI), Ente Ospedaliero Cantonal, Lugano, Switzerland; Department of Medical Epidemiology and Biostatistics, Karolinska Institutet and Department of Surgery, Capio St. Göran's/Department of Surgery, Capio St. Göran's Hospital, Stockholm, Sweden; Department for Surgical Sciences, Faculty of Pharmacy and Medicine, Uppsala University/Section for Breast Surgery, Department of Surgery, Uppsala University Hospital, Uppsala, Sweden; University Hospital Basel and Faculty of Medicine University of Basel, Basel, Switzerland; Department of Gynecology and Obstetrics, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany; Department of Gynecology and Obstetrics, University Hospital Rostock, Rostock, Germany; Department of Gynecology and Obstetrics, University of Ulm; Breast Cancer Center, Die Filderklinik, Ulm; Filderstadt, Germany

Background: In the last decades, the proportion of breast cancer patients receiving breast-conserving surgery has increased, reaching 70-80% in developed countries. In case of non-palpable lesions, surgical excision requires some form of breast localization. While wire-guided localization has long been considered gold standard, it carries several limitations, including logistical difficulties, the potential for displacement and patient discomfort, and re-excision rates reaching 21% (in DCIS up to 30%). Other techniques (radioactive seed or radio-occult lesion localization, intraoperative ultrasound, magnetic, radiofrequency, and radar localization) have been developed with the aim of overcoming these disadvantages. However, comparative data on the rates of successful lesion removal, negative margins, and re-operations are limited. In most studies, the patient perspective, addressing e.g. discomfort and pain, has not been evaluated. The aim of MELODY (MEthods for LOcalization of Different types of breast lesions) is to evaluate different imaging-guided localization methods with regard to oncological safety, patient-reported outcomes, surgeon and radiologist satisfaction and economic impact. **Methods:** The EUBREAST and the iBRA-NET have initiated the MELODY study to assess breast localization techniques and devices from several perspectives (NCT05559411, http://eubreast.org/melody). MELODY is a prospective intergroup cohort study which enrolls female and male patients. planned for breast-conserving surgery with imaging-guided localization for invasive breast cancer or DCIS. Multiple or bilateral lesions and neoadjuvant chemotherapy are allowed. Primary outcomes are: 1) Intended target lesion and/or marker removal, independent of margin status on final histopathology, and 2) Negative resection margin rates at first surgery. Secondary outcomes are, among others: rates of second surgery and secondary mastectomy, Resection Ratio (defined as actual resection volume divided by the calculated optimum specimen volume), duration of surgery, marker dislocation rates, rates of marker placement or localization failure, patient-reported outcomes, rates of "lost markers", radiologist and surgeon satisfaction, and health economic evaluation of the different techniques. Target accrual is 7,416 patients. Enrollment started in January 2023. Until 24 January 2025, 3938 patients from 20 countries were enrolled in the study. The study is expected to complete patient enrollment in year 2026. The study will be conducted in 30 countries and is supported by the Oncoplastic Breast Consortium (OPBC), AWOgyn, AGO-B, SENATURK, the American Society of Breast Surgeons (ASBS) and the Korean Breast Cancer Study Group (KBCSG). Clinical trial information: NCT05559411. Research Sponsor: None.

TPS628 Poster Session

Radiation omission in patients with clinically node-negative breast cancer undergoing lumpectomy (ROSALIE).

Elena Parvez, Mark Basik, Sameer Parpia, Mark Norman Levine, Timothy Joseph Whelan, Thierry Muanza; McMaster University, Hamilton, ON, Canada; Segal Cancer Center, Montreal, QC, Canada; Ontario Clinical Oncology Group, Hamilton, ON, Canada; Jewish General Hospital, McGill University, Montreal, QC, Canada

Background: Currently, the standard of care for patients undergoing neoadjuvant chemotherapy (NAC) and breast conserving surgery (BCS) is adjuvant radiation (RT). However, high rates of pathologic complete response (pCR) after NAC have raised questions regarding the necessity of WBRT in these cases. A meta-analysis of 9 German NAC trials demonstrated a 5-year locoregional recurrence (LRR) of only 4% in patients with pCR who underwent BCS with radiation therapy. Data from two large National Surgical Adjuvant Breast and Bowel Project (NSABP) neoadjuvant trials (B.18 and B.27) demonstrated a local recurrence risk of 5.1% at 10 years (2.5% at 5 years) in patients >50 years with node negative breast cancer who had a pCR and were treated with BCS and RT. With such low rates of recurrence, we postulated that the absolute benefit that RT can offer is limited. Radiation therapy is not without side effects, which include both short-term and long-term toxicity. As such, a trial of de-escalation of RT is warranted. **Methods:** This study is a prospective, multi-center, single arm cohort study of omission of WBRT following BCS in patients with a pCR following NAC. Eligible and consenting female patients with newly diagnosed T1-3 node negative breast cancer age >50 years with no clinical evidence of distant metastatic disease, who have been treated with NAC, BCS and axillary staging surgery with final pathology demonstrating a pCR (ypT0N0) will be enrolled to the study and followed. Negative lymph node involvement at initial presentation must be documented by imaging (US or MRI), fine needle aspiration (FNA) or core needle biopsy. Marker clip must have been placed in the tumour bed prior to or during neoadjuvant chemotherapy when the tumour can still be identified. Study participants will not receive adjuvant RT, the current standard of care. Study participants will be followed and assessed for local recurrence, regional recurrence, distant recurrence, DFS and OS. Any additional breast cancer treatments received by the participant for the first recurrence event including repeat BCS, mastectomy, additional systemic therapy and radiation therapy (RT) will be documented. The primary outcome is ipsilateral breast tumour recurrence (IBTR) at median 5-year follow-up. A local recurrence of 5% without RT was felt to be acceptable. Based on a postulated 5-year IBTR risk of 3.0%, 4 years of accrual plus an additional 3 years of follow-up, a 90% two-sided CI for a postulated LR rate of 3.0% at 5 years would have an upper bound of <5% with 300 patients. To account for a 5% potential loss to follow-up and 10% receiving RT contrary to protocol, a sample size of 352 patients will be required. The trial opened in March 2024. Clinical trial information: NCT05866458. Research Sponsor: Canadian Institutes of Health Research (CIHR).

TPS629 Poster Session

HERTHENA-Breast03: A phase 2, randomized, open-label study evaluating neoadjuvant patritumab deruxtecan + pembrolizumab before or after pembrolizumab + chemotherapy for early-stage TNBC or HR-low+/HER2− breast cancer.

Joyce O'Shaughnessy, Julie Marie Collins, Lili Yao, Karen L. Smith, Jaime A. Mejia, Michael A. Danso; Baylor University Medical Center, Texas Oncology, Dallas, TX and Sarah Cannon Research Institute, Dallas, TX; Daiichi Sankyo, Inc., Basking Ridge, NJ; Merck & Co., Inc., Rahway, NJ; Virginia Oncology Associates, Norfolk, VA

Background: The standard of care for patients with high-risk, early-stage TNBC is neoadjuvant pembrolizumab (pembro) + chemotherapy followed by adjuvant pembro. Patients with HR-low+/HER2− breast cancer may also be treated per recommendations for TNBC. There is a need for improved neoadjuvant therapy to increase the rate of pCR, as patients who do not achieve pCR have a high risk of recurrence, and to reduce risk of long-term toxicities associated with cyclophosphamide and anthracyclines. HER3 is frequently expressed in breast cancer and implicated in drug resistance. Patritumab deruxtecan (HER3-DXd) is an antibody-drug conjugate comprising a fully human anti-HER3 IgG1 monoclonal antibody linked to a topoisomerase I inhibitor (DXd) via a stable tetrapeptide-based linker that is selectively cleaved within tumor cells. This phase 2 study (NCT06797635) will evaluate neoadjuvant HER3-DXd + pembro before or after carboplatin + paclitaxel + pembro for early-stage TNBC or HR-low+/HER2− breast cancer. **Methods:** Eligible participants (pts) are adults (≥18 y) with untreated, locally advanced nonmetastatic (AJCC stage cT1c, N1–N2 or cT2–cT4, N0–N2) TNBC or HR-low+/HER2− breast cancer. Pts (N ≥10 and ≤30) in part 1 of the study (safety lead-in) will receive neoadjuvant HER3-DXd + pembro followed by carboplatin + paclitaxel + pembro (Table) then surgery. DLT evaluation and dose finding for HER3-DXd (three dose levels of 5.6 mg/kg Q3W, 4.8 mg/kg Q3W and 3.2 mg/kg Q3W) during cycle 1 of neoadjuvant HER3-DXd + pembro will be performed in part 1 to determine an acceptable dose of HER3-DXd for part 2. Pts (N ~342) in part 2 will be randomly assigned 1:1:1 to arm A, B or C (Table) for neoadjuvant treatment. Randomization will be stratified by cancer type (TNBC vs HR-low+/HER2−) and, in the TNBC subgroup, PD-L1 status (combined positive score ≥10 vs <10), overall stage (II vs III) and HER3 expression (low vs high). After neoadjuvant treatment, pts will undergo surgery (with postoperative radiotherapy if clinically indicated) and receive adjuvant pembro 400 mg Q6W for 5 cycles. Pts with residual disease may receive additional adjuvant treatment of physician's choice. Primary endpoints are safety (part 1 and 2) and pCR (ypT0/Tis ypN0) (part 2). Enrollment is ongoing. Clinical trial information: NCT06797635. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). This study is part of a collaboration between MSD and Daiichi Sankyo, Inc.

	Neoadjuvant cycles 1-4	Neoadjuvant cycles 5-8
Part 1 Arm A	HER3-DXd 5.6 or 4.8 or 3.2 mg/kg Q3W + pembro[a]	Carboplatin[b] + paclitaxel[c] + pembro[a]
Part 2 Arm A	HER3-DXd (selected dose from Part 1) + pembro[a]	Carboplatin[b]+ paclitaxel[c] + pembro[a]
Part 2 Arm B	Carboplatin[b] + paclitaxel[c] + pembro[a]	HER3-DXd (selected dose from Part 1) + pembro[a]
Part 2 Arm C	Carboplatin[b] + paclitaxel[c] + pembro[a]	Doxorubicin[d] OR epirubicin[e] + cyclophosphamide[f] + pembro[a]

[a]200 mg Q3W; [b]AUC 1.5 mg/mL/min QW; [c]80 mg/m^2 QW; [d]60 mg/m^2 Q3W; [e]90 mg/m^2 Q3W; [f]600 mg/m^2 Q3W.

TPS630 **Poster Session**

Eliminating breast surgery for triple negative or HR-/HER2+ breast cancer patients with clinical complete response to combined neoadjuvant chemotherapy and neoadjuvant radiotherapy: A multicenter, phase 2 trial (EBCS).

Zhengjun Yang, Xin Wang, Xuchen Cao, Aoxiang Chen, Qingsong Pang, Jing Wang, Hong Lu, Ying Zhu, Xiaojing Guo, Fengxia Qin, Xiaolong Qian, Jiangrui Chi, Lin Li, Qian Li; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Tianjin Medical University Cancer Institute and Hospital, Tianjian, China; Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China; Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China; Department of Radiotherapy, Tianjin Medical University Cancer Institute & Hospital, Tianjin, Tianjin, China; Department of Breast Surgery, the First Afiliated Hospital of Zhengzhou University, Zhengzhou, China; The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background: Recent advancements in immunotherapy and targeted therapies have significantly improved pathological complete response (pCR) rates in patients with triple-negative breast cancer (TNBC) and HER2-positive breast cancer undergoing neoadjuvant chemotherapy. The combination of neoadjuvant chemotherapy with radiotherapy may further enhance pCR rates through synergistic effects, prompting a reevaluation of traditional surgical approaches. The Sound trial demonstrated that omitting sentinel lymph node biopsy in node-negative patients is safe and feasible, supporting further de-escalation of surgical interventions. For patients achieving pCR, the necessity of breast and axillary surgery is increasingly questioned, given the potential to reduce surgical morbidity without compromising outcomes. Our study investigates whether omitting surgery in patients with pCR confirmed by vacuum-assisted core biopsy (VACB) yields non-inferior 5-year event-free survival (EFS) compared to standard surgery. **Methods:** This multicenter, phase 2 trial enrolls patients aged ≥18 years with untreated cT1-2 N0 M0 TNBC or HER2-positive breast cancer and ECOG 0-1. Patients receive four cycles of TCb (HP)* neoadjuvant chemotherapy, followed by neoadjuvantradiotherapy starting from the fifth cycle (50 Gy in 25 fractions + 14 Gy boost in 7 fractions). The TCb (HP)* regimen is tailored based on tumor subtype: triple-negative patients receive TCb (nab-paclitaxel + carboplatin) with or without immunotherapy (pembrolizumab), while HER2-positive patients receive TCbHP (nab-paclitaxel + carboplatin + trastuzumab and pertuzumab) regimens. After six cycles, patients undergo MRI. If MRI suggests complete clinical response (cCR), VACB of the primary lesion is performed under ultrasound/stereotactic guidance (6 cores, 7-10 G needle). If no residual tumor or atypical cells are found, breast and axillary surgery are omitted. Patients receive indicated immunotherapy/targeted therapy and are followed every 6 months for 5 years. The primary endpoint is 5-year EFS. Secondary endpoints include breast pCR rate (bpCR: ypT0), overall survival (OS), patient-reported outcomes (PROs), and safety. TheThis trial is designed to determine whether the 5-year EFS of patients who avoid breast surgery after pCR confirmed by VACB is non-inferior to that of patients who undergo standard breast surgery with confirmed pCR. Based on a 90.3% 5-year EFS in pCR patients (cT1-2N0 TNBC/HER2+), the trial uses a one-sided test (non-inferiority margin: 5%; power: 80%; α: 0.1) to determine if omitting surgery is non-inferior. 185 patients are needed to omit surgery. Assuming 80% pCR and 10% dropout, 256 participants will be enrolled. The trail is actively recruiting. Clinical trial information: NCT06498154. Research Sponsor: None.

TPS631 Poster Session

A randomized trial of trastuzumab deruxtecan and biology-driven selection of neoadjuvant treatment for HER2-positive breast cancer (ARIADNE).

Alexios Matikas, Bjorn Naume, Hans Wildiers, Maria Vittoria Dieci, Gabe S. Sonke, Andreas Karakatsanis, Aglaia Schiza, Kevin Punie, Christos Sotiriou, Matteo Lambertini, Claudio Vernieri, Guillermo Villacampa, Mats Hellström, Jonas C. S. Bergh, Johan Hartman, Theodoros Foukakis; Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden; Oslo Universitetssykehus, Oslo, Norway; Medical Oncology Department, UZ Gasthuisberg, Leuven, Belgium; Department of Surgery, Oncology and Gastroenterology, University of Padova; Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy; The Netherlands Cancer Institute, Amsterdam, Netherlands; Department for Surgical Sciences, Faculty of Pharmacy and Medicine, Uppsala University/Section for Breast Surgery, Department of Surgery, Uppsala University Hospital, Uppsala, Sweden; Dpt of Oncology, Uppsala University Hospital, Uppsala, Sweden; Ziekenhuis Aan de Stroom, Antwerp, Belgium; Institut Jules Bordet, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles, Brussels, Belgium; U.O. Clinical Oncology, IRCCS Ospedale Policlinico San Martino, University of Genova, Genova, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; SOLTI Cancer Research Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Karolinska Universitetssjukhuset, Stockholm, Sweden; Karolinska Institutet, Stockholm, Sweden

Background: Neoadjuvant therapy is the standard of care for the treatment of non-metastatic HER2-positive breast cancer. Studies on first generation antibody-drug conjugates (ADC) such as trastuzumab emtansine (T-DM1) showed equal or slightly lesser efficacy than chemotherapy combined with dual HER2 blockade. Trastuzumab deruxtecan (T-DXd) is a next generation ADC approved for the treatment of metastatic HER2-positive breast cancer, with greatly improved efficacy compared with T-DM1. **Methods:** ARIADNE is an academic, international, open label, randomized, comparative phase IIB trial, actively enrolling in Sweden (ten sites) and in Norway (seven sites), with sites in Belgium (three), Netherlands (one) and Italy (three) activating during Q2 2025. A total of 370 patients with non-metastatic HER2-positive primary breast cancer and an indication for neoadjuvant therapy will be offered inclusion and randomized 1:1 to receive either i) a taxane, carboplatin, trastuzumab and pertuzumab for three cycles or ii) T-DXd for three cycles. Further treatment is based on the PAM50-defined intrinsic molecular subtype from a pretreatment biopsy: HER2-enriched (approximately 65%) patients continue with the same treatment for three more cycles. Estrogen receptor (ER) positive and luminal (approximately 25%) patients receive trastuzumab and pertuzumab for three cycles, combined with letrozole and ribociclib for two cycles. Finally, ER-negative and luminal or basal-like (approximately 10%) patients either continue with the same treatment for three additional cycles in case of radiologic complete response, or they receive four cycles of dose-dense epirubicin and cyclophosphamide in case of lack of complete response. The primary endpoint of ARIADNE is locally assessed rate of pathologic complete response (pCR) in patients with molecularly HER2-enriched tumors, defined as ypT0/Tis, ypN0, as determined by a pathologist blinded to treatment assignment (intention-to-treat analysis). Key secondary endpoints are rates of complete radiologic response at three cycles; rates of pCR in the other two molecular groups and in the two groups of the initial randomization; event-free survival, defined as the time from randomization to disease progression, locoregional or distant recurrence, contralateral breast cancer, other cancer, or death due to any cause. Tissue and plasma samples are collected at baseline, during treatment and surgery, as well as during follow-up. The first patient was randomized on 26th October 2023; 46 patients had been enrolled to the study until January 2025. Clinical trial information: NCT05900206. Research Sponsor: None.

TPS632 Poster Session

OPERETTA: A phase II study evaluating neoadjuvant and adjuvant olaparib plus pembrolizumab following platinum-based chemotherapy plus pembrolizumab for germline BRCA mutated triple negative breast cancer.

Yuko Takahashi, Kumiko Kida, Meiko Nishimura, Kaori Terata, Manabu Futamura, Atsushi Yoshida, Tadahiko Shien, Takayuki Ueno, Toshimi Takano; Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan; Department of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan; The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Breast and Endocrine Surgery, Akita University Hospital, Akita, Japan; Gifu University, Graduate School of Medicine, Gifu-Shi, Japan; The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; Breast Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Triple negative breast cancer (TNBC) remains the most challenging phenotype of breast cancer. There is still an unmet clinical need for improving the fine-tuning of indications for targeted treatments in this population. In TNBC, the frequency of germline BRCA (gBRCA) 1/2 mutations was reported to be up to 19.5%. This has led to promising clinical strategies based on poly adenosine diphosphate (ADP)-ribose polymerase inhibitors that inhibit single-stranded DNA damage repair and/or modified chemotherapy approaches targeting the DNA damage response, using platinum-based regimens. Based on the results of the OlympiA and KEYNOTE522 study, the adjuvant treatment with olaparib for gBRCAm and neoadjuvant and adjuvant pembrolizumab for patients with a high risk of recurrence TNBC has been treatment options as the standard of care. We hypothesize that neoadjuvant and adjuvant combination treatment with olaparib and pembrolizumab following combination treatment with platinum-based chemotherapy and pembrolizumab would synergistically increase the anti-tumor effect through the enhancement of immunogenicity and DNA damage in patients with gBRCA mutated breast cancer. **Methods:** OPERETTA is a multi-centered, prospective single-arm phase II feasibility study of patients treated with neoadjuvant olaparib plus pembrolizumab following platinum-based chemotherapy plus pembrolizumab in gBRCA 1/2 mutated TNBC. The patients with stage IIA-IIIB TNBC known as gBRCA 1/2 mutated will be registered. The primary objective is the pCR rate defined as the absence of residual invasive disease in the breast and axilla. The secondary objectives include additional efficacy measures (i.e., Residual Cancer Burden [RCB] 0/1rate, 3 years overall survival [3y-OS], 3 years event-free survivals [3y-EFS]), and safety. The estimated sample size using Simon's two-stage design, with a null hypothesis of a 45% pCR rate and an alternative hypothesis of 70%, was calculated. Given a significance level of 0.1 and 80% power, the design allows a maximum of 23 patients to be included. Eligible patients will be received combination treatment with paclitaxel (80 mg/m2 qw), carboplatin (AUC 1.5 qw or AUC 5 q3w), and pembrolizumab (200mg q3w) for first 12 weeks followed by olaparib (300mg BID) with pembrolizumab (200mg q3w) for another 12 weeks as neoadjuvant treatment. Breast/axillary surgery and radiotherapy are recommended per standard of care. After surgery, the combination of olaparib plus pembrolizumab will be continued for another 27 weeks as adjuvant treatment. This study is recruiting in Japan, and 2 patients are enrolled as of January 2025. This study is part of the West Japan Oncology Group (WJOG) breast cancer study group: WJOG14020B. Clinical trial information: NCT05485766. Research Sponsor: Merck; AMED.