Phase III NATALEE trial of ribociclib + endocrine therapy as adjuvant treatment in patients with HR+/HER2— early breast cancer.

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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, 2023, issue of the Journal of Clinical Oncology.
Efficacy and safety results by age in monarchE: Adjuvant abemaciclib combined with endocrine therapy (ET) in patients with HR+, HER2-, node-positive, high-risk early breast cancer (EBC).

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Background: Adjuvant abemaciclib (a CDK4 & 6 inhibitor) combined with ET demonstrated a sustained benefit in invasive disease-free survival (IDFS) and a tolerable safety profile in patients (pts) with HR+, HER2-, node-positive, high-risk EBC. Almost half of the newly diagnosed breast cancers occur in women older than 65 years. Older pts often have a higher incidence of comorbidities and increased risk for toxicities. Here, we report efficacy and safety by age subgroups in monarchE to help guide management of older pts receiving adjuvant abemaciclib. Methods: Pts were randomized (1:1) to receive ET for up to 10 years +/- abemaciclib for 2 years (study treatment period). Efficacy in IDFS and distant relapse-free survival (DRFS) was assessed in the intent-to-treat population by the pre-specified age groups of <65 and ≥65 years, with hazard ratios (HR) estimated using unstratified Cox proportional hazard model within each subgroup. Safety was evaluated among older pts (≥65 years) in two subgroups; 65-74 and ≥75 years. Results: In monarchE (NCT03155997), 4787 pts (84.9%) were aged <65 years and 850 pts (15.1%) were ≥65 years. At median follow-up of 42 months, a numerically favorable IDFS effect was observed in both the <65 (270 vs 414 events; HR = 0.646, 95% CI: 0.554, 0.753) and ≥65 (66 vs 85 events; HR = 0.767, 95% CI: 0.556, 1.059) groups for abemaciclib + ET vs ET alone. Similar findings were observed in DRFS. Older pts (≥65 years) had ~5% higher incidence of grade ≥3 adverse events (AEs) than younger pts, mainly diarrhea and fatigue. Neutropenia was not increased among older pts and similarly, venous thromboembolic events occurred at similar rates (≥65 years, 3.0%; <65 years, 2.5%). Serious AEs (SAEs) and treatment discontinuations due to AEs were more common in older pts. Older pts required more dose reductions to manage AEs. Conclusions: In pts with high-risk EBC, adjuvant abemaciclib + ET showed treatment benefit across age subgroups with a manageable safety profile. Older pts did have higher rates of AEs and discontinuations, especially those older than 75 years, suggesting that more frequent surveillance with early intervention may be key to the management of these pts. Clinical trial information: NCT03155997. Research Sponsor: Eli Lilly and Company.
Detection of circulating tumor DNA following neoadjuvant chemotherapy and surgery to anticipate early relapse in ER positive and HER2 negative breast cancer: Analysis from the PENELOPE-B trial.

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Background: The PENELOPE-B phase III trial investigated the addition of one year of palbociclib to endocrine therapy (ET), in patients with hormone receptor positive HER2 negative breast cancer with residual invasive disease after neoadjuvant chemotherapy. Prior research has demonstrated that detection of circulating tumor DNA (ctDNA) in the adjuvant setting is associated with a high risk of disease relapse. We assessed the potential of ctDNA analysis to predict future clinical relapse for patients enrolled in the PENELOPE-B trial.

Methods: Patients who were endocrine naïve at the time of study entry were selected for ctDNA analysis. Plasma samples were collected at baseline (after completion of neoadjuvant chemotherapy and surgery), prior to cycle 7 (approximately 6 months into ET + palbociclib), end of treatment (EOT), and progressive disease. A tumor sample was subjected to exome sequencing, and up to 50 tumor somatic mutations were tracked in plasma using error-corrected sequencing combined with a proprietary algorithm for ctDNA detection (RaDaR assay). Detection of ctDNA was associated with invasive disease-free survival (iDFS) and distant metastasis-free survival using Cox proportional hazard models.

Results: Of 1250 patients enrolled in PENELOPE-B, 129 were endocrine naïve at trial entry, and 78 had a baseline ctDNA sample analyzed. The ctDNA analysis group was representative of the overall endocrine naïve group, with median follow-up of 42.9 months. Seven patients had baseline ctDNA detected, with detection strongly associated with iDFS (HR 8.8, 95% CI 3.3-23.4, p < 0.0001). Detection of ctDNA at cycle 7 (4 patients) was also strongly associated with iDFS (HR 25.9, 95% CI 6.5-99.6, p < 0.0001). Of the 7 patients with baseline ctDNA detection, 2 had undetectable ctDNA at cycle 7 and remained progression free at 30 months, although one later relapsed; the 3 patients with detectable ctDNA at cycle 7 all relapsed within 25 months. Of the 12 patients with a distant relapse within 24 months, only 4 had ctDNA detected at baseline and 3 first at cycle 7/EOT. Of the 8 patients with distant relapse after 24 months, 2 had ctDNA detected at baseline and none first at cycle 7/EOT.

Conclusions: Detection of ctDNA following neoadjuvant chemotherapy, and surgery, is associated with a very high risk of early relapse suggesting limited efficacy of adjuvant ET. Clinical imaging and studies of experimental therapy are warranted in this patient population. Testing ctDNA after recent neoadjuvant chemotherapy in luminal-A like breast cancer has relatively low ‘sensitivity’ for predicting future relapse, in particular for later relapses, in part suggesting that response to neoadjuvant chemotherapy may reduce ctDNA detection. Clinical trial information: NCT01864746.

Research Sponsor: Pfizer.
Effects of ovarian ablation or suppression on breast cancer recurrence and survival: Patient-level meta-analysis of 14,993 pre-menopausal women in 25 randomized trials.

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Background: Suppressing ovarian function of women with breast cancer may improve outcome by preventing estrogenic stimulation of any residual cancer, particularly for pre-menopausal women with estrogen receptor (ER)-positive tumors. We report a collaborative meta-analysis of individual participant data from randomized trials of ovarian ablation or suppression. Methods: Data were sought from randomized trials that compared ovarian ablation or suppression versus not. Primary analyses included only premenopausal women age < 55 with ER-positive or unknown tumors, stratified into those who received no chemotherapy, or remained premenopausal following chemotherapy, and those whose menopausal status following chemotherapy was not ascertained. Standard log-rank methods estimated ER-weighted annual event rate ratios (RR). Results: Individual patient data were provided for 25 of 27 relevant trials, comprising 14,993 (98.7%) of 15,195 women randomized. Overall, fewer breast cancer recurrences were seen with ovarian ablation/suppression than control (RR = 0.82, 95%CI 0.77–0.88; p < 0.0001). Recurrence reductions were significantly (p = 0.0003) larger among women (n = 7,213) known to be premenopausal prior to ovarian suppression (RR = 0.70, 0.63–0.78; p = 0.0003) than among those (n = 7,786) whose menopausal status was uncertain after chemotherapy (RR = 0.91, 0.83–0.99; p = 0.03). For known premenopausal women, 15-year risk of recurrence was improved by 12.1% (28.9% vs 41.0%; p < 0.0001). 15-year breast cancer and all-cause mortality were improved by 8.0% (20.9% vs 28.9%; RR 0.69, 0.60–0.80; p < 0.0001) and 7.2% (26.0% vs 33.1%; RR = 0.73, 0.64–0.82; p < 0.0001), respectively, with no increase in deaths without recurrence (RR = 0.88, 0.67–1.14; p = 0.33). Recurrence reductions were significantly (p = 0.003) larger among premenopausal women aged under 45 (RR = 0.63, 0.55–0.72; p < 0.0001) than among those aged 45-54 (RR = 0.84, 0.70–1.00; p = 0.045), but did not differ significantly by other recorded patient or tumor characteristics. Conclusions: For pre-menopausal women aged under 45, ovarian ablation or suppression substantially reduces the 15-year risk of recurrence and death from breast cancer without increasing mortality from other causes. Research Sponsor: Cancer Research UK medical charity; NDPH, University of Oxford.
Evaluation of PAM50 intrinsic subtypes and risk of recurrence (ROR) scores in premenopausal women with early-stage HR+ breast cancer: A secondary analysis of the SOFT trial.

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Background: The landmark Suppression of Ovarian Function Trial (SOFT) in premenopausal breast cancer patients revealed that the addition of ovarian function suppression (OFS) to adjuvant endocrine therapy with either tamoxifen (T+OFS) or exemestane (E+OFS) reduces the risk of recurrence compared with adjuvant tamoxifen alone. There are no biomarkers to aid decision-making about intensification of endocrine therapy with OFS. The purpose of this study is to assess the prognostic and predictive ability of PAM50 intrinsic subtypes and ROR scores in premenopausal women with HR+/HER2- breast cancer in the SOFT trial. Methods: Gene expression analyses were performed via the NanoString Breast Cancer 360 assay on RNA isolated from FFPE tumor samples from the SOFT trial that were HR+/HER2- (n=1245/3047). PAM50 subtype and ROR score were determined centrally by NanoString Technologies (Seattle, WA, USA), blinded to clinical characteristics, treatment and outcome. Median follow-up was 12 years. Primary endpoint in this study was distant recurrence-free interval (DRFI). Secondary endpoints were breast cancer-free interval (BCFI) and disease-free survival (DFS). Kaplan-Meier analysis and Cox proportional hazards regression models, stratified by prior chemotherapy and lymph node status, were used to evaluate the predictive performance of PAM50 intrinsic subtypes and ROR categories (low vs intermediate vs high), and secondarily ROR score as a continuous variable. We also investigated differences between very young (<40yrs) vs young (≥40yrs) women. Results: Tumor samples from 1084/1245 (87%) patients successfully completed PAM50 testing and are included in this analysis. Patient characteristics in this cohort were similar to the entire SOFT trial population. Intrinsic subtype and ROR category distribution is described below. Subtype distribution significantly differed between very young vs young premenopausal women, with fewer luminal A and more luminal B and non-luminal tumors seen in the very young (p<0.001). The ROR score distribution also differed significantly: in node-negative patients there were significantly more ROR-high scores amongst very young compared to young women (36% vs 14%, p<0.001). Conclusion: Breast cancer diagnosed in very young women has aggressive disease biology. Prognostic and predictive analyses of both intrinsic subtypes and the ROR score are ongoing and will be presented at the meeting. Clinical trial information: NCT00066690. Research Sponsor: Breast Cancer Foundation New Zealand, National Breast Cancer Foundation of Australia, Breast Cancer Research Foundation, NHMRC and the Royal Australasian College of Physicians, Fundación SEOM.

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<th>Very young (&lt;40 yr)</th>
<th>Young (≥40 yr)</th>
<th>Overall</th>
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<tr>
<td><strong>N patients</strong></td>
<td>309</td>
<td>775</td>
<td>1084</td>
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<tr>
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<td>26%</td>
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<tr>
<td>ROR (Low/Int/High)</td>
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<td>64% / 22% / 14%</td>
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<tr>
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Association of tumor-infiltrating lymphocytes (TILs) with clinicopathologic characteristics and prognosis in young women with HR+/HER2- breast cancer (BC).

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Background: Increased TILs are associated with better prognosis in triple-negative BC, including in patients (pts) age < 40. However, the role of TILs remains unclear in HR+/HER2- BC and little data exist in young pts, in whom immune microenvironment could be altered by age-related host/tumor differences. We assessed the extent and composition of immune infiltration in HR+ tumors of young women and correlated with clinicopathologic features and survival outcomes. Methods: From a prospective cohort study of women with BC diagnosed age ≤40, we identified those with stage I-III HR+/HER2- BC and available pre-treatment (tx) tumor tissue. Multiplexed immunofluorescence was used to quantify cytotoxic T (CD8+), T helper (Th, CD3+CD8-), T regulatory (Tregs, FOXP3+CD3+) and exhausted T (PD1+CD8+) cells in stroma and tumor. Univariate analyses tested associations between clinicopathologic variables and immune markers by high or low expression, divided based on median. High vs. low TILs were evaluated in Cox regression analyses for invasive breast cancer-free survival (iBCFS), distant disease-free survival (DDFS) and overall survival (OS). Results: In 390 pts, median age was 37 years (21-40), most had grade 2 (51%), T1 (65%), N0 (63%) tumors and 67% received adjuvant chemotherapy. Black pts (n = 17) had higher expression of stromal CD8+ (P=.010), FOXP3+CD3+ (P=.027) and PD1+CD8+ TILs (P=.043); intratumoral TILs did not differ by race. Older age (36-40) was associated with high expression of CD8+ (P=.033) and PD1+CD8+ TILs (P=.031) within stroma and CD3+CD8- TILs within tumor (P=.046). Grade 3 tumors had higher stromal and intratumoral expression of CD3+CD8- (P=.002; P<.001) and FOXP3+CD3+ TILs (P=.020; P<.001). No differences in TILs were seen according to recency of pregnancy, BRCA1/2 status or T/N stage. Over a median follow up of 8 years, 85 iBCFS events, 64 DDFS events and 37 deaths occurred. High stromal expression of CD3+CD8- TILs was associated with better iBCFS (HR 0.49, P=.002) and DDFS (HR 0.57, P=.046), which remained significant when adjusted for T/N stage, grade and chemotherapy (iBCFS HR 0.41, P<.001; DDFS HR 0.45, P=.008). High stromal expression of CD3+CD8- and FOXP3+CD3+ TILs was associated with better OS (HR 0.47, P=.038) and iBCFS (HR 0.58, P=.018), respectively, on adjusted analyses only. High intratumoral expression of CD3+CD8- and FOXP3+CD3+ TILs was associated with better iBCFS (HR 0.59, P=.025; HR 0.63, P=.043) after adjustment only. Conclusions: The distribution of TIL subtypes in young women's HR+ BC varied according to race, age and grade. High stromal and intratumoral expression of Th and Tregs was associated with improved BC outcomes. Characterization of immune cell subsets could help refine the prognostic value of TILs in HR+ BC, particularly in young pts who may benefit from individualized escalated/de-escalated tx strategies. Research Sponsor: Breast Cancer Research Foundation, Susan G. Komen.

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LBA506 Oral Abstract Session

3-year invasive disease-free survival (iDFS) of the strategy-based, randomized phase II PHERGain trial evaluating chemotherapy (CT) de-escalation in human epidermal growth factor receptor 2-positive (HER2[+]) early breast cancer (EBC).

Javier Cortes, José Manuel Pérez-García, Manuel Ruiz-Borrego, Agostina Stradella, Begona Bermejo, Santiago Escrivá-de-Román, Lourdes Calvo Martínez, Nuria Ribelles, Alfonso Cortés Salgado, Cinta Albacar, Marco Colleoni, Geraldine Gebhart, Aleix Prat, Kerrou Khaldoun, Peter Schmid, Serena Di Cosimo, Crina Popa, Daniel Alcalá-López, Miguel Sampayo-Cordero, Antonio Llombart-Cussac; International Breast Cancer Center (IBCC), Pangea Oncology, Quiron Group, Barcelona, Spain, Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain, Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; International Breast Cancer Center (IBCC), Pangea Oncology, Quiron Group, Barcelona, Spain, Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain; Virgen del Rocio University Hospital, Seville, Spain; Institut Català d’ Oncologia L’Hospital (ICO), Barcelona, Spain; Medical Oncology, Hospital Clínico Universitario de Valencia, Biomedical Research Institute INCLIVA, Valencia; Medicine Department, Universidad de Valencia. Oncology Biomedical Research National Network (CIBERONC-ISCIII), Madrid, Spain; Medical Oncology, Vall d’Hebron University Hospital and Vall, Barcelona, Spain; Medical Oncology, Breast Cancer Unit, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain; University Hospital Virgen de la Victoria, Málaga, Spain; Medical Oncology Department, Ramón y Cajal University Hospital, Madrid, Spain; Hospital Universitari Sant Joan de Reus, Reus, Spain; Senologia Medica, IEO, Istituto Europeo di Oncologia, IRCCS, Milano, Italy; Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institute Jules Bordet, Service de Médecine Nucléaire, Brussels, Belgium; Hospital Clínico Barcelona, Barcelona, Spain; APHP, Tenon Hospital IUC-UPMC, Nuclear Medicine and PET Center Department, Sorbonne University & INSERM U938 - Cancer Biology & Therapeutics, Paris, France; Barts ECMC, Barts Cancer Institute, Queen Mary University of London, and Barts Hospital NHS Trust, London, United Kingdom; Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, MI, Italy; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain; Hospital Arnau de Vílanova, Universidad Católica de Valencia, Medica Scientia Innovation Research (MEDSIR), Barcelona, Valencia, Spain

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, 2023, issue of the Journal of Clinical Oncology.
Differential impact of proliferation signature on efficacy of neoadjuvant chemo-immunotherapy in sTIL-high and sTIL-low triple-negative breast cancer (TNBC): Biomarker analysis of the NeoPACT trial.

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Background: TNBCs with enrichment of stromal tumor-infiltrating lymphocytes (sTILs) and/or immune gene expression are more sensitive to neoadjuvant systemic therapy (NAST) and exhibit higher rates of pathologic complete response (pCR). Other biomarkers, including proliferation, are also prognostic in TNBC patients treated with NAST. We aim to investigate the impact of proliferation gene expression on efficacy of NAST in sTIL-high and sTIL-low TNBC. Methods: 110 TNBC patients treated with neo-adjuvant chemoimmunotherapy (Carboplatin+Docetaxel+Pembrolizumab) on the phase II NeoPACT trial (NCT03639948) with available whole exome RNA sequencing were included. sTILs were scored in 5% increments by H&E. Tumors were defined as sTIL-high (>20% sTILs) or sTIL-low (<20% sTILs). The ImSig Proliferation Signature score (ProlifSig) was computed from RNA sequencing data and samples were classified as ProlifSig-high (≥median) or ProlifSig-low (<median). ProlifSig was tested for prediction of pCR in sTIL-high and sTIL-low groups. Logistic regression was used to examine the independent prognostic utility of sTILs and ProlifSig on pCR. Results: 63/110 (57%) patients achieved a pCR. 56/110 (51%) patients were classified as sTIL-high, and 54/110 (49%) classified as sTIL-low. sTILs and ProlifSig as continuous variables were each predictive of pCR (OR = 1.022, 95% CI = 1.009-1.035, P = 0.001 for sTILs; OR = 2.682, 95%CI = 1.23-5.85, P = 0.01 for ProlifSig). In the sTIL-high group, ProlifSig was not associated with pCR either as a continuous score (AUC = 0.56) or when assessed as high/low categories (pCR 78% vs. 67% in ProlifSig-high and ProlifSig-low groups, respectively; OR = 1.79, 95%CI = 0.54-5.89, P = 0.34). In contrast, in the sTIL-low group, ProlifSig was significantly associated with pCR both as a continuous score (AUC = 0.74) and when assessed as high/low categories (pCR 75% vs. 29% in ProlifSig-high and ProlifSig-low groups, respectively; OR = 3.18, 95%CI = 1.03-9.86, P = 0.045). On multivariate analysis, sTILs and ProlifSig were independent predictors of pCR (OR = 1.02, 95%CI = 1.01-1.03, P = 0.004 for sTILs; OR = 3.13, 95%CI = 1.44-6.83, P = 0.004 for ProlifSig). Conclusions: In TNBC patients treated with chemoimmunoablation sTILs and ProlifSig provide complimentary information for prediction of pCR. ProlifSig is positively associated with pCR in sTIL-low tumors but not in sTIL-high tumors. We hypothesize that the therapeutic response in sTIL-high tumors is dominated by lymphocyte-dependent cytotoxic mechanisms, while in sTIL-low tumors, the response may be dominated by proliferation-dependent responses. ProlifSig could identify a subgroup of immune low TNBCs that can achieve substantial rates of pCR with neoadjuvant chemoimmunotherapy. Research Sponsor: University of Kansas Clinical and Translational Science Institute, Team Michelle, ACS-IRG.
Do tumor infiltrating lymphocytes (TILs) predict benefits from trastuzumab therapy for HER2 positive breast cancer? Meta-analysis of individual patient data from 4097 women in 5 trials.

Robert Kerrin Hills, Rosie Bradley, Jeremy Braybrooke, Richard G. Gray, Hannah Taylor, Carsten Denkert, Sunil S. Badve, Rim S. Kim, Magali Lacroix-Triki, Meredith M. Regan, Daniel F. Hayes, Mitchell Dowsett, Andrew NJ Tutt, Richard D. Gelber, David A. Cameron, Jonas C. S. Bergh, Sandra M. Swain, Stefan Michiels, Sherene Loi, Roberto Salgado, Early Breast Cancer Trialists’ Collaborative Group & International Immuno-Oncology Biomarker Working Group; University of Oxford, Oxford, United Kingdom; Institut für Pathologie, Philippus-Universität Marburg und Universitätsklinikum Marburg, Marburg, Germany; Emory University School of Medicine, Atlanta, GA; NSABP, Pittsburgh, PA; Institut Gustave Roussy, Villejuif, France; Dana-Farber Cancer Institute, Boston, MA; University of Michigan Health System Comprehensive Cancer Center, Ann Arbor, MI; The Royal Marsden NHS Foundation Trust, London, United Kingdom; The Institute of Cancer Research, London, United Kingdom; Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, United Kingdom; Karolinska Institutet, Stockholm, Sweden; Georgetown University Medical Center, Washington, DC; Office of Biostatistics and Epidemiology, Gustave Roussy, Villejuif, France; Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Pathology, GZA-ZNA Hospitals, Antwerp, Belgium

Background: High TIL counts are associated with a lower risk of breast cancer recurrence, especially in women with ER negative, HER2 negative tumors and, possibly, greater benefit from trastuzumab in women with HER2 positive cancer: the FinHER trial reported a differential effect of trastuzumab based upon TIL status. We performed a meta-analysis of randomized trials of trastuzumab in early breast cancer to attempt to validate this finding. Methods: TILs were quantified in 4097 women in 5 randomized controlled trials (NSABP B-31, FinHER, HERA, Intergroup N9831, PACS-04). All trials contributed to the Early Breast Cancer Trialists’ Collaborative Group individual patient data meta-analysis of trastuzumab for women with HER2 positive tumors which found a significant benefit for trastuzumab therapy. TILs were assessed using established International Guidelines, with HERA using digital TIL-scores. The primary outcome was time to first recurrence. Cox regression analyses, adjusted for trial, treatment allocation, and nodal status, were used to quantify the prognostic value of TILs; and standard stratified logrank tests were used to assess the differential effect of trastuzumab therapy. Results: The median percentage TILs was 13% (Interquartile Range 5-30), with fewer than 10% of patients exhibiting TILs >50%. The prognostic value of TILs was confirmed, with patients with higher TILs being at lower risk for recurrence (adjusted hazard ratio per 10% increase in TILs 0.87 (95% CI 0.84-0.90), p<.0001) with similar effects in both treatment groups. Outcomes improved steadily with increasing TILs, and unadjusted 10-year recurrence rates fell from 30% in women with TILs <10% to 15% in those with TILs 70% or greater. Consequently, analyses of the predictive effect of TILs were stratified into 5 groups (0-9, 10-19, 20-39, 40-59, 60+). Overall, there was a highly significant benefit of trastuzumab on recurrence (HR 0.62 (0.54-0.70) p<.0001), but there was no evidence of any interaction between TILs and the proportional reduction in recurrence (p=0.8 for heterogeneity and trend). Conclusions: While higher TILs are associated with lower recurrence rates, there was no indication that the proportional reduction in recurrence with trastuzumab varied by TILs, although the number of patients with high levels was limited. Owing to a lower underlying recurrence rate, absolute benefits from trastuzumab were lower, but still substantial, in women with high TIL tumors. Clinical trial information: NCT00045032, IsRCTN76560285, NCT00005970, NCT00004067, NCT00054587. Research Sponsor: Cancer Research UK.
Assessment of risk of overall and late distant recurrence by Breast Cancer Index in postmenopausal women with early-stage, HR+ breast cancer in the TEAM trial.

John MS Bartlett, Keying Xu, Jenna Wong, Gregory Russell Pond, Yi Zhang, Melanie Spears, Ranelle C. Salunga, Elizabeth Mallon, Karen J Taylor, Annette Hasenburg, Christos Markopoulos, Luc Yves Dirix, Caroline M. Seynaeve, Cornelis J.H. Van De Velde, Daniel William Rea, Catherine A Schnabel, Kai Treuner, Jane Bayani; Cancer Research UK Scotland Centre, University of Edinburgh, Edinburgh, United Kingdom; Unity Health Toronto, Toronto, ON, Canada; Biotheranostics, A Hologic Company, San Diego, CA; McMaster University, Hamilton, ON, Canada; Ontario Institute for Cancer Research, Toronto, ON, Canada; Department of Pathology, Glasgow, United Kingdom; University Medical Center Mainz, Mainz, Germany; National and Kapodistrian University of Athens, Medical School, Athens, Greece; GZA Ziekenhuizen Antwerpen campus Sint-Augustinus, Antwerpen, Belgium; Erasmus MC - Kanker Instituut locatie Daniel den Hoed, Rotterdam, Netherlands; Leiden University Medical Center, Leiden, Netherlands; University of Birmingham, Cancer Research UK Clinical Trials Unit (CRCTU), Birmingham, United Kingdom

Background: Individual risk assessment of distant recurrence (DR) is particularly relevant for early-stage HR+ breast cancer patients, as they face a prolonged risk of recurrence even after adjuvant endocrine therapy. Previously, we have shown that the Breast Cancer Index (BCI) and BCIN+ risk groups are significantly prognostic for risk of overall (0-10y) and late (5-10y) distant recurrence in N0 and N1 breast cancer patients, respectively, enrolled in the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial. Here, the prognostic performance of BCI and BCIN+ as a continuous risk score for overall and late distant recurrence was evaluated in the TEAM trial. Methods: BCI testing was performed blinded to clinical outcome with BCI/BCIN+ risk scores calculated as previously described. Cox proportional hazard models adjusted for age, tumor size, grade and treatments were used to estimate hazard ratios (HRs) and the associated 95% confidence intervals (CIs) for BCI/ BCIN+ continuous risk scores. The 10y risk of overall and late DR were estimated as a function of risk scores from the Cox models using Breslow estimates. Results: Continuous risk curves for overall and late DR were obtained in patients who did not receive adjuvant chemotherapy and those who remained DR-free at 5 years regardless of chemotherapy, respectively, to reflect the two key time points for breast cancer treatment decision-making. In N0 patients not treated with chemotherapy (N = 1197), BCI was significantly prognostic for overall DR with a HR of 1.39 (95% CI 1.25-1.54; p < 0.001), while BCIN+ was significantly prognostic in N1 patients who did not receive chemotherapy (N = 1319) with a HR of 4.29 (95% CI 2.93-6.28; p < 0.001). Among patients who remained DR-free at 5 years, in the N0 subset (N = 1285), BCI was significantly prognostic for late DR with a HR of 1.23 (95% CI 1.07-1.42; p < 0.001), while BCIN+ remained to be significantly prognostic in the N1 subset (N = 1762) with a HR of 2.78 (95% CI 1.75-4.43; p < 0.001). Similar results were observed in the HER2- subset for both overall and late DR. Continuous risk curves for BCI and BCIN+ for overall and late DR showed an increasing risk of DR with higher BCI/BCIN+ scores. Conclusions: Results from this largest BCI study to date further support the use of BCI to provide individualized risk estimates for both overall and late DR in women with HR+ breast cancer to aid in personalized decision-making for adjuvant therapy. Research Sponsor: Hologic.

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<th>N</th>
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Prognosis and trends in chemotherapy use for patients with stage IA triple-negative breast cancer (TNBC): A population-based study.

Paolo Tarantino, Julieta Leone, Carlos Teodoro Vallejo, Rachel A. Freedman, Adrienne Gropper Waks, Olga Martínez-Sáez, Ana Christina Garrido-Castro, Filipa Lynce, Nabihah Tayob, Nancy U. Lin, Sara M. Tolaney, Jose Pablo Leone; Dana-Farber Cancer Institute, Boston, MA; Cooperative Oncological Group of Sur, Neuquén, Argentina; Unidad Oncologica de Neuquen, Neuquen, Argentina; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Outcomes for patients with stage IA TNBC in the modern era remain poorly characterized, and the benefit and utilization of adjuvant chemotherapy (chemo) in this setting remains controversial. Methods: We analyzed data from women diagnosed with pathological stage IA TNBC in the Surveillance, Epidemiology, and End Results (SEER) database during 2010 to 2019. We evaluated the associations of adjuvant chemo with breast-cancer specific survival (BCSS) stratified by tumor size, using multivariate cox models adjusted for tumor size (overall cohort only), age at diagnosis, race, tumor grade, histology, radiation, marital status, income, and rurality. Frequency of chemo use over time was examined by tumor size. Multivariate logistic regression assessed variables associated with chemo administration. Results: In total, we examined data from 8,601 women with stage IA TNBC. Median age at diagnosis was 62 years. Most patients had high-grade tumors (70.1%), ductal histology (92.8%), and received adjuvant chemo (61.6%). Median follow up was 48 months (IQR: 20 – 83). The use of chemo significantly increased during 2010-2019 for both T1b tumors (p for trend = 0.001) and T1c tumors (p for trend < 0.001), with 52.5% and 63% of the patients with T1b and T1c TNBCs receiving chemo in 2010, respectively, compared with 60.5% and 71.1% in 2019. No significant differences were observed in the use of chemo for T1mic (p for trend = 0.567) and T1a (p for trend = 0.637) tumors, with low utilization seen in both cohorts (9.5% overall in T1mic, 22.5% overall in T1a). Variables associated with chemo use included younger age, white race, married status, higher income, more recent diagnosis, higher tumor grade, ductal histology, and larger tumor size (all p < 0.02). Overall, 5-year BCSS was high across T groups (> 90%; Table). Receiving chemo (vs. none/unknown) was associated with an improved 5-year BCSS (adjusted HR for BCSS = 0.70, p = 0.006). For T1c tumors specifically, adjuvant chemo (vs. none/unknown) was also associated with BCSS (adjusted HR 0.64, p = 0.002). The small number of BCSS events precluded comparisons for other tumor size subgroups. Table shows sample sizes and 5-year BCSS rate by chemo receipt for each T group. Conclusions: In a large population-based cohort of patients with stage IA TNBC, we observed excellent 5-year BCSS outcomes, supporting the good prognosis of this patient population. The use of adjuvant chemo increased over time for T1b and T1c TNBCs, and was associated with improved BCSS for T1c tumors, although evaluation of benefit is limited by the inherent treatment bias in registry data. Research Sponsor: None.

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<th>T1b,N0 (n = 2175)</th>
<th>T1c,N0 (n = 5234)</th>
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Racial/ethnic differences in 21-gene recurrence score and survival among estrogen receptor-positive breast cancer patients.

Jasmin Gill, Sung Jun Ma, Keerti Yendamuri, Udit Chatterjee, Song Yao, Oluwadamilola Temilade Oladeru, Anurag K. Singh; University at Buffalo, The State University of New York, Buffalo, NY; Roswell Park Comprehensive Cancer Center, Buffalo, NY; University of Florida COM, Gainesville, FL; Roswell Park Cancer Institute Department of Cancer Prevention and Population Sciences, Buffalo, NY

Background: Despite studies on racial/ethnic disparities in breast cancer patients, there is limited literature evaluating association of racial/ethnic differences with 21-gene recurrence score (RS) and survival differences stratified by RS risk categories. We performed an observational cohort study to evaluate such disparities in context of RS. Methods: The National Cancer Database (NCDB) was queried for patients with ER-positive, pT1-3N0-1aM0 breast cancer who received surgery followed by adjuvant endocrine therapy with available RS from 2006 to 2018. Racial/ethnic groups were stratified by non-Hispanic White (NHW), Hispanic White (HW), Black, and Asian/Pacific Islander (API). Our primary endpoint was overall survival (OS). Logistic multivariable analysis (MVA) was built upon baseline patient and tumor characteristics to evaluate variables associated with RS > 25. Cox MVA was used to evaluate OS. Interaction term analysis was used to identify heterogeneous association of racial/ethnic groups and RS; if significant, subgroup analyses compared magnitude of racial/ethnic differences stratified by RS. To address immortal time bias, Cox MVA analyses were repeated after excluding patients with post-diagnosis survival < 6 months. P values were two-sided. Bonferroni correction was used for multiple comparisons (NHW vs HW women, NHW vs Black women, and NHW vs API women) with p values less than 0.017 being statistically significant. Results: A total of 140,133 women (median [interquartile range (IQR)] age, 60 [52-67] years) were included for analysis. 115,651 (82.5%), 8,213 (5.9%), 10,814 (7.7%), and 5,455 (3.9%) were NHW, Hispanic, Black, and API women respectively. Median (IQR) follow up was 66.2 mo. (48.0-89.8). Logistic MVA showed compared to NHW women, Black women were associated with higher RS (26 or higher vs <26: adjusted odds ratio [aOR] 1.19, 95% confidence interval [CI] 1.12-1.26, p < 0.001), while HW (aOR 0.93, 95% CI 0.86-1.00, p = 0.04) and API (aOR 1.03, 95% CI 0.95-1.13, p = 0.45) were not. Cox MVA showed compared to NHW, Black women were associated with worse OS (adjusted hazards ratio [aHR] 1.10, 95% CI 1.02-1.19, p = 0.012) while HW (aHR 0.85, 95% CI 0.77-0.94, p = 0.001) and API (aHR 0.66, 95% CI 0.56-0.77, p < 0.001) were not. There was significant interaction between race/ethnicity and RS (interaction p = 0.006). Subgroup analysis found similarities in those with RS < 26, while only API women were associated with improved OS among those with RS ≥ 26. After excluding those with post-diagnosis survival < 6 mo., our findings remained comparable. Conclusions: To our knowledge, this is the largest nationwide oncology database study to suggest that Black women are associated with higher RS, while HW and API are not. It also suggests that Black women are associated with worse OS among those with RS < 26, while API are associated with improved OS regardless of RS compared to NHW women. Research Sponsor: U.S. National Institutes of Health.
Rapid Abstract Session

A randomized controlled trial of a mobile app and tailored messages to improve outcomes among women with breast cancer receiving adjuvant endocrine therapy.

Ilana Graetz, Xin Hu, Mehmet Kocak, Rebecca A Krukowski, Janeane Nicole Anderson, Teresa Waters, Andrea Curry, Andrew J. Paladino, Edward Stepanski, Gregory A. Vidal, Lee S. Schwartzberg; Emory University, Rollins School of Public Health, Atlanta, GA; International School of Medicine, Instabul, Turkey; University of Virginia Cancer Center, Charlottesville, VA; Department of Community and Population Health, College of Nursing, University of Tennessee Health Science Center, Memphis, TN; University of Kentucky College of Public Health, Lexington, KY; West Cancer Center, Germantown, TN; College of Medicine, University of Tennessee Health Science Center, Memphis, TN; Ovation.io, Cambridge, MA; The West Cancer Center, Germantown, TN; University of Nevada, Reno, Reno, NV

Background: Adjuvant endocrine therapy (AET) use among women with early-stage, hormone receptor-positive breast cancer reduces the risk of cancer recurrence, but adverse symptoms contribute to lower adherence. We evaluated the effectiveness of an app that integrates patient-reported outcomes with electronic health records and tailored messages. Methods: Women with early-stage breast cancer initiating AET (November 2018-June 2021) were randomized into three arms: (1) an “App” group that received instructions and access to the study app and weekly text reminders to use it; (2) an “App+Feedback (AF)” group received additional weekly tailored messages about managing symptoms, adherence, and communication; or (3) a “Usual Care (UC)” group without access to the app. The intervention lasted 6-months and participants completed surveys at enrollment, 6-, and 12-months. Increasing/severe symptoms and missed doses triggered alerts that prompted follow-ups from the oncology team. Outcomes included AET adherence, captured using an electronically monitored pillbox and self-reported adherence, symptom burden (FACT-ES), mental and physical health quality of life (SF-12), self-efficacy for managing symptoms (PROMIS 1.0), and 6-month count of emergency department visits/urgent care/hospitalizations [higher cost encounters] and office visits. Results: Overall, 300 women were randomized (102 UC, 96 App, and 102 AF). Median age was 60 years (range: 31–83), 34% identified as Black, 21% had incomes below 200% of the federal poverty level, and 20% had a high school degree or less education. Retention at 12-months was 88% (N=264). Mean app logins were 14.4 among intervention participants, which resulted in 4.2 mean alerts, with 58.0% having at least one alert during the 6-month intervention. AET adherence over 12-months measured using the pillbox was similar across groups: 76% for UC, 73% for App, and 71% for AF (p=0.57). At 12-months, AF participants had fewer higher cost care encounters over the previous 6 months (0.30, 95% CI: 0.15 to 0.45, p=0.01) compared to UC (0.71, 95%CI: 0.44 to 0.97) but not for App only vs. UC (0.46, 95% CI: 0.25 to 0.66, p=0.15). Mean mental health scores were 2.0 points better (95% CI: 0.21 to 3.84) at 6-months for AF (43.0) compared to UC (41.0). There were no statistically significant differences by group in self-reported adherence, symptom burden, physical health, self-efficacy for managing symptoms, and office visits at 6- or 12-months. Conclusions: While the intervention did not improve AET adherence, the app combined with tailored messages resulted in better self-reported mental health during the intervention and fewer higher cost care encounters at 12-months without increasing office visits. Symptom monitoring apps with tailored messages may be scalable and effective strategies for improving outcomes for patients with breast cancer. Clinical trial information: NCT03592771. Research Sponsor: U.S. National Institutes of Health.
Correlation of HER2 low status in I-SPY2 with molecular subtype, response, and survival.

Hope S. Rugo, Denise M. Wolf, Christina Yau, Emanuel Petricoin, Paula R Pohlmann, Lajos Pusztai, W. Fraser Fraser Symmans, Alexander Borowsky, Sandra Finestone, Douglas Yee, Nola Hylton, Laura van ’t Veer, Laura Esserman, Angela DeMichele, I-SPY Investigators; University of California Comprehensive Cancer Center, San Francisco, CA; University of California San Francisco, San Francisco, CA; University of California, San Francisco, San Francisco, CA; George Mason University, Manassas, VA; University of Texas MD Anderson Cancer Center, Houston, TX; Yale University, New Haven, CT; UC Davis, Davis, CA; Research Advocacy Network/Komen AIS, Irvine, CA; Masonic Cancer Center, Minneapolis, MN; University of Pennsylvania, Philadelphia, PA

Background: HER2low, defined as immunohistochemical (IHC) 1+ or 2+ without HER2 gene amplification, predicted improved progression free and overall survival with trastuzumab deruxtecan (TDXd) compared to chemotherapy in patients (pts) with metastatic breast cancer in Destiny Breast04. Controversy exists regarding the correlation of HER2low with molecular subtypes and outcome. We evaluated these associations in the neoadjuvant ISPY2 trial.

Methods: We investigated HER2 IHC class in pts with clinically HER2-negative breast cancer (BC) enrolled in the first 10 arms of ISPY2. To explore the biology of HER2low, we used Fisher’s exact test to assess association of IHC class (0 vs 1+ or 2+) with Response Predictive Subtypes-5 (RPS-5; based on immune, DNA repair damage (DRD), HER2, and luminal markers; PMID: 35623341), SET index [endocrine responsiveness], and Mammaprint high1 (MP1) vs high2 (MP2). Association with pathologic complete response (pCR) was assessed using Fisher’s exact test, and association with distant recurrence free survival (DRFS) was assessed using Cox Proportional Hazards modeling.

Results: Of 742 HER2negative pts enrolled in the first 10 arms of ISPY2, local HER2 IHC is available for 585; 299 hormone receptor + (HR+) and 286 triple negative (TN). 63% of pts are HER2low, with HER2low status more frequent in HR+ (71%) compared to TN BC (55%; OR = 1.97; p = 0.00011). There was no clear relationship between HER2low IHC and RPS-5 subtypes or endocrine sensitivity measured by the SET index. There was no significant association of HER2low with pCR overall or within treatment arms (p > 0.05); this was true for TN and HR+ subsets. 562 pts with HER2negative disease have distant recurrence free survival (DRFS) data with a median follow-up of 4.23 yrs. Pts with pCR had excellent outcome (5yr DRFS > 94%), with no impact from HER2low vs 0 status. For pts with nonpCR, after adjusting for HR+ status, the DRFS hazard ratio for HER2low vs 0 status is not significant (0.68(0.46-1.02)). Within HR+, HER2low is found in > 70% for both SET low and high. HR+/MP1 pts (with generally low pCR rates) are significantly more likely to be HER2low (75%; (172/219)) compared to HR+/MP2 (61%; (49/80)) (OR: 1.79; Fisher p = 0.044). Importantly, 70% of HER2-Immune-/DRD- (78% HR+ and 56% TN), a subtype with low response to all ISPY2-tested agents, are HER2Low.

Conclusions: In ISPY2 which enrolls patients with MP high risk BC, HER2low by IHC was frequent and higher in HR+ than TN disease. There was no clear association with molecular markers, pCR or DRFS. The frequency of HER2low in the immune-/DRD-subtype raises the potential for exploring T-DXd in this high risk, low-response setting. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health; Quantum Leap Healthcare Collaborative.
ECOG-ACRIN E2197: Comparison of HER2 gene expression by RT-PCR across all HER2 immunohistochemistry groups with recurrence analysis.

Nhu Thuy Can, John Bennett, Cynthia A. Flannery, Helen Bailey, Lori J. Goldstein, Nancy E. Davidson, Joseph A. Sparano, Frederick L. Baehner, Sunil S. Badve; Genomic Health Inc, an Exact Sciences Corporation (Redwood City, CA), Redwood City, CA; Exact Sciences, Madison, WI; Exact Sciences, Redwood City, CA; Genomic Health, Inc., Redwood City, CA; Fox Chase Cancer Center, Philadelphia, PA; Fred Hutchinson Cancer Research Center, Seattle, WA; Icahn School of Medicine, Tisch Cancer Institute, New York, NY; Emory University School of Medicine, Atlanta, GA

Background: Accurate assessment of HER2-low [immunohistochemical (IHC) score of 1+ or 2+ and in-situ hybridization negative] breast cancer is clinically relevant following DESTINY-Breast04. In hormone receptor positive breast cancers, Oncotype DX assay Recurrence Score results are widely used to guide adjuvant chemotherapy selection, and standardized quantitative HER2 mRNA reference-normalized expression levels by RT-PCR are included in patient reports. Previously, a high degree of concordance between central IHC and quantitative HER2 by RT-PCR was demonstrated in E2197. Here, we compare quantitative HER2 gene expression using Oncotype DX assay within all IHC subgroups and risk of recurrence in E2197.

Methods: Data analyzed were from a case-control sample from E2197 (no adjuvant anti-HER2 therapy) of 755 patients. Central IHC for HER2 used duplicate 1.0 mm microarrays (HercepTest, Dako) and scored per 2007 ASCO/CAP guidelines. Based on quantitative reference-normalized RT-PCR measures of HER2 expression, cases were assigned: positive ≥11.5 units, equivocal ≥10.7 to <11.5 units, and negative <10.7 units (1 unit increase represents ~2-fold increase in RNA). Spearman’s rank correlation was used to measure strength of association between the 2 methods. Cox proportional hazards regression was used to evaluate the association between quantitative HER2 expression and recurrence (defined as invasive breast cancer in local, regional, or distant sites). Analyses were weighted to account for study design. Results: 48% were IHC 0, 11% were IHC 1+, 23% were IHC 2+, and 18% were IHC 3+. 85% were HER2 negative, 3% equivocal, and 11% positive by RT-PCR. While there was moderately strong correlation between HER2 IHC and HER2 gene expression by RT-PCR [Spearman’s rho: 0.63 (95% CI: 0.59, 0.67); p<0.001], there were wide and overlapping ranges of HER2 gene expression across all IHC categories with almost identical medians and inter-quartile ranges for HER2 IHC 1+ and 2+ (n=248; see table). An exploratory analysis showed 86% of IHC 0, 97% of IHC 1+, and 99% of IHC 2+ had HER2 >8 units. After controlling for baseline clinicopathologic features (age, hormone receptor status, grade, size, and nodal status), continuous quantitative HER2 expression was associated with time to recurrence in HER2 IHC 0 to 2+ [HR 1.17 per 1-unit increase in HER2 (95% CI 1.01, 1.35; p=0.036)]. Conclusions: There was a wide range of quantitative HER2 gene expression using Oncotype DX assay across all IHC categories; continuous HER2 expression is independently associated with recurrence. Quantitative HER2 expression may be useful for identification of HER2-low breast cancer. Further studies are needed. Research Sponsor: None.
AI-based HER2-low IHC scoring in breast cancer across multiple sites, clones, and scanners.

Patrick Frey, Andreas Mamilos, Evgeny Minin, Ralf Banisch, Stefan Günther, Carolin Schmidt, Niklas Abele, Arndt Hartmann, Peter A. Fasching, Matthias Rübner, Hanna Huebner, Tobias Lang, Ramona Erber; Mindpeak GmbH, Hamburg, Germany; Institute of Pathology, University of Regensburg, Regensburg, Germany; Institute of Pathology, Clinical Center Osnabrueck, Osnabrueck, Germany; Institute of Pathology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Comprehensive Cancer Center Erlangen-EMN (CCC ER-EMN), Erlangen, Germany; Department of Gynaecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Comprehensive Cancer Center Erlangen-EMN (CCC ER-EMN), Erlangen, Germany

Background: Assessment of immunohistochemical (IHC) HER2 expression plays a pivotal role in breast cancer diagnostics. In the era of HER2-low and HER2-targeted antibody drug conjugates, accurate discrimination of defined HER2 IHC scores is essential. At the same time, HER2 IHC scoring suffers from poor interobserver concordance. Artificial intelligence (AI) may optimize this scoring in regard to standardization, accuracy and efficiency, but previous approaches fail to show the required consistency across samples from different sites, clones and scanning hardware.

Methods: We have investigated the use of an AI-based HER2 IHC quantifier software to support pathologists in standardized HER2 IHC assessment in breast cancer. Validation specimens were derived from four institutions and five scanners. Using the “region of interest” (ROI) software version (part I), pathologists choose the ROI to be assessed within the whole slide image (WSI). In contrast, the fully automatic version (part II) analyzes the complete WSI. Part I: Three pathologists selected one ROI per slide from a cohort of n = 150 specimens. They scored HER2 expression in these ROIs (path-only) according to ASCO/CAP 2018 guidelines (each pathologist n = 50). After a 2-week washout period, the same pathologists were presented with the same ROIs and corresponding AI-suggested results (AI-only), and then decided on final HER2 scores (AI-assisted). Scoring times were recorded. Part II: Fully automatic AI accuracy without human intervention was analyzed using the WSI cohort of part I and an additional cohort of n = 94 WSIs. For both parts, IHC scores were compared to the clinical workflow derived ground truth defined as the manually assessed HER2 IHC score.

Results: Part I: In discriminating HER2-neg from HER2-low/pos cases, AI-assisted and AI-only ROI scoring showed agreement rates of 91.3% and 86.7%, respectively, with path-only decisions across all institutions and scanners. In discriminating the four HER2 scores (0, 1+, 2+, 3+) individually, interrater-agreement of AI-assisted vs. path-only ROI HER2 scoring was 78.7%, exceeding literature rates of < 70%, with the mean scoring time per ROI being 29 sec vs. 50 sec, respectively; interrater-agreement of AI-only vs. AI-assisted was 85.3%. Part II: In discriminating HER2-neg from HER2-low/pos cases, fully automatic AI WSI scoring showed 89.1%/86.2% agreement for both cohorts, respectively.

Conclusions: Across challenging validation data from four institutions and five scanners, scoring with the support of an AI HER2 IHC quantifier software showed very high agreement when discriminating HER2-neg from HER2-low/pos cases and high accuracy for general HER2 scoring. When using AI-assistance, scoring time was reduced by almost 50%. Altogether, these results demonstrate the potential of AI solutions to increase consistency and efficiency of HER2 scoring and ultimately to improve patient outcome. Research Sponsor: None.

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Outcomes according to treatment received for small node-negative HER2+ breast tumors in the Surveillance, Epidemiology, and End Results (SEER) database, 2010-2019.

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Background: The magnitude of systemic therapy (tx) benefit for small, node-negative HER2+ breast tumors is unknown, with uncertainty about how benefit varies across stage I tumor sizes. We analyzed treatment patterns and outcomes for patients (pts) with stage IA (pT1N0) HER2+ breast cancer in the national SEER database. Methods: Pts with one lifetime diagnosis of pT1N0 HER2+ breast cancer between 2010-2019 were included. Receipt of chemotherapy (chemo) was categorized as yes vs no/unknown; receipt of endocrine tx is not available in SEER. All systemic tx was administered in the adjuvant setting. The primary outcome variable was breast cancer-specific survival (BCSS; recurrence events are not available in SEER), which was compared between treatment groups using a multivariate Cox model adjusted for age at diagnosis (dx), race, tumor grade/histology/size, hormone receptor (HR) status, radiation, marital status, income, rurality. Chemo use predictors were evaluated by multivariable logistic regression. Results: We identified 12,861 pts with pT1N0 HER2+ breast cancer; 9,513 (74%) HR-positive and 3,348 (26%) HR-. Median age at dx was 59 yrs. Median follow-up was 46 months. In the overall cohort, BCSS at 3, 5, and 7 yrs was: 99.3% (with chemo) vs 99.1% (without chemo); 98.6% (with chemo) vs 97.4% (without chemo); and 97.5% (with chemo) vs 96.4% (without chemo), respectively. Adjusted hazard ratio (HzR) for BCSS events in the chemo vs no chemo group of the overall cohort was 0.63 (p=0.004). BCSS events by tumor size and HR status are shown; p values are not shown where event rates were too low to run an adjusted model. Chemo use increased significantly between 2010-2019 within each tumor size category (all p for trend < 0.04), except for T1a HR+/HER2+ and T1mi HR-/HER2+. Pts were less likely to receive chemo if they were older, Hispanic (vs non-Hispanic White), separated/divorced/widowed (vs single), or had lower median household income (vs $75K). Pts were more likely to receive chemo if they had larger tumor size, HR- tumor, higher tumor grade, were married (vs single), or had later yr of dx. Conclusions: Receipt of chemo was associated with higher BCSS in the overall stage IA cohort and among pts with HR+/HER2+ stage IA tumors. Tumors ≤ 1cm had excellent outcomes with or without chemo. Sociodemographic factors including income, race, and marital status impacted chemo receipt. Research Sponsor: None.

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Gene expression signatures, stromal tumor infiltrating lymphocytes (sTILs), and change in tumor cellularity to predict pathological complete response (pCR) after 12 week de-escalated neoadjuvant endocrine therapy (ET) vs paclitaxel + dual HER2 blockade in the WSG-TP-II trial.

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Background: There are limited data on predictive biomarkers for de-escalated ET or chemotherapy with dual anti-HER2 blockade in HR+/HER2+ early breast cancer (BC). In this translational pre-planned project of the WSG-TP-II phase II-trial (NCT03272477), we aimed to identify associations of gene expression signatures and sTILs with pCR. Methods: Patients with cT1c-cT4c, cN0-3 centrally confirmed HR+/HER2+ BC were randomized to 12 weeks of standard ET (n = 100) or paclitaxel (Pac; n = 107). All patients received trastuzumab + pertuzumab (T+P) q3w as neoadjuvant and adjuvant treatment. Gene expression signatures were analyzed using NanoString BC360 panel in baseline biopsies (T+P+ET: n = 72; T+P+Pac: n = 78). sTILs were analyzed in 93 (T+P+ET) and 97 patients (T+P+Pac) at baseline and in 65 (T+P+ET) and 57 patients (T+P+Pac) at week 3. Impacts of standardized BC360 gene expression signatures and sTILs on pCR (ypT0/is ypN0; primary endpoint) expressed in odds ratios (OR) were estimated by logistic regression analysis. Results: pCR rate in patients with BC360 analysis was 39.3% (T+P+ET: 23.6%; T+P+Pac: 53.9%). Overall, ERBB2 (OR 2.37; 95%CI 1.55, 3.62) and cytotoxic cells signature (OR 1.42; 95%CI 1.02, 1.99) were favorable for pCR, while apoptosis (OR 0.64; 95%CI 0.44, 0.92), estrogen receptor 1 (OR 0.60; 95%CI 0.42, 0.85), estrogen receptor signaling (OR 0.64; 95%CI 0.45, 0.91), and progesterone receptor (OR 0.67; 95%CI 0.47, 0.94) signatures were unfavorable. Analyzing by treatment arm, a similar pattern was observed in the T+P+Pac arm (ERBB2: OR 2.01; apoptosis: OR 0.59; estrogen- and progesterone-related signatures: OR 0.41-0.58), but not in the T+P+ET arm where only ERBB2 was prognostic for pCR (OR 7.24; 95%CI 2.12, 24.05). Baseline ≥30% sTIL levels (vs < 30% sTILs; n = 16 vs n = 174) were associated with pCR (OR 5.16; 95%CI 1.60, 16.66); significance was not achieved in either trial arm. Compared to < 30% sTILs (n = 90), low tumor cellularity at week 3 precluding sTILs analysis (< 500 invasive tumor cells, n = 22), but not ≥30% sTILs (n = 10), was prognostic for pCR in all patients (OR 4.47; 95%CI 2.94, 30.50) and in individual trial arms (OR 6.00-11.79). Conclusions: This hypothesis-generating translational results suggest that gene expression signatures (particularly ERBB2), baseline sTILs, and low tumor cellularity at week 3 predict pCR after ET + double HER2 blockade. Future neoadjuvant trials are needed to prospectively test the use of baseline gene expression and sTILs analysis, and early on-treatment cellularity measurement to select patients with HR+/HER2+ tumors for de-escalated endocrine-therapy-based approaches. Clinical trial information: NCT03272477. Research Sponsor: Roche Pharma AG.
Oral paclitaxel, carboplatin, and dostarlimab (OPE/Cb/D) without and with trastuzumab in early-stage, high-risk breast cancer: Results from the neoadjuvant I-SPY 2 TRIAL.

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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, 2023, issue of the Journal of Clinical Oncology.
MammaPrint Index as a predictive biomarker for neoadjuvant chemotherapy response and outcome in patients with HR+HER2- breast cancer in NBRST.

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Background: Hormone receptor positive (HR+), HER2- early stage breast cancer (ESBC) is a heterogeneous disease that has shown lower response to neoadjuvant chemotherapy (NCT) compared with other clinicopathologic subtypes. Genomic profiling may help inform neoadjuvant treatment decisions for ESBC by predicting likelihood of pathological complete response (pCR) or chemosensitivity. The 70-gene MammaPrint (MP) test classifies ESBC patients as having a Low or High Risk of distant metastasis. In the ISPY2 trial, further stratification of MP High Risk into High 1 (H1) or High 2 (H2) improved prediction of chemosensitivity, with significantly higher pCR rates in H2 vs. H1 tumors, particularly in response to immune therapy. Here we evaluate the utility of H1/H2 risk as a biomarker for chemosensitivity and 5 year distant-metastasis free survival (DMFS) in NCT treated patients from the Neoadjuvant Breast Registry Symphony Trial (NBRST).

Methods: NBRST (NCT01479101) is an observational prospective study that included 1069 patients with ESBC who received neoadjuvant therapy. Patients with HR+HER2-, MP High Risk tumors who received NCT were included in this analysis (n = 327). Patients were further stratified into H1 (score ≤ 0, > -0.57) or H2 (score ≤ -0.57) groups. Differences in pCR between MP High Risk subcategories were assessed by two-sided proportional z-test. Differences in DMFS was evaluated by Kaplan Meier analysis and log-rank test. Results: MP classified 198 (61%) patients with H1 tumors and 129 (39%) patients with H2 tumors. Age, tumor stage, and lymph node status were comparable between both groups. However, there was a higher proportion of Grade 3 tumors in the H2 group. A significantly higher percentage of pCR was achieved in H2 tumors (30/129; 23%) vs. H1 tumors (12/198; 6.1%) (p = 0.001). Median follow-up was 5.3 years. The 5-year DMFS (%) [95% CI]) was significantly worse for patients with H2 tumors (64.8 [55.9 – 75.1]), with most events occurring early (< 3 years), compared with H1 tumors (77.1 [70.4 – 84.3]; p = 0.012). Patients with H1 tumors that achieved pCR had improved 5-year DMFS (81.8 [61.9 – 100]) compared to H1 tumors that did not achieve pCR (76.8 [69.9 – 84.4]; p = 0.009). Patients with H2 tumors that had a pCR demonstrated significantly better 5-year DMFS (80.7 [65.3 – 99.8]) than patients with residual disease (60.2 [50.1 – 72.4]; p = 0.009). Conclusions: These data suggest MammaPrint predicts pCR in HR+HER2- BC patients, with H2 risk tumors exhibiting higher chemosensitivity than H1 tumors. Patients with either H1 or H2 tumors that achieved pCR had similar outcomes, which were significantly improved compared to those with residual disease. Notably, the worst outcomes were observed among patients with H2 risk and residual disease; it should be investigated whether addition of immune therapy to standard NCT would enhance the pCR rates in this patient population. Clinical trial information: NCT01479101. Research Sponsor: Agendia Inc.
Primary efficacy analyses of NeoRHEA, neoadjuvant biomarker research study of palbociclib combined with endocrine therapy in estrogen receptor positive/HER2 negative breast cancer.

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Background: CDK4/6 inhibitors (CDK4/6i) and endocrine therapy (ET) are standard of care in the treatment of estrogen receptor (ER) positive, HER2-negative (ER+/HER2-) advanced breast cancer (BC). We tested palbociclib + ET as neoadjuvant therapy to identify baseline biomarkers of no response.

Methods: NeoRHEA (NCT03065621) was a phase II, single arm trial evaluating 4 months of neoadjuvant palbociclib and ET in pre- or post-menopausal women with ER+/HER2- early BC. The primary objective was to identify biomarkers of no response by locally-assessed ultrasound (US) using RNA-seq on baseline (pretreatment) tumor biopsies. No response to treatment was defined as stable or progressive disease (SD or PD) at post-treatment US based on WHO criteria. Secondary endpoints included residual cancer burden (RCB) of 3 and absence of complete cell cycle arrest (CCCA) defined as Ki67 by immunohistochemistry (IHC) ≤ 2.7% at surgery. We evaluated baseline clinicopathological characteristics, RNA-seq derived PAM50 subtypes and mRNA expression of ESR1, Ki67, CCNE1, RB1 and CDK6 single genes according to US response and CCCA. We also performed gene set enrichment analysis (GSEA) for 50 gene sets related to cancer hallmarks according to US response and CCCA.

Results: 73 of 100 patients enrolled had baseline frozen tumors with enough cellularity and successful RNA-sequencing performed. Among the 73 patients, 70% were post-menopausal, 84% had cT2 and 70% cN0 tumors, 75% had invasive ductal carcinoma and 66% had histological grade 2 tumors. RNA-seq derived PAM50 subtypes were Luminal A, Luminal B, and non-Luminal in 56%, 36% and 8% of patients, respectively. Among the 73 patients, 31 (42%) had absence of US response (28 and 3 patients had stable and progressive disease by US, respectively) and 23 (31%) had RCB 3 tumors. Fifty-three of 73 patients had Ki67 by IHC available at surgery out of whom, 14 (26%) had absence of CCCA. Neither baseline clinicopathological characteristics nor PAM50 subtypes nor expression of ESR1, Ki67, CCNE1 and RB1 were associated with absence of US response or absence of CCCA. Interestingly, we observed higher baseline mRNA expression of CDK6 in patients with absence of US response (p = 0.039) or those with no CCCA (p = 0.004). We observed an enrichment in inflammatory / IFN-γ response and proliferation-related, G2M checkpoint gene sets in patients with US response (NES: 2.06, 2.30, 1.47; FDR: 7.04e-9, 5.48e-17, 0.0193 respectively) and an enrichment in early estrogen response gene set in patients with absence of US response (NES: -1.78, FDR: 0.0006). No signaling pathway was enriched in patients without CCCA. Conclusions: High pre-treatment mRNA expression of the CDK6 gene was associated with no US response or absence of CCCA in patients treated with neoadjuvant palbociclib and ET. Independent validation is needed. Clinical trial information: NCT03065621. Research Sponsor: Pfizer; Fondation Contre le Cancer.
A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group study JCOG1017.

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Background: The possibility of primary tumor resection (PTR) improving the survival of de-novo Stage IV breast cancer (dn-StIV BC) patients has been evaluated by several prospective studies but remains controversial. We designed this phase 3 trial (JCOG1017) comparing with/without primary dissection after initial systemic therapy based on clinical subtype in dn-StIV BC patients. Methods: Dn-StIV BC patients were enrolled in the first registration. All patients received systemic therapies according to clinical subtypes. The patients not showing refractory disease were randomized to systemic therapy alone (arm A) or PTR plus systemic therapy (Arm B). The same systemic therapy was continued after randomization as additional therapy, for as long as possible. The primary endpoint was overall survival (OS). Secondary endpoints included the proportion of patients without progression at metastatic sites after initial systemic therapies for 3 months, local relapse-free survival (LRFS), primary tumor resection-free survival, and incidence of local ulcer/local bleeding and adverse events. The median overall survival time (MST) after initial systemic therapy for patients with dn-StIV BC was 20 months, on average, and a clinically relevant prolongation of the MST of Arm B was considered to be 6.0 months or longer (hazard ratio: 0.77). The required number of events was 359, to obtain a statistical power of 80% with a one-sided significance level of 0.05. Thus, the planned sample size was 410 patients for the second registration, assuming an accrual period of 7 years and a follow-up time of 4 years. Results: 570 patients were enrolled between 11/5/2011 and 31/5/2018 in the first registration. Of these, 407 eligible patients were randomized to either Arm A (N = 205) or Arm B (N = 202). The patient characteristics were well balanced between the two arms. The MST of randomized patients was 70 months, with 221 deaths. The difference in OS was not statistically significant (HR 0.857, 90% CI 0.686-1.072, one-sided p = 0.1283). MST was 69 months in Arm A and 75 in Arm B. The proportions of patients without progression at metastatic sites in Arms A and B were 81.5% and 67.3%, respectively (p = 0.0014). LRFS in Arm B was significantly longer than that in Arm A (median LRFS 20 vs 63 months: HR 0.415, 95% CI 0.327-0.527, p < 0.0001). In Arm B, patients with incomplete resection had poorer outcomes than those in whom resection was complete (94 vs. 61 months, HR 1.971 (1.161-3.347) p = 0.0120). In the subgroup analysis, PTR improved survival in patients with ER-positive tumors, pre-menopausal status or single-organ metastasis. Conclusions: PTR is not recommended for all dn-StIV BC patients but can control local disease and is acceptable in a select population of patients because of the clear improvement in local control. Clinical trial information: UMIN000005586. Research Sponsor: Japan Agency for Medical Research and Development, the National Cancer Research and Development Fund.
Axillary surgery efficacy for patients with breast cancer receiving neoadjuvant chemotherapy on NSABP B40 and B41.

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Background: Alliance A011202 is evaluating the efficacy of axillary lymph node dissection (ALND) compared to regional nodal irradiation (RNI) for patients with cN1 breast cancer who receive neoadjuvant chemotherapy (NCTX) that becomes ycN0 but remains pN+. In the absence of its publication, level I guidance does not exist regarding the optimal axillary surgery for patients receiving NCTX. We sought to evaluate outcomes across two national contemporary clinical NCTX trials based on axillary and breast response to NCTX, particularly if more aggressive surgery was associated with more favorable outcomes. Methods: With IRB approval (IRB201802781), we obtained data from NCTX trials NSABP B40 and B41. B40 enrolled women with HER2- disease, and B41 enrolled those with HER2+ disease. RNI and axillary surgery were selected at physician discretion and not protocolled. Patients received sentinel lymph node biopsy (SLNB), SLNB+ALND (S+ALND), or ALND. We examined outcomes of locoregional recurrence (LRR), distant recurrence (DR), disease free survival (DFS), and overall survival (OS). Univariable and multivariable analyses of B40 and B41 data were performed to evaluate the associations of axillary surgery with the outcomes above, adjusting for age, tumor subtype, mastectomy or not, breast pathologic complete response (pCR), axillary pCR, tumor subtype, regional nodal irradiation, and grade. Kaplan-Meier estimation was used for OS and DFS, with cumulative incidence function for LRR and DR.

Results: Median follow-up for studies B40 and B41 were 4.5 and 5.1 years, respectively, including 1154 and 504 patients for analysis. A total of 786 (47%) patients were cN+, and of those, 377 had a pCR (48%). 440 (27%), 505 (31%), and 663 (41%) patients had SLNB, S+ALND, and ALND respectively. 855 (52%) and 803 (48%) patients had mastectomy and lumpectomy, respectively. 783 (51%) received RNI. For the 518 ypN+ patients on B40, 725 (SLNB), 69/234 (S+ALND), and 107/259 (ALND) experienced an event. DFS at 5 years was 71%, 68%, and 56% for the SLNB, S+ALND, and ALND groups respectively with ypN+ on B40. For the 112 ypN+ patients on B41, 3/6, 15/43, and 27/63 experienced an event. DFS at 5 years was 50%, 64%, and 55% for the SLNB, S+ALND, and ALND groups, respectively, with ypN+ on B41. In multivariable analyses for the combined population of B40 and B41 for LRR, DR, DFS, and OS, SLNB was never associated with a higher chance of relapse or inferior survival (HR > 1) compared to S+ALND or ALND.

Conclusions: Among women prospectively treated on national trials with NCTX and axillary surgery and RNI selected at physician discretion, receipt of SLNB alone was not associated with a higher likelihood of recurrence compared to S+ALND or ALND. Anticipated results of A011202 will provide level I guidance on axillary surgery for patients with cN1 disease converting to cN0 post-NCTX. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; U.S. National Institutes of Health.
Long-term oncologic outcomes after omitting axillary surgery in older women with early stage, node-negative breast cancer: A systematic review and meta-analysis.

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Background: In 2016, Choosing Wisely recommended the omission of routine sentinel lymph node biopsy (SLNB) in early stage, clinically node-negative, hormone receptor-positive, Her2-negative breast cancer in women ≥70 years old, although data supporting this was limited. Our study aimed to examine the long-term impact of omitting axillary staging in elderly women undergoing surgery for early stage, clinically node-negative breast cancer. Methods: A systematic review and meta-analysis was conducted. Medline (Ovid) and Embase were searched for published papers and abstracts using a systematic search strategy. Randomized and observational studies comparing women aged ≥70 years of age with early-stage, clinically node-negative breast cancer undergoing surgery for breast cancer with and without axillary staging, were included. Included studies reported at least one of the following outcomes: axillary recurrence (primary outcome), disease-free survival (DFS), breast cancer-specific survival (BCSS), and overall survival. Risk ratios (RR) were calculated as summary estimates for all outcomes. A weighted pooled mean difference and 95% CI was calculated using a random-effects inverse variance meta-analysis for each outcome. Heterogeneity was calculated using I² statistics, and explored using meta-regression. The Newcastle-Ottawa Scale was used to assess the methodological quality of eligible trials, based on the selection of patients, comparability of cohorts, and the methods of outcome assessment. Results: Nine studies were eligible for meta-analysis, including data for 48,523 patients. For the primary outcome of axillary recurrence, data for 3,591 patients was meta-analyzed. Axillary staging was found to reduce the risk of axillary recurrence compared to no axillary staging, although this was not statistically significant (RR 0.59, 95% CI: 0.26 to 1.35, I²= 46.6%, p = 0.21). For overall mortality, data for 14,981 patients was meta-analyzed, and a statistically significant protective effect of axillary staging on overall mortality was demonstrated (RR 0.55, 95% CI: 0.33 to 0.90, I²= 78.1%, p= 0.003). No significant differences were observed in DFS (RR 1.02, 95% CI: 0.51 to 2.07, I² = 0.0%, p = 0.37) and BCSS (RR 0.96, 95% CI: 0.57 to 1.62, I² = 0.0%, p = 0.78). Conclusions: Omission of axillary surgery to stage the axilla may be associated with a higher risk of overall mortality in older women with early-stage breast cancer compared to those who undergo axillary surgery. Omission of axillary surgery in this patient population should be carefully tailored to the individual patient, taking into consideration co-morbidity, life expectancy, and formal measures of frailty. Randomized trials are required to further explore the oncologic safety of omitting axillary staging in women aged 70 years or older undergoing breast cancer surgery. Research Sponsor: None.
Differences of prediction performances by multigene assays in patients with breast cancer with distinct genetic backgrounds.

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Background: The 21-gene (Oncotype Dx), PAM50 (Prosigna) and Chinese-based 28-gene (RecurIndex) are validated genomic assays that provide prognostic information for distant recurrence risk in patients with hormone receptor (HR)-positive, HER2-negative early breast cancer (EBC). In this study, we aim to compare the differences in prediction performance by different multigene assays and gene expression profiles between the Eastern and the Western. Methods: Under the Affymetrix U133 platforms, the differences in gene expressions and risk scores from the Eastern population comprised of GSE20685 (n = 327) and part of GSE45255 (n = 95), and the Western population GSE25066 (n = 508) and the European in GSE45255(n = 44) were analyzed respectively. Patients were stratified by 21-gene Recurrence Scores (RS) of low (0-10), intermediate (11-25) and high (26-100) and categorized by ROR-S score of PAM50 of low (0-40), intermediate (41-60) and high (61-100). For 28-gene, a recurrence index for distant recurrence (RI-DR) cutoff of 33 was used to classify patients into high- and low-risk groups. Wilcoxon rank test was used to test for continuous variables and the chi-square test was used for categorical variables. Results: The Western population has significantly higher RS (85.9 vs. 65.5, p < 0.001) and ROR-S (57.4 vs.53.7, p = 0.034) scores than the Eastern population. The distribution of 28-gene risk groups was significantly different between races with a higher proportion of high-risk in the Western (10.5% vs. 6.6%, p = 0.035). The low-risk patients in the Eastern stratified by 28-gene assay had significantly higher distant metastasis-free survival (DMFS) rates than high-risk (80% vs. 52%, p < 0.001), which compared with Oncotype Dx RS (96% vs. 76%, p < 0.001) and PAM50 ROR-S (93% vs. 72%, p < 0.001). At the same time, the analysis of gene expressions revealed significantly high expressions of YWHAB, SF3B5, CKAP5, and DDX39A in the Eastern than that in the Western. However, most genes from 21-gene and ROR-S were more highly expressed in the Western than that in the Eastern. Conclusions: 21-gene and PAM50 provide the good performance and show similar patterns in the prognosis of EBC; However, the DMFS rate of the high-risk in the Eastern population determined by 28-gene was much lower than 21-gene and PAM50, which means there are bigger chemo-benefit in the high-risk from 28-gene. In conclusion, 28-gene has better performance in the prognosis of the Eastern population and is a more suitable tool for Eastern breast cancer patients. Research Sponsor: None.
Efficacy of ovarian function suppression of 3-monthly versus monthly GnRH agonist as endocrine therapy for premenopausal breast cancer patients.

Daniella Audi Blotta, Jessica Ribeiro Gomes, Shermann Brandão Rodrigues Moreira, Danielle Fortes Colosimo, Carolina Cavalcanti Gonçalves Ferreira, Elaine Aparecida Forgiarini, Debora De Melo Gagliato, Antonio C. Buzaid; Hospital Beneficência Portuguesa de São Paulo, São Paulo, Brazil; Hospital Beneficência Portuguesa de São Paulo, São Paulo, Sao Paulo, Brazil

Background: The combined analysis of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) trials have shown significant survival benefit of adding ovarian function suppression (OFS) with GnRH agonists (GnRHa) to aromatase inhibitors (AI) versus tamoxifen in high-risk premenopausal patients (pts) with estrogen receptor (ER)-positive breast cancer (BC). In both studies, GnRHa was administered every 4 weeks. However, the efficacy of 3-monthly GnRHa plus AI has not been well studied. We conducted a retrospective study designed to assess the efficacy of OFS with 3-monthly compared with monthly goserelin, associated with AI, in premenopausal pts with ER-positive BC.

Methods: Medical records of premenopausal pts with ER-positive BC who received OFS with 10.8mg 3-monthly goserelin plus AI or 3.6mg monthly goserelin plus AI, between June/2013 and January/2023 were reviewed. Patient characteristics, such as age, body mass index (BMI) and prior chemotherapy were analyzed. Estradiol (E2) levels were measured by gas chromatography tandem mass spectrometry. Pts with at least one E2 level above 2.72 pg/ml were considered to have ineffective OFS. Analysis of E2 measurements was divided into periods: < 3, 3 to 6, 6 to 9, 9 to 12, 12 to 18, 18 to 24 and > 24 months. E2 levels greater than 2.72 pg/ml were evaluated at each timepoint.

Results: A total of 88 pts were included. 27 (30.7%) received monthly goserelin and 61 (69.3%) 3-monthly goserelin. Patient characteristics were well balanced between the groups. Relevant demographic data are shown in table. For E2 analysis, 20 (22.7%) pts had at least one measurement greater than 2.72 pg/ml, 11 (40.7%) in the monthly group and 9 (14.8%) in the 3-monthly group (p = 0.007). The percentages of E2 measurements ≥ 2.72 pg/ml, in each time period, were 0%, 40%, 12.5%, 16.7%, 33.3%, 50% and 50% in monthly group versus 8%, 4.2%, 10%, 14.3%, 4.8%, 8.3% and 5.6%, in 3-monthly group, respectively.

Conclusions: Our study demonstrated that more pts who underwent 3-monthly goserelin had E2 levels below the defined threshold of 2.72 pg/ml compared with monthly goserelin, when associated with AI, with statistical significance. These findings suggest that 3-monthly goserelin may result in better efficacy in OFS when comparing with monthly and provide greater convenience for pts. Research Sponsor: None.

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<th>Variable</th>
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<th>3-Monthly Goserelin, n (%)</th>
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<td>23 (21-26)</td>
<td>p = 0.693</td>
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<td>21 (72.4%)</td>
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<td>7 (11.5%)</td>
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<td>HER2-positive status</td>
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<td>12 (19.7%)</td>
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<td>17 (77.3%)</td>
<td>50 (92.6%)</td>
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Differential benefit of capecitabine-based chemotherapy among TNBC subtypes in the context of the CBCSG010 study.

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Background: Our previous study classified TNBCs into four mRNA subtypes, provided additional insights into TNBC heterogeneity and potential therapeutic options. Then we conducted a phase Ib/II subtyping-based and genomic biomarker-guided umbrella trial (FUTURE, NCT03805399), demonstrated the clinical benefit of subtyping-based targeted therapy for refractory metastatic TNBC. Here, we further evaluate the prognosis and predictive value of molecular classification in early TNBC in CBCSG010 trial (NCT01642771), which is a prospective, randomized phase III trial confirmed adding capecitabine to anthracycline-taxane-based adjuvant chemotherapy significantly improved survival in TNBC.

Methods: Tumor tissues and pathological sections were retrospectively collected. Immunohistochemical (IHC) staining and hematoxylin and eosin (HE) staining were performed on paraffin-embedded sections to conduct TNBC IHC subtype staining. RNA-sequencing were performed to characterize the intrinsic molecular features of TNBC microenvironment. Results: 585 patients enrolled in the CBCSG010 trial, 450 patients had pathological sections, among which 207 patients achieved successfully stained sections. PDL1, CD8 and stromal tumor infiltrating lymphocytes (sTILs) were chosen for identified TNBC Immune enriched phenotype. Patients with ≥20% positive tumor cell proportion score (TPS) of PDL1, ≥10% positive cells of CD8, and ≥10% positive sTILs were significantly associated with better 5y-DFS (disease-free survival). Among Immune enriched TNBC, kaplan-Meier curves showed that DFS rates were 96.4% and 73.7% in the capecitabine and control groups. Transcriptome data was used to picture the immune microenvironment landscape, showed that “immune-hot” patients (immune cells or immune genes enriched) were more likely to benefit from capecitabine treatment. Conclusions: TNBC subtypes is significantly associated with DFS, with Immune enriched phenotype achieving the best outcome, and “immune-hot” patients are more likely to benefit from adjuvant capecitabine. Designing future clinical trials adding immunotherapy in adjuvant treatment of TNBC might base on molecular features. Research Sponsor: the National Natural Science Foundation of China (Grant No. 82172576).
Assessing the marginal costs of radiation therapy and antiestrogen therapy for post-lumpectomy, early-stage breast cancer across Medicaid and Medicare plans.

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Background: With recent Level I evidence (FAST FORWARD) supporting radiation therapy (RT) duration as short as one week and Level I evidence (CALGB9343) supporting RT omission in favor of antiestrogen endocrine therapy (ET) alone in select patients, the necessity of both RT and ET, adjuvantly, in early-stage breast cancer (BC) has been questioned. Evidence providing granular details on the role of insurance in the aggregate cost of RT and ET is lacking. This project disaggregates costs by insurance plan to increase transparency of out-of-pocket (OOP) cost estimates. Methods: National Comprehensive Cancer Network guidelines were utilized to determine the proper treatments, with FAST FORWARD radiation dose/fractionation (26 Gy in 5 fractions) representing RT. Treatments were identified using Current Procedural Terminology and Healthcare Common Procedure Coding System codes. OOP costs, deductibles, and copay/coinsurance were calculated for Medicaid, Original Medicare, Medigap Plan G, and Medicare Part D Rx. The medicare.gov, medicaid.oh.gov, aarpmedicareplans.com, and cms.gov were used to determine pricing. Price estimates reflect actual costs per insurance plan rather than costs estimated from claims data. All procedures were considered to be performed in an Ohio hospital setting, insurance coverages were based on the zip code 44106, and total expenses were based on all treatments plus a 5-year follow-up (not adjusted for inflation). Results: Treatment charges for ET include medical oncology initial consultation, biannual medical oncology follow-up, baseline bone density study, and Anastrozole cost (5-years). Treatment charges for RT include initial consultation, treatment planning, dosimetry calculations, treatment device, simulation and verification, RT delivery, on-treatment visits, and medical physics consultation. Original Medicare beneficiaries face an OOP cost of 20% for Medicare Part B claims with no cost cap for approved procedures after the deductible. Medications are covered under Medicare Part D with copays. This results in a marginal OOP treatment charge (after 5-year follow-up) of $767.54 for ET alone and $1,416.78 for ET + RT. Medigap Plan G beneficiaries face a marginal OOP charge of $1,225 for both ET alone and ET + RT, assuming the $226 Medicare Plan B deductible is met by the cost of lumpectomy during the year of RT. For Medicaid beneficiaries (assuming all treatments are approved by Medicaid), all expenses are covered without limit, resulting in no OOP expense for either treatment plan. Conclusions: Discussions of adding RT to ET for post-lumpectomy early-stage BC often involves considerations of treatment costs. This model (based on actual cost estimates per insurance plan rather than claims data) can help to enhance cost transparency by comparing expenses between Medicare and Medicaid plans. Research Sponsor: None.
Association between patient-reported outcomes and therapeutic outcomes in patients with breast cancer: A pooled individual-participant data analysis.

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Background: Patient-reported outcomes (PROs) are captured in validated tools to provide the patients’ perspective and voice on their physical, social, emotional, functional, and cognitive abilities. Pretreatment PROs have shown prognostic importance in other cancer types, however, the prognostic value of PROs in breast cancer has been minimally explored. Methods: In a pooled analysis of contemporary clinical trial IPD from patients with breast cancer, cox-proportional hazard analysis and binary logistic regression was used to assess the association between potential predictors with overall survival (OS) and adverse event (grade ≥ 3) outcomes, respectively. PROs were recorded using the EORTC QLQ-C30 version 3.0 questionnaire in the pooled cohort. Statistical significance was set at a threshold of P<0.05 and was determined via the likelihood ratio test. Model fit and linearity of variable associations were assessed via the Akaike information criterion (AIC). All analyses were stratified by age, performance status, treatment arm, and study. The primary assessed outcome was OS, with grade ≥ 3 adverse events assessed as a secondary outcome. A forward inclusion process (starting with the variable of lowest AIC, PRO domains were retained in the model if they decreased the AIC by 2 or more on addition, and remained statistically significant) was used to evaluate the value of multiple PRO domains on prognostic performances. Results: Within data available, the EORTC QLQ-C30 version 3.0 questionnaire was used in a pooled cohort of 8,544 patients across 8 clinicals trials. In the pooled cohort, the association between PROs and outcomes was best described by a linear association. Patient-reported physical functioning, appetite loss, and pain were significantly associated with OS. On forward-inclusion, only physical functioning remained within the OS prognostic model. Except for patient-reported financial difficulties, all PRO domains were significantly associated with grade ≥ 3 adverse events. On forward-inclusion, physical functioning, pain, and constipation all remained statistically significant. Conclusions: Within large high-quality IPD, pre-treatment PROs demonstrated significant prognostic relationships with therapeutic outcomes in patients with breast cancer initiating contemporary anticancer treatments. Patient-reported physical functioning was found to be the most prognostic PRO domain for OS, while patient-reported physical functioning, pain, and constipation were retained in a multivariable model prognostic of grade ≥ 3 adverse events. Research Sponsor: Cancer Council South Australia and NHMRC (APP2008119 & APP2005294).
The impact of the 4R Oncology model on OncotypeDx turnaround time.

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Background: The OncotypeDx genomic assay has been widely used to predict recurrence in those with early-stage ER positive breast cancer to determine whether adjuvant chemotherapy is beneficial. Receiving OncotypeDx results in a timely manner prior to medical oncology appointment is critical to inform adjuvant therapy decisions. In this quality improvement project, we implemented a care delivery optimization for patients with breast cancer receiving OncotypeDx assays in an integrated healthcare system. The optimization was conducted as part of implementing the 4R Oncology model (Right Info / Right Care / Right Patient / Right Time), a novel care model that aims to optimize patient-centric care planning, team-based delivery and patient self-management. Herein, we assess the impact of implementing this model on improving OncotypeDx turnaround time.

Methods: We examined two patient groups with newly diagnosed early-stage ER positive breast cancer who attended a multidisciplinary clinic and underwent surgery at a single medical center. The historical control (HC) group received care pre-4R implementation, from January 2019 through June 2020, while the 4R Intervention group received care from July 2020 to December 2021. The OncotypeDx-related care optimization was a team effort of 5 medical specialties that involved establishing an OncotypeDx reflex testing practice, updating workflows, working with a testing company to streamline the process and implementing a method to align result timing with scheduling medical oncology appointments. Bivariate analyses were used to compare the HC and 4R groups on demographic characteristics and OncotypeDx turnaround time. Results: Within the 4R group (N = 208), 72 (34.6%) patients received OncotypeDx and 89 (32.5%) patients from the HC cohort (N = 274) received OncotypeDx. The groups were balanced by median age at time of multidisciplinary clinic visit (HC: 59 years vs 4R: 60 years), female gender (HC: 99.6% vs 4R: 99.5%), race, combined race and ethnicity, language spoken, Charlson Comorbidity Index and tumor characteristics. The average turnaround time from surgery date to delivery of OncotypeDx results was significantly reduced in the 4R cohort (19.4 days) compared to that of the HC cohort (23.1 days), a difference of 3.8 days, p = 0.004. The availability of OncotypeDx results by the first medical oncology visit after surgery increased from 40% in the HC cohort to 69% in the 4R cohort, p = 0.0003, helping optimize the transition to adjuvant therapy for the appropriate population. Conclusions: The implementation of the 4R Oncology model within an integrated healthcare system significantly reduced turnaround time for patients with breast cancer awaiting OncotypeDx results, improving patient-centric care and enabling informed discussions at medical oncology visits. The 4R Oncology model is an effective method to optimize delivery of time-sensitive care. Research Sponsor: Genentech (for 4R).
A multicenter phase II study of vaccines to prevent recurrence in patients with HER-2-positive breast cancer.

Hyo S. Han, Robert Wesolowski, Carla Fisher, Shipra Gandhi, William R Gwin, Maria J Kowzun, Keerthi Gogineni, Hien Liu, Ricardo L Costa, Julian Guerrero, Stephy Mathew, Michael J. Schell, Hatem Hussein Soliman, Mary L. Disis, Brian J. Czerniecki; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Ohio State University Wexner Medical Center, Columbus, OH; Indiana University School of Medicine, Indianapolis, IN; Roswell Park Comprehensive Cancer Center, Buffalo, NY; University of Washington, Cancer Vaccine Institute, Seattle, WA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Emory University Winship Cancer Institute, Atlanta, GA; H. Lee Moffitt Cancer Center, Tampa, FL; University of Washington, Seattle, WA

Background: Patients (pts) with early stage HER2-positive breast cancer are commonly treated with neoadjuvant HER2-targeted therapy. Pts who have residual invasive disease have a less favorable outcome and increased risk of recurrent disease than pts with a complete pathologic response (pCR). It also has been observed that pts who do not achieve a pCR have low or absent anti-HER-2 CD4 Th1 responses. We hypothesized that correcting anti-HER-2 CD4 Th1 response using vaccines will be safe, induce anti-tumor immunity in HER2-positive breast cancer and reduce the risk of recurrence. We conducted a multi-center, phase 2, randomized study to determine the safety, immunogenicity and recurrence free survival of two HER2 vaccines (multivalent anti-oncodriver DNA vaccine (WOKVAC) or HER-2-pulsed dendritic cell vaccine (DC1)).

Methods: Pts with HER2-positive early breast cancer were eligible if they had residual invasive disease at surgery after receiving neoadjuvant chemotherapy plus HER2-targeted therapy. Patients were randomly assigned in a 1:1 ratio, with stratification according to residual cancer burden (RCB) (1+2 vs 3) to receive adjuvant HER2 vaccination with either DC1 or WOKVAC. For the initial vaccination phase, DC1 was delivered via US guided inguinal lymph node administration, weekly x 6 weeks and WOKVAC was given intradermally on weeks 1, 4, and 7. Booster vaccines were given at months 6, 9 and 12. The primary end point is to evaluate the safety and tolerability of each vaccine and assess immune response rate as measured by ELISPOT. Each treatment arm will be assessed separately. Secondary endpoints include recurrence-free survival. Exploratory analyses include the assessment of prognostic and predictive biomarkers including circulating tumor cells, serum HER2 levels, and other immune correlating biomarkers. Here we are reporting the initial safety results. Results: Total of 110 eligible pts (55 WOKVAC vs 55 DC1) were enrolled from 2/2018 to 12/2022 and received at least one dose of treatment and 38 pts pending completion of the booster phase. Most pts had clinical stage II/III 56/35 (82%) and 50% had positive node disease at diagnosis. 82% had hormone receptor positive disease. 37/38/8 patients had RCB 1/2/3. For patients without known RCB status, ypTNM was used to randomize (yp stage I/II/III = 13/13/1 pts). The most frequently observed treatment related adverse events (TRAES) were injection site pain/reaction (38%) and chills (34%), fever (25%) and fatigue (40%) for DC1 arm. For WOKVAC, the most common toxicities included injection site reaction (68%) and fatigue (37%). All of these were grade 1 and 2. Nine patients had events including new primary cancer (1), local recurrence (2), metastatic disease recurrence (6).

Conclusions: Both DC1 and WOKVAC HER2 vaccines were well tolerated without significant toxicities. Updated results will be presented at the meeting including correlatives. Clinical trial information: NCT03384914. Research Sponsor: Department of Defense.
Does RSClin provide additional information over classic clinico-pathologic scores (PREDICT 2.1, Influence, CTS-5)? A TEAM Pathology substudy.

Ana-Alicia Beltran-Bless, Gregory Russell Pond, Jane Bayani, Sarah Barker, Melanie Spears, Elizabeth Mallon, Karen J Taylor, Annette Hasenburg, Christos Markopoulos, Luc Yves Dirix, Caroline M. Seynaeve, Cornelis J.H. Van De Velde, Daniel William Rea, Lisa Vandermeer, John Frederick Hilton, John Bartlett, Mark J. Clemons; The Ottawa Hospital, Ottawa, ON, Canada; McMaster University, Hamilton, ON, Canada; Ontario Institute for Cancer Research, Toronto, ON, Canada; Diagnostic Development, Ontario Institute for Cancer Research, Toronto. ON, Canada, Canada; Department of Pathology, Glasgow, United Kingdom, Glasgow, United Kingdom; Cancer Research UK Scotland Centre, University of Edinburgh, Edinburgh, United Kingdom; University Medical Center Mainz, Mainz, Germany; National and Kapodistrian University of Athens, Medical School, Athens, Greece, Athens, Greece; GZA Ziekenhuizen Antwerpen campus Sint-Augustinus, Antwerpen, Belgium; Erasmus MC - Kanker Instituut locatie Daniel den Hoed, Rotterdam, Netherlands; Leiden University Medical Center, Leiden, Netherlands; Cancer Research UK Institute for Cancer Studies, Birmingham, United Kingdom; Ottawa Hospital Research Institute, Ottawa, ON, Canada; The Ottawa Hospital Cancer Center, Ottawa, ON, Canada; The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background: Gene-expression profiling tests (e.g. Oncotype, Mammaprint, Prosignia, Breast Cancer Index and EndoPredict) are widely used in the care of patients with early-stage hormone positive breast cancer (node negative or 1-3 lymph nodes). However, these tests are resource intensive, and few studies have compared their value with either free and widely available clinico-pathologic risk calculators (e.g. PREDICT 2.1, INFLUENCE 2.0, and CTS-5) or tools that combine genomic testing with clinico-pathologic data (e.g. RSClin). The TEAM pathology substudy population was used to compare these different predicted model scores with outcomes. Methods: The TEAM pathology study consists of 3284 postmenopausal hormone positive breast cancer patients treated with either exemestane or tamoxifen followed by exemestane. Accrual was from 2001 to 2006. Genes comprising the multi-parametric Oncotype Dx were used to train signatures to create true assay results. Patient data was then used to calculate recurrence scores through various tools. This included clinico-pathologic models and their respective endpoints PREDICT 2.1 (overall survival at 5 years), INFLUENCE 2.0 (distant metastasis at 5 years), CTS-5 (distant recurrence risk at year 5-10), the purely genomic Oncotype Dx trained results (distant recurrence risk at 9 years), as well as the new clinico-pathologic RSClin (distant recurrence risk at 10 years). We compared the level of association between these predictive model scores using Spearman correlation coefficients. The prognostic ability of each model was contrasted for each outcome using Harrell’s C-statistic. Results: Results were available for CTS-5 (3022 patients), INFLUENCE 2.0 (3485 patients), ODx-trained (3825 patients), and RSClin (3029 patients). Correlation coefficients showed low correlation between Influence (r= 0.25) and CTS-5 (r= 0.17) with Oncotype-Dx trained results, and high correlation between RSClin (r = 0.84) and Oncotype-Dx trained results. The concordance index was similar (0.65 to 0.68) for all models with distant metastasis-free survival as the outcome. Analysis is ongoing and further results will be available at the time of presentation. Conclusions: Other clinico-pathologic tools such as Influence 2.0 and CTS-5 have good prognostic ability when compared to Oncotype Dx-trained results and RSClin. Research Sponsor: None.

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Real-world impact of TAILORx on chemotherapy use and SOFT/TEXT on ovarian function suppression uptake in a population based-cohort of women 40 years and under with HR-positive, HER2-negative, axillary lymph node negative breast cancer.

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Background: Gene expression profiling (GEP) testing is prognostic for distant recurrence risk in women with hormone receptor positive (HR+), human epidermal growth factor receptor-2 negative (HER2-), axillary lymph node negative (LN-) breast cancer (BC). The TAILORx trial generated prospective evidence demonstrating the 21-gene recurrence score (RS) is also predictive of chemotherapy (CT) benefit. The literature suggests that GEP testing reduces adjuvant CT prescription and is cost-effective. In the same era, the SOFT/TEXT trials demonstrated disease-free survival benefit for the addition of ovarian function suppression (OFS) to endocrine therapy in premenopausal women. Real-world uptake and impact of these advances in the management of HR+, HER2-, LN- BC in young women may be limited due to complex reasons. This retrospective study evaluated GEP and CT use post TAILORx and OFS use post SOFT/TEXT in women 40 years old or younger diagnosed with HR+, HER2-, LN BC from 2011 to 2020 in Alberta, Canada. Methods: Clinical variables were retrieved from the Alberta Health Services Cancer Care Breast Data Mart and through review of the electronic medical record. GEP testing and CT use were compared between 3 cohorts of women defined by diagnosis: pre RS funding/pre TAILORx (before April 2014), post RS funding/pre TAILORx (April 2014-May 2018), post TAILORx (June 2018 and beyond). OFS use was compared between 2 cohorts of women defined by diagnosis pre- and post SOFT/TEXT (May 2015). In subgroup analyses, we compared CT use by GEP status and RS category and OFS use by CT status. Results: Among the 291 women identified, GEP testing increased by 37% post GEP funding (pre 2% vs. post 39%; P = .0001) and by additional 15% post TAILORx (pre 39% vs. post 54%; P < .0001) whereas overall CT use declined by 15% post GEP funding (pre 85% vs. post 70%; P = .01) and by additional 16% post TAILORx (pre 70% vs. post 54%; P = .01). Although not significant, OFS use increased by 8% post SOFT/TEXT (pre 13% vs. post 21%; P = .08). In subgroup analyses, post TAILORx was associated with a significant reduction in CT use of 19.5% in non-GEP tested women (pre 85% vs. post 65%; P = .01) and non-significant increase in CT use of 6% in RS tested women (pre 40% vs. post 46%; P = .61) mainly driven by high mid range RS 21-25 and lower high range RS 26-30. There was no significant change in OFS use in non-CT treated women post SOFT/TEXT (Pre 5.3% vs. Post 8%, P = .68) whereas OFS use increased by 15% in women treated with CT post SOFT/TEXT (pre 15% vs. post 30%; P = .01). Conclusions: Public GEP funding and TAILORx led to widespread adoption of GEP and real-world decline in CT use in women 40 years of age or younger diagnosed with HR+, HER2-, LN- BC in Alberta. SOFT/TEXT led to real-world incline in OFS use in those treated with CT but adoption remained suboptimal. Research Sponsor: None.
Disease-free survival (DFS) as a surrogate for overall survival (OS) in patients (pts) with HR+/HER2—early breast cancer (EBC): A correlation analysis.

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Background: DFS has been widely adopted as a clinically meaningful primary endpoint in EBC trials in place of OS, which needs extensive follow-up to observe sufficient events and fails to assess survival benefit early. However, a rigorous validation of DFS as a surrogate endpoint for OS is required for each given setting. The objective of this analysis was to evaluate DFS as surrogate for OS in the adjuvant treatment of HR+/HER2—EBC. Methods: A systematic literature review (SLR) was conducted using biomedical literature databases (ie, Embase, PubMed, and Medline [from database inception to January 2023]) and key conferences to identify published studies in EBC. The eligibility criteria for the SLR were RCTs that included ≥80% of adult pts with HR+/HER2—EBC and assessing different treatment options (ie, cyclin-dependent kinase 4/6 inhibitors [CDK4/6i], endocrine therapies [ET], and chemotherapies [CT]). Studies were considered for correlation analysis if hazard ratios (HRs) were reported for both DFS and OS. The analysis excluded observational studies and trials with immature OS data. Spearman rank correlation (rs) and weighted linear regression analyses (measured by coefficient of determination [R²]) were performed to evaluate the correlation between HRs for OS and DFS. Considering heterogeneity, multiple scenario analyses were conducted. Surrogate threshold effect (STE) was also estimated; STE is defined as the maximum value of the HR for DFS that needs to be observed in a trial to ensure the possibility of concluding that a significant effect on OS occurred. Correlation was also assessed using pt-level data from the FACE trial (letrozole vs anastrozole in postmenopausal pts with HR+/HER2—EBC) to validate findings of the trial-level analysis. Results: A total of 14 RCTs (N = 31,668) were included (CDK4/6i, 2; ET, 7; CT, 5). Trial-level analysis showed that rs between OS and DFS was 0.81 (95% CI, 0.56-0.94), which when weighted by variance was 0.81. Regression analysis showed that 84% of the variability in OS was explained by DFS (R² = 0.84). A meta-regression model estimated an STE of 0.82 for HR of DFS, which can be leveraged to validate the surrogacy based on the DFS estimated from a future trial. Analysis of pt-level data from the FACE trial demonstrated a correlation between DFS and OS (rs = 0.75). Additionally, correlation coefficients estimated by the Pearson method and iterative imputation were 0.83 and 0.89, respectively. Conclusions: Both trial-level and pt-level analyses demonstrate a positive correlation between DFS and OS. These results support the use of DFS as a reliable surrogate endpoint for OS in HR+/HER2—EBC trials to give an early access to innovative therapies. Research Sponsor: Novartis Pharmaceuticals Corporation.
Image-only deep learning risk model performance in patients with known germline mutations.

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Background: Mammograms contain highly predictive biomarkers of future breast cancer risk, which can be identified by deep learning (DL) risk stratification models. DL model performance in discerning risk in patients with known germline mutations has yet to be established. The aim of this study is to assess image-only DL model risk score performance in patients with and without a germline mutation undergoing screening breast MRI. Methods: This retrospective, multisite study included the first screening MRI of consecutive females ≥30 years from 3/1/2011 to 11/30/2021 at four facilities, with a prior bilateral screening mammogram containing a DL risk score and at least one year of follow-up. A mammography-based DL five-year model was used to assess risk, with an increased-risk threshold of ≥2.2 and high-risk of ≥5.8. Patient demographics, germline mutation status, and traditional risk factors were extracted from electronic medical records. Standard screening performance metrics including cancer detection rate (CDR) within one year of MRI were determined. Cancer outcomes were determined via linkage to a regional tumor registry. DL model performance was compared using Pearson’s chi-squared tests. Results: 4025 patients who underwent screening breast MRI met inclusion criteria. 381 (9.5%) had a known germline mutation. There was no significant difference in age of those with or without a germline mutation (54.9 ± 10.5 vs 54.8 ± 8.8, p = 0.284) or family history of breast cancer (68.5% vs 65.3%, p = 0.205). Patients with a germline mutation were more likely to be White (95.0 vs 91.4%, p < 0.05), have non-dense breasts (52.8% vs 35.3%, p < 0.001) and less likely to have a personal history of breast cancer (25.7% vs 36.3%, p < 0.001). The CDR in those with a germline mutation was higher than those without a mutation (39.4 vs 20.3, p = 0.05). The median DL risk score in those with a germline mutation was lower than those without a mutation: 1.9 (IQR: 1.4-2.5) vs 2.3 (IQR: 1.7-3.8), p < 0.001. In patients with a germline mutation, the CDR in those with elevated DL scores was higher than those with low DL scores (47.6 vs 34.2, p = 0.512: increased-risk threshold; 60.6 vs 37.4, p = 0.512: high-risk threshold). A similar trend was seen in those without a germline mutation (26.4 vs 12.8, p < 0.01: increased-risk threshold; 27.1 vs 19.0, p = 0.203: high-risk threshold). Trends were demonstrated across all comparisons, but significance was only reached in the largest group. Conclusions: Compared to patients without germline mutations, those with mutations had higher CDRs on MRI but lower DL risk scores. Patients with higher DL risk scores had higher CDRs in those identified as increased or high-risk by DL model, regardless of germline mutation status. Further study to elucidate mechanisms to explain differential performance of DL models in patients with germline mutations is ongoing. Research Sponsor: MGH, Ralph Schlaeger Fellowship Award.
Effect of astragalus polysaccharides (PG2) treatment of adjuvant chemotherapy-induced fatigue in premenopausal patients with breast cancer.

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Background: Fatigue is one of the most common symptoms of breast cancer (BC) patients who are receiving adjuvant chemotherapy. Astragalus Polysaccharides (PG2) had been proved to relieve cancer-related fatigue in advanced BC patients. The aim of this study is to evaluate the efficacy of PG2 as a complementary treatment among stage II/III BC patients with adjuvant chemotherapy of epirubicin-cyclophosphamide (EC) regimen in reduction of chemotherapy-induced toxicity and encouraging compliance with chemotherapy. Methods: This double blind, multicenter, phase II trial randomized stage II/III BC patients who would receive adjuvant EC at least 4 cycles to either PG2 500 mg or placebo on day 1, 3, 8 every 21 days as the combination. Changes in chemotherapy-related fatigue score (CRFS) was evaluated by the Brief Fatigue Inventory-Taiwanese Form and incidence of Grade 3/4 neutropenia were the primary endpoints. Results: A total of 66 eligible patients were enrolled and equally randomized to PG2 and placebo groups, 30 cases in each group completed this trial. In general, there was no significant difference in the mean change of CRFS and fatigue intensity between the groups. But the CRFS and fatigue intensity in premenopausal-PG2 group were less aggravated after 4 cycles of EC than that of postmenopausal-placebo group. Persisted significance difference in CRFSs from cycle 1 day 5 (PG2: 0.6; Placebo: 1.9, P = 0.023) to cycle 4 day 15 (PG2: -0.3; Placebo: 0.7, P = 0.002). In all population, a lower proportion of patients suffered from grade 3/4 neutropenia from cycle 1 to cycle 4 were observed in the PG2 group compared to the placebo group (78.8% vs. 87.9% in intent-to-treat population). Conclusions: PG2 combined with adjuvant EC significantly improved adjuvant EC-induced fatigue in premenopausal BC patients. PG2 assists these patients with maintaining normal daily life and job activities, also less need of family support during chemotherapy. Furthermore, patients treated with PG2 might have better compliance to complete the whole course of adjuvant chemotherapy. Clinical trial information: NCT03314805. Research Sponsor: PhytoHealth Corporation.
Prognostic impact of adjuvant endocrine therapy for estrogen receptor-positive and HER2-negative T1a/bN0M0 breast cancer.

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Background: Adjuvant endocrine therapy (ET) is the standard of care for Estrogen Receptor (ER)-positive early-stage breast cancer. However, many patients suffer from adverse events associated with ET. The prognosis of patients with T1a/bN0 breast cancer with ER-positive and human epidermal growth factor 2 (HER2)-negative is excellent, and it is not clear whether adjuvant ET should be recommended. Here we evaluate the effect of adjuvant ET for ER-positive and HER2-negative T1a/bN0M0 breast cancer.

Methods: This study was a multicenter, retrospective cohort study that evaluated adjuvant ET for patients with ER-positive and HER2-negative T1a/bN0M0 breast cancer. Patients who underwent surgery between 2008 and 2012 in 47 institutions of the Japan Clinical Oncology Group (JCOG) breast cancer group were eligible. We analyzed the cumulative incidence of distant metastasis as primary endpoint using the Gray test model and time to event endpoints (distant disease free survival and overall survival) using log-rank test between patients treated with and without adjuvant ET. We also used Gray test model for the analysis of the cumulative incidence of ipsilateral and contralateral breast cancer. Predictive factors were assessed using the Fine-Gray model and the Cox proportional hazards model.

Results: The median follow-up period was 9.2 years. Of 4758 eligible patients (1202 T1a [25.3%] and 3556 T1b [74.7%] diseases), 3991 (83.9%) received adjuvant ET. The 9-year cumulative incidence of distant metastasis was 1.5% with ET and 2.6% without ET (adjusted subdistribution hazard ratio [sHR], 0.54; 95% CI, 0.32-0.93). In the multivariate analysis, the independent risk factors of distant metastasis were no ET, mastectomy, high grade, and lymphatic invasion. The 9-year overall survival was 97.0% and 94.4% (HR, 0.54; 95% CI, 0.38-0.77). Adjuvant ET reduced the incidence of ipsilateral and contralateral breast cancer (9-year rates: 1.1% vs 6.9%; sHR, 0.17; 95% CI 0.11-0.28, and 1.9% vs 5.2%; sHR, 0.33; 95% CI, 0.22-0.49). Conclusions: Adjuvant endocrine therapy significantly reduces distant metastases, however the absolute difference is small for ER-positive and HER2-negative T1a/bN0M0 breast cancer. Furthermore, it reduced ipsilateral and contralateral breast cancer as well. Shared decision making regarding the omission of adjuvant endocrine therapy is crucial, especially in patients with low risk of distant metastasis. Research Sponsor: None.
HRD signature and HRD genomic landscape of tumors from 896 patients with early-stage breast cancer (BC).

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Background: Pathologic mutations in BRCA1, BRCA2 and PALB2 lead to impaired homologous recombination repair (HRR). Cells with defects in HRR are dependent on non-homologous DNA end joining for DNA repair through the poly(ADP-ribose) polymerase (PARP) catalytic activity. PARP inhibitors (olaparib, talazoparib) are FDA-approved therapies that are toxic to tumors with HRR deficiency (HRD) and are recommended as adjuvant therapy in high-risk germline BRCA (gBRCA) positive BC. Despite the clinical implications of HRD, the prevalence of HRR alterations and HRD signature in early-stage primary BC and its association with hormone receptor (HR) status has not been well characterized.

Methods: This study used the nationwide (US-based, ~280 US cancer clinics) de-identified Flatiron Health-Foundation Medicine BC clinico-genomic database and included patients (pts) who underwent tissue comprehensive genomic profiling (FoundationOne/FoundationOneCDx) between 2014 and 2022. The analysis included all pts with BC who presented with “early” stage I-III disease, had a primary tissue specimen collected within 3 months of diagnosis, and had a reportable novel scar-based HRD signature (HRDsig). Results: A total of 896 primary BC pts with stage I-III met our inclusion criteria. Of these early BC pts 21% (188/896) were HRDsig+ (stage I: 17% (32/188); stage II: 22% (84/376); and stage III: 22% (72/332)). For early BC pts, high rates of HRDsig+ were seen in gBRCA (87% [34/39]), somatic BRCA (sBRCA, 78% [14/18]), and gPALB2 (71% [5/7]) mutated tumors, with a lower rate seen with other HRR genes [16% (10/63); ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, sPALB2, RAD51B, RAD51C, RAD51D and RAD54L]. HRDsig+ was also detected in 16% (135/832) of BC without g/s BRCA or g PALB2 mutations. BC pts who presented with stage I-III disease has similar prevalence of HRDsig+ when compared to those with stage IV disease (21% [188/896] vs 23% [177/767], p = 0.31), with similar trends in HR+ disease (HR+/HER2+: 7% [4/57] vs 9% [4/45], p = 0.73; and HR+/HER2-: 17% [78/466] vs 18% [82/463], p = 0.73). Conversely, in HR- cohorts, decreased prevalence of HRDsig+ was observed in the stage I-III vs stage IV cohort (HR-/HER2+: 3% [1/38] vs 18% [6/33], p = 0.04; HR-/HER2-: 31% [99/321] vs 38% [83/216], p = 0.08). Conclusions: In this study, HR+/HER2- group was the most common early BC subtype, followed by HR-/HER2-, HR+/HER2+, and HR-/HER2+. This distribution is similar to the SEER study, and closely reflects that of the general population. We observed the expected high rates of HRDsig+ in early-stage BC pts with g/s BRCA or g PALB2 mutations where clinical trial data already support the use of PARP inhibitors for early and advanced disease. Importantly, HRDsig positivity was also seen in 16% of early BC without g/s BRCA or g PALB2, and clinical trials will be needed to determine if these pts could also benefit from HRD directed therapies. Research Sponsor: Foundation Medicine.
Pulsed electrical fields in combination with anti-PD1 and survival of mice with TNBC (EMT6) murine breast tumor.

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Background: Delivery of pulsed electric field (PEF) energy is used to destabilize cells through multiple biochemical processes. We questioned whether a specific PEF treatment type could synergize with anti-PD1 in an orthotopic Triple Negative Breast Cancer (TNBC) EMT6 mouse model. Our previous studies have demonstrated that PEF treatment induces neo-antigen presentation and triggers an innate and adaptive immune response. Anti-PD1 therapy is ineffective at blocking growth of (TNBC) EMT6 tumors that are orthotopically implanted in mice. We evaluated whether a biphasic monopolar form of PEF could synergize with anti-PD1 when it was administered intraperitoneally or intra-tumorally, and whether there was a change in immune response post treatment. Methods: Forty-eight female Balb/c mice were implanted with 200,000 EMT6 cells into the mammary fat pads. Once tumor diameter reached 5 mm they were randomized into 6 groups of 8 animals: 1) Sham/IgG; 2) intra-tumoral (IT) anti-PD-1; 3) intra-peritoneal (IP) anti-PD-1; 4) PEF + anti-PD-1(IP); 5) PEF + anti-PD-1(IT) 6) 2X PEF on day 0 and day 7 + anti-PD-1(IT administered weekly). Sham-PEF mimicked the same procedure but without PEF. Anti-PD1 was administered weekly, IT or IP at 200 μg/mouse and PEF was delivered once on day of randomization. Tumors were measured three times per week, and animal survival was monitored until tumor volume necessitated euthanasia (≥2000mm³). Blood was collected on day 14 for flow cytometric analysis of systemic immune response which included quantifying CD3 positive T cells, B cells and NK cells. Results: Anti-PD1 treatment (IT or IP) did not reduce tumor growth, nor did it prolong survival compared to Sham/IgG treated animals. All anti-PD1 alone (IT or IP) as well as Sham treated animals had to be euthanized by day 35. In contrast, PEF combined with anti-PD1 given IT and IP significantly reduced tumor growth by 83% and 70%, respectively, on Day 14 compared to anti-PD-1 only treated animals (p = 0.03). Interestingly, EMT6 bearing mice treated with double PEF + IT administered anti-PD1 survived longer compared to mice treated with single PEF + IT administered anti-PD1. On day 65, 71% of double PEF + IT administered anti-PD1 were still alive compared to 12.5% of mice treated with PEF + IT administered anti-PD1 (p = 0.002). Flow cytometry analysis on day 14 indicated an increase in circulating adaptive (T- and B-cells) and innate (NK cells) immunocytes in the PEF + anti-PD1 treated animals compared to the control. Conclusions: Collectively, these results indicate that some types of PEF ablation synergize with weekly anti-PD1 in stimulating an increase of CD3+ T cells, B cells and NK cells, reducing tumor growth and prolonging survival of tumor bearing mice. These results suggest the synergistic potential of combining Immunotherapy with some forms of PEF, which warrants further study in patients. Research Sponsor: Galvanize Therapeutics.
Impact of endocrine therapy adherence on racial disparities in breast cancer survival.

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Background: Black women have worse breast cancer outcomes compared to their White counterparts, even for hormone receptor positive (HR+) HER2 negative (HER2-) breast cancer (BC). This tumor type is usually treated with 5-10 years of adjuvant endocrine therapy (ET) to reduce risk of BC recurrence and improve survival. We investigated the impact of adherence to ET on racial differences in survival for HR+ HER2- BC survivors. Methods: We conducted a population-based, retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, which links demographic and clinical data with cause of death for persons with cancer and Medicare claims for covered health services. We examined 9,039 women with HR+ HER2- stage I-III BC diagnosed between 2007 and 2016, who received primary breast surgery and initiated ET. Adherence to ET was measured using the medication possession ratio (MPR), which assesses the proportion of time a patient has medication available via filled prescriptions. As in established literature, we defined ET adherence as MPR ≥ 80%. Causal mediation analysis was performed to measure impact of adherence on survival disparities between Black and White BC survivors. Results: Mean age at diagnosis was 72 years, 6.5% were Black, and 20.9% were dual eligible for Medicaid (a surrogate for socioeconomic hardship). Most had stage I or II breast cancer (69.3%) and mastectomy as primary surgery (69.7%). Nineteen percent received chemotherapy and 62.5% received radiation. In univariate analyses, factors associated with ET adherence were Black race (OR 0.62, 95% CI 0.54-0.75), insured by Medicaid (OR 0.72, 95% CI 0.65-0.81), being married (OR 1.14, 95% CI 1.03-1.25), and increased comorbidities (Charlson score ≥ 2) (OR 0.88, 95% CI 0.78-0.99). Age, BC stage, type of surgery, and receipt of chemotherapy or radiation were not associated with ET adherence. In multivariable models adjusting for age, race, marital status, Medicaid eligibility, and Charlson score, Black race and Medicaid eligibility remained inversely associated with ET adherence (OR 0.70, 95% CI 0.59-0.83 and OR 0.77, 95% CI 0.69-0.87 respectively). Among those who were adherent to ET, Black women had 43% higher risk of mortality compared to White women (HR 1.43, 95% CI 1.17-1.76). In mediation analysis, 4.25% of the observed survival disparity between Black and White women can be explained by differences in ET adherence. Conclusions: We identified racial disparities in ET adherence and overall survival among women with BC. Adherence to ET accounted for a small percentage of racial disparities in survival. Further research is needed to delineate other factors contributing to ET non-adherence among Black women and to investigate additional factors contributing to known disparities in BC survival. Research Sponsor: Breast Cancer Research Foundation-AACR Career Development Awards to Promote Diversity and Inclusion.
Real-world outcomes with adjuvant nonsteroidal aromatase inhibitors (NSAIs) vs tamoxifen (TAM) in patients with hormone receptor—positive/human epidermal growth factor receptor 2—negative (HR+/HER2—) early breast cancer (EBC): A US database analysis.

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Background: Randomized controlled trial (RCT) meta-analysis data have shown a significantly greater disease-free survival (DFS) benefit with aromatase inhibitors than TAM in patients with HR+/HER2—EBC. Here we compare real-world outcomes in patients with HR+/HER2—EBC who received adjuvant endocrine therapy (ET) with NSAIs or TAM. Methods: This was a retrospective analysis of ConcertAI’s deidentified electronic medical records data set of patients treated at US academic and community oncology clinics from January 1, 1995 to April 30, 2021. The cohort included patients with stage II-III (if IIIB or IIIC, confirmation was required on residual tumor status) HR+/HER2—EBC who underwent surgery and initiated adjuvant ET (excluding those who switched classes of ET); ovarian function suppression (OFS) was permitted. Menopausal status was determined using age (≥ 50 years) as a proxy for undocumented status. Invasive DFS (IDFS; risk of disease recurrence, death, or second primary tumor), distant DFS (DDFS; risk of distant recurrence, death, or second primary tumor), and overall survival (OS; risk of death) were assessed and defined as the time interval between start of ET and first event. Multivariate Cox regression analyses were performed, adjusting for age, stage, Charlson Comorbidity Index, and prior adjuvant or neoadjuvant chemotherapy for the ET cohort. Results: Of the total 3133 patients analyzed, 2507 were included in this analysis (NSAI ± OFS, n = 1854; TAM ± OFS, n = 653). Among these patients, the median (range) age was 59.5 (22.8-86.6) years, 25.4% were premenopausal, and 56.2% had tumor node involvement. The mean (SD) time to ET discontinuation was 46.2 (35.9) months overall and was similar between the NSAI and TAM cohorts. Reasons for ET discontinuation were undocumented or missing from the database for 76.8% of patients. Multivariate Cox regression analyses suggested a significant risk reduction with NSAIs vs TAM, with a 17% reduction in risk of an IDFS event (hazard ratio (HR), 0.83 [95% CI, 0.69-0.98]) and an 18% reduction in risk of a DDFS event (HR, 0.82 [95% CI, 0.69-0.98]). Although there were few events, OS analysis suggested a numerical trend favoring NSAIs over TAM, with a 12% reduction in risk of death (HR, 0.88 [95% CI, 0.69-1.13]). Conclusions: This real-world data analysis revealed a reduction in risk of IDFS and DDFS events with adjuvant NSAIs vs TAM in patients with HR+/HER2—EBC. Collectively, RCT and real-world data demonstrate greater benefit with adjuvant NSAIs vs TAM with respect to risk of recurrence in this patient population. Research Sponsor: Novartis Pharmaceuticals Corporation.
The worldwide impact of HER2-targeted treatments in women with breast cancer: An epidemiological modeling study.

David J. Press, Melina Arnold, Svenn Hansen; Genentech Inc., South San Francisco, CA; F. Hoffmann-La Roche, Basel, Switzerland

**Background:** HER2-targeted therapies (trastuzumab, pertuzumab, and T-DM1) have revolutionized the treatment and epidemiological landscape of HER2+ breast cancer, resulting in population-level increases in survival and decreases in disease recurrence. The aim of this epidemiological modeling study was to quantify the estimated global impact of HER2-targeted therapies, by estimating the number of women diagnosed with HER2+ early breast cancer (eBC) who have avoided (or will avoid) metastatic disease recurrence following treatment. **Methods:** We used data and projections from cancer registries, observational studies, clinical trials, and drug sales volumes (ie, utilization) to create annual country-level synthetic cohorts of patients diagnosed with HER2+ eBC, for the years 2004-2033 in 185 countries. The real-world uptake of HER2-targeted treatments and treatment flow was estimated in the main scenario. The impact of chemotherapy alone was estimated in the counterfactual scenario, assuming 100% chemotherapy worldwide. The occurrence of distant recurrences was modeled in both scenarios using weighted transitional probability averages based on invasive disease-free survival curves from clinical trials. **Results:** In total, during the 3-decade study period, we predicted that 11.9 million (M) women would be diagnosed with HER2+ eBC, out of which 7.5M were estimated to be treated with HER2-targeted therapies in a real-world uptake scenario. In the counterfactual scenario with only chemotherapy available, a total of 2.9M women were estimated to experience a metastatic disease recurrence, compared to only 2.1M women in the base scenario of predicted real-world uptake of HER2+ targeted therapies. This corresponds to a reduction of 26% or 768,000 women who may avoid metastatic recurrence since the introduction of HER2-targeted therapies (Table). **Conclusions:** HER2+ targeted therapies have substantially improved breast cancer outcomes and continue to contribute to the reduction in breast cancer recurrence rates. Further research may elucidate treatment-related reductions in costs to society as a result of population-level improvements in disease outcomes for breast cancer survivors. Given the expected rise in the burden of breast cancer globally, therapeutic advances and increased treatment utilization may further accelerate global patient benefit. Research Sponsor: Hoffmann-La Roche.

### Estimated number of women globally diagnosed with BC and experiencing distant recurrence, by year and treatment scenario.

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Total</td>
<td>15.3</td>
<td>21.0</td>
<td>26.9</td>
<td>63.2</td>
</tr>
<tr>
<td>HER2+ eBC</td>
<td></td>
<td>1.9</td>
<td>4.0</td>
<td>5.9</td>
<td>11.9</td>
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<tr>
<td>Treated with any HER2-targeted therapies</td>
<td></td>
<td>0.7</td>
<td>2.3</td>
<td>4.4</td>
<td>7.5</td>
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<tr>
<td>Women experiencing distant disease recurrence (in thousands)</td>
<td>Counterfactual: Chemotherapy alone</td>
<td>408</td>
<td>886</td>
<td>1,610</td>
<td>2,904</td>
</tr>
<tr>
<td></td>
<td>With predicted real-world uptake of HER2+ therapies</td>
<td>380</td>
<td>723</td>
<td>1,033</td>
<td>2,136</td>
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</table>
Pathologic complete response after neoadjuvant systemic therapy for breast cancer in BRCA mutation carriers and noncarriers.

Sara P. Myers, Varadan Sevilimedu, Andrea Veronica Barrio, Audree Tadros, Anita Mamtani, Mark E. Robson, Monica Morrow, Minna Lee; Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; Biostatistics Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; Breast Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Distinct pathological characteristics and mutational signatures in BRCA-associated breast cancers may result in differential response to chemotherapy but understanding of treatment response after neoadjuvant chemotherapy (NAC) is limited. We describe a single-institutional experience to compare rates of pathologic complete response (pCR) after NAC in BRCA carriers (gBRCA1/2) and noncarriers. Methods: From 11/2013 to 01/2022, 1426 consecutive women with clinical stage I-III breast cancer were treated with NAC followed by surgery. Baseline disease characteristics were compared between gBRCA1/2 and noncarriers using two-sample non-parametric tests. Conditional logistic regression was used to evaluate the association between BRCA status and pCR (i.e., ypT0/is pN0) adjusting for variables selected using backward elimination. Results: 92 (6.5%) and 73 (5.1%) had deleterious mutations in BRCA1 and BRCA2, respectively. Compared to noncarriers, gBRCA1/2 were younger (p<0.001) with clinical T1 (p=0.002) and triple negative disease (TN) (57% vs 25% noncarriers, p<0.001). Almost all patients received doxorubicin/cyclophosphamide/paclitaxel therapy (93%) with gBRCA1/2 more likely to receive carboplatin (p<0.001). pCR rate was 42% of gBRCA1, 21% of gBRCA2, and 26% of noncarriers (p=0.001). Among clinically node positive (cN+) patients, nodal pCR was higher in gBRCA1/2 compared to noncarriers (53/365 (55%) vs 371/856 (43%), p=0.012). This difference was seen in ER+/HER2- (36% gBRCA1/2 vs 20% noncarriers; p=0.027) and TN subtypes (79% gBRCA1/2 vs 45% noncarriers; p<0.001). Poorly differentiated tumors (p<0.001), cN+ (p=0.010), lower cT stage (p=0.028), ductal histology (p<0.001), TN and HER2+ receptor status (p<0.001), absence of lymphovascular invasion (p<0.001), carboplatin receipt (p=0.041), and BRCA1 status (p=0.001) were also associated with pCR on univariate analysis. After adjusting for differentiation and molecular subtype, BRCA1 status remained independently associated with pCR. Conclusions: gBRCA1 undergoing NAC have higher pCR rates relative to gBRCA2 and patients with sporadic disease. Across breast cancer subtypes, gBRCA1/2 more frequently converted to pN0. Defining biological mechanism for these findings would allow customization of treatment based on germline genetics. Research Sponsor: None.

<table>
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<tr>
<th>Characteristic</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
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<td>BRCA1</td>
<td>2.40 (1.47, 3.89)</td>
<td>&lt;0.001</td>
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<tr>
<td>BRCA2</td>
<td>1.10 (0.55, 2.06)</td>
<td>0.8</td>
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<tr>
<td>Well/moderately differentiated†</td>
<td>0.30 (0.20, 0.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Molecular subtype§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td>3.75 (2.53, 5.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR+ HER2+</td>
<td>4.77 (3.17, 7.31)</td>
<td></td>
</tr>
<tr>
<td>HR- HER2+</td>
<td>16.3 (10.3, 26.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI= confidence interval; IQR= interquartile range; HR= hormone receptor; HER2= human epidermal growth factor 2.

† Relative to poorly differentiated. § Relative to HR+ HER2-.
Validation of a novel and rapid reagent free assay to predict outcomes for adjuvant therapy decision making in hormone receptor-positive breast cancer.

Charles Coombes, Hemmel Amrania, Christina Angelou, Zamzam Al-Khalili, Ian O. Ellis, Darius Francescatti, Chris Phillips, Andrew R. Green, Nicholas Wright, Emad A. Rakha, Carlo Palmieri; Imperial College, London, United Kingdom; Imperial College London, London, United Kingdom; Imperial College, London, London, United Kingdom; Nottingham University Hospitals Trust, Nottingham, United Kingdom; Rush University Medical College, Chicago, IL; Barts Cancer Institute, London, United Kingdom; University of Nottingham, Nottingham, United Kingdom; Charing Cross Hospital, London, United Kingdom

Background: Digistain is a mid-infrared imaging technology that assesses aneuploidy by measuring the nuclear-to-cytoplasmic chemical ratio in the cellular content of tissues to generate the Digistain Index (DI). DI correlates with tumor grade and shows promise for risk stratification. Here we investigated whether DI could predict clinical outcomes in patients with early breast cancer to guide decision making regarding subsequent adjuvant chemotherapy. Methods: Infrared spectrometry was performed on existing tissue microarrays to determine the DI of 801 patients with hormone receptor-positive, HER 2-negative primary breast cancer with \( \leq 3 \) positive lymph nodes who had received systemic endocrine therapy only. Multivariate logistic modelling incorporated the DI with pathological features to generate the Digistain Prognostic Score (DPS). Receiver operator characteristics curves were used to assess the ability of DPS to predict 5- and 10-year progression-free survival (PFS), recurrence and overall survival (OS).

Results: In a Cox-regression analysis, the hazard ratio (HR) of DI to predict OS was 4.49 (95% CI 1.08–18.67; \( P=0.039 \)) compared with HRs in the range of 1.04–1.81 (all \( P < 0.001 \)) for age, tumor grade, tumor size and lymph node stage. In multivariate modelling analysis, DPS was consistently highly accurate and had negative predictive values for PFS, recurrence, and OS at 5 and 10 years that were similar, if not superior, to existing genomic-based tests. Using the DPS, the HRs for Kaplan-Meier curves for low- vs. high-risk classification were statistically significant (\( P<0.001 \)) for PFS, recurrence and OS (1.80, 1.83 and 2.49, respectively). Conclusions: In patients with early breast cancer, DPS showed high accuracy and predictive performance, and was able to stratify patients into low or high risk. Considering its low cost and ability to provide almost immediate prognostic information, DPS has the potential to offer clinical utility to reduce the use of unnecessary chemotherapy. Research Sponsor: National Institute of Health Research UK.
Influence of hormone therapy timing intake on disease free survival (DFS) for patients with high-risk early breast cancer: Results of the UCBG-UNIRAD phase III randomized trial.

Sylvie Giacchetti, Enora Laas, Thomas Bachelot, Jerome Lemonnier, Fabrice Andre, David A. Cameron, Judith Bliss, Sylvie Chabaud, Anne-Claire Hardy-Bessard, Magali Lacroix-Trik, Jean-Luc Canon, Marc Debled, Mario Campone, Paul H. Cottu, Florence Dalenc, Annabelle Ballesta, Frederique Madeleine Penault-Llorca, Fabien Reyal, Francis Lévi, Anne-Sophie Hamy; APHP University Hospital Saint Louis, Senopole, Paris, France; Surgery Department, Institut Curie, Universite Paris Cite, Paris, France; Medical Oncology, Centre Léon Bérard, Lyon, France; R&D Oncoparc, Paris, France; Institut Gustave Roussy, Villejuif, France; Edinburgh University Cancer Centre, Edinburgh, Scotland, United Kingdom; Medical Oncology, Western General Hospital, Edinburgh, United Kingdom; Department of Clinical Research and Innovation, Centre Léon Bérard, Lyon, France; Medical Oncology, CARIO - HPCA, Plerin-Sur-Mer, France; Gustave Roussy, Villejuif, France; Medical Oncology, Grand Hopital de Charleroi, Charleroi, Belgium; Medical Oncology, Institut Bergonie, Bordeaux, France; Medical Oncology, Institut Cancerologie de l’Ouest, Saint-Herblain, France; Medical Oncology, Institut Curie, Universite, Paris, France; Institut Claudius Regaud, Institut Universitaire du Cancer – Oncopo, Toulouse, France; Inserm Unit 900, Institut Curie, MINES ParisTech CB10 - Centre for Computational Biology, PSL Research University, Saint Cloud, France; Pathology department, Centre Jean Perrin, Clermont-Ferrand, France; Surgery Department, Institut Curie, Universite Paris, Paris, France; Chro-notherapy, Cancers, and Transplantation Unit, Faculty of Medicine, Paris-Saclay University, Villejuif, France; Medical Oncology, Institut Curie, Universite Paris Cite, Paris, France

Background: Circadian rhythms regulate the cellular and molecular processes that determine treatment effects. Scarce data suggest that daily timing could influence endocrine therapy (ET) pharmacology. We prospectively tested this hypothesis within the UNIRAD adjuvant phase III trial (NCT01805271) in patients (pts) with hormone receptors positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC).

Methods: Between June 2013 and March 2020, 1,278 pts with high-risk HR+/HER2- primary BC were randomly assigned to adjuvant ET combined with EVE or placebo. Pts were stratified according to lymph node involvement, progesterone receptor status, ET (tamoxifen or aromatase inhibitors (AI)), prior neoadjuvant or adjuvant chemotherapy, and duration of ET before randomization. Throughout their participation in the trial, patients were asked to declare prospectively in a daily diary the timing of ET intake within four 6-h slots (06:00 to11:59 (morning), 12:00 to 17:59 (afternoon), 18:00 to 23:59 (evening), or 24:00 to 05:59 (night). The prognostic impact of the timing of ET and EVE/placebo on DFS was a prespecified secondary endpoint.

Results: A total of 855 patients (67%) recorded ET intake daily timings (n = 401 in the EVE arm, n = 454 in the placebo arm). Morning intake was preferred by 465 pts (54%), whilst 344 pts (40%) chose evening intake, and minor proportions took ET in the afternoon (49 patients, 5%) or at night (5 patients, 1%). Pts choosing morning or afternoon intake were significantly older than those preferring evening or night intakes (mean age: morning: 56.4 y.o.; afternoon: 58.4 y.o.; evening: 53.1 y.o.; night: 50.8 y.o.; p < 0.001). Only 10 patients (1.1%) reported changing ET timing during the study. With a median follow-up of 72.5 months, 118 patients relapsed (locally n = 30, metastases n = 84), and 41 patients died. In the whole population, ET intake timing was not associated with DFS (HR 0.77 [95%CI, 0.53-1.12], p = 0.17). ET intake timing effects according to the stratification factors revealed a significant interaction between its prognostic impact and ET agent (tamoxifen versus AI, p for interaction = 0.01). DFS was prolonged in those pts taking tamoxifen in the evening/night rather than in the morning/afternoon (HR = 0.43 [0.22 - 0.85], p = 0.015), while no such effect was found for those on AI (HR = 1.07 [0.68 - 1.7], p = 0.761). Such interaction remained statistically significant at multivariate analysis (HR 0.38, p = 0.003). Conclusions: Tamoxifen intake in the evening was associated with an improved DFS in high-risk HR+/HER2- breast cancer pts and could be recommended at no cost in the adjuvant setting. Clinical trial information: NCT01805271. Research Sponsor: French Ministry of Health PHRC; La Ligue contre le Cancer; Novartis.
Prognostic role of HER2 expression in patients with ER-positive/HER2-negative breast cancer: Results from a population-based cancer registry study.

Antonino Musolino, Olga Serra, Benedetta Pellegrino, Chiara Tommasi, Daniele Zanoni, Laura Cortesi, Fabio Canino, Federico Piacentini, Paolo Sgargi, Maria Michiara; Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), Parma, Italy; University Hospital of Parma, Parma, Italy; University of Parma, Parma, Italy; University Hospital Modena, Modena, MO, Italy; University Hospital of Modena, Modena, Italy

Background: Estrogen Receptor (ER)-positive (+)/Human Epidermal Growth Factor Receptor 2 (HER2)-negative (-) breast cancers (BCs) express variable protein levels of both ER and HER2, which can influence prognosis. Methods: We evaluated all invasive ER+/HER2- BCs (n = 3633) that were diagnosed and systematically collected by the Parma Province Cancer Registry, Italy, from 2004 to 2018. Tumors were classified by HER2 (IHC score of 0, 1+ or 2+ with negative FISH) and ER status (ER-low [1-9%], ER-moderate [10-79%] or ER-high [80-100%]). Comparisons of clinicopathologic characteristics and disease outcome were performed. Results: BCs with late-stage diagnosis (P = 0.04), high histologic grade (P = 0.0001), or high proliferative rate (P < 0.0001) were more likely HER2 2+/FISH-. The rate of ER-high BCs did not change from 2675 of 2938 (91%) HER2 0 tumors to 508 of 560 (90.7%) HER2 1+, and 124 of 135 (91.9%) HER2 2+/FISH- tumors. Correspondingly, ER-low BCs were not enriched among HER2 0 tumors compared to the other tumors with different HER2 expression (P = 0.6). The 5-year overall survival (OS) for HER2 2+/FISH- BCs was lower than that for HER2 0 or 1+ tumors (P = 0.03). ER-low/moderate tumors were associated with poorer OS in comparison with ER-high BCs (P < 0.0001). HER2 2+/FISH- status was detrimental to OS among patients (pts) with ER-high tumors (P = 0.04), while this finding was not observed among ER-low/moderate BCs (P = 0.21). An interaction between HER2 2+/FISH- expression and ER-high status was found for poorer OS after adjusting for prognostic variables (HR = 1.7; 95% CI: 1.1-2.9). Conclusions: The prognostic role of HER2 expression in pts with ER-positive/HER2-negative BCs seems to be restricted to ER-high tumors, while the worse prognosis of tumors with lower ER expression is not associated with HER2 status. These findings may help identify optimal patient inclusion criteria for clinical trials with novel anti-HER2 therapies in ER-positive/HER2-negative disease. Research Sponsor: None.
Additional prognostic value of the BCT score in patients with ER+HER2- breast cancer receiving 21-gene assay-guided adjuvant treatments.

Sung Gwe Ahn, Yoonwon Kook, Sae Byul Lee, Eun-Gyeong Lee, Jonghan Yu, Young-Won Lee, Yeon Jin Kim, Sang Uk Woo; Gangnam Severance Hospital, Yonsei University, Gangnam-Gu, NA, Korea, Republic of (South); Gangnam Severance Hospital, Seoul, Korea, Republic of (South); Asan Medical Center, Seoul, Korea, Republic of (South); Center for Breast Cancer, Research Institute and Hospital, National Cancer Center, Goyang, South Korea; Samsung Medical Center, Gangnam-Gu, South Korea; Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.; Seoul, South Korea; Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Korea University Guro Hospital, Guro-Gu, South Korea

Background: In early estrogen receptor (ER)+HER2- breast cancer, a 21-gene expression assay-guided decision-making for adjuvant treatments has been widely utilized as a standard-of-care. The GenesWell BCT is a multigene assay that is designed to predict the risk of distant recurrence (DR) in patients with ER+HER2- breast cancer. This assay consists of nine genes, which are used to generate a risk score that can help guide treatment decisions. We addressed an additional value of the GenesWell Breast Cancer Test (BCT) score using the cohort of ER+HER2- breast cancer patients receiving a 21-gene assay-guided adjuvant treatments, focusing the chemotherapy untreated subset with low 21-gene recurrence score (RS).

Methods: This multicentre, observational follow-up study was done in 4 academic institutions in South Korea. Patients with ER+HER2- breast cancer who received RS-guided adjuvant treatments were enrolled. A total of 705 patients were included. Of these, the rate of women with node-positive disease was 21.6% (152/705), and the rate of women with younger than 50 years of age was 61.4% (433/705). The BCT score was obtained using the specimens which were previously analyzed for RS. The primary endpoint was recurrence-free survival (RFS), and the secondary endpoint was distant recurrence-free survival (DRFS).

Results: Among the 705 patients, the RS assigned 110 (15.6%) as high risk (≥26), whereas the BCT score assigned 239 (33.9%) as high risk (≥4). The agreement between two tests was noted in 494 (70.1%); concordances were made in 69 for high and in 425 for low, respectively. At a median follow up of 85 months, 80 had tumor recurrences, 38 had distant recurrences, and the 7-year RFS was 90.0% (95% CI, 87.6%-92.5%). In the 595 patients with low RS, 556 (93.4%) did not receive adjuvant chemotherapy. Within the 556 chemotherapy-untreated patients with low RS, the RFS differed significantly according to the BCT score (p= .014); the 7-year RFS was 92.9% in the BCT-low, while it was 85.7% in the BCT-high. Within the group, the BCT score was demonstrated as an independent prognostic factor for both RFS and DRFS adjustment of tumor size, nodal stage, and histologic grade. In addition, the RFS of the low-BCT score group was superior to that of the high-BCT group in either women younger than 50 years of age with an RS of 21 to 25 or all women with an RS of 21 to 25. Conclusions: We found that the BCT score was useful in stratifying the risk of relapse in chemotherapy-untreated patients with a low recurrence score (RS). This indicates that the BCT score could provide additional clinical value in identifying patients with a long-term risk of relapse, particularly in young women with an RS of 21 to 25. Research Sponsor: Gencurix.
An analysis of breast cancer index scores predicting benefit of extended endocrine therapy by race.

Nicholas Siu-Li, Ian Pagano, Jami Aya Fukui; University of Hawaii John A. Burns School of Medicine, Honolulu, HI; University of Hawaii Cancer Center, Honolulu, HI

Background: Patients with early-stage hormone receptor-positive (HR+) breast cancer have a good prognosis. Prior studies have shown that extending endocrine therapy beyond the first 5 years reduces the risk of late distant recurrence. The Breast Cancer Index (BCI) is a gene expression assay that provides both a prognostic risk of late distant recurrence in addition to a yes/no prediction of benefit from receiving extended endocrine therapy. To date, no studies have examined the relationship between race and BCI score. This study aims to investigate the interaction between race and BCI scores in women with early-stage HR+ breast cancer. Methods: We analyzed BCI scores, demographics, and tumor characteristics from 89 women diagnosed with early-stage HR+ breast cancer. Univariate logistic regression analysis was run using race, BCI recurrence risk, hormone status, tumor size, or tumor grade as predictor variables. BCI prediction of benefit was used as the outcome variable. Results: Compared to Caucasians, Native Hawaiians had significantly greater odds of having a BCI score predicting benefit from receiving extended endocrine therapy (OR = 7.00, p = 0.04). Additionally, there were significantly greater odds of having a score predicting benefit among those who had a recurrence risk of 5-10% (OR = 3.84, p = 0.04), or ≥10% (OR = 9.16, p < 0.001) compared to a recurrence risk < 5%. Conclusions: Our findings highlight the utility of characterizing differences in BCI predictive and prognostic scores by race among breast cancer patients with early-stage HR+ tumors. Notably, Native Hawaiian women had 7.0 times increased odds of having a score predicting benefit of extended endocrine therapy compared to Caucasians. This result is salient given the high incidence of breast cancer among Native Hawaiians. Though not statistically significant, our data also demonstrated Filipinos had increased odds of a score predicting benefit as well. Furthermore, our findings show a direct correlation between prognostic risk of late distant recurrence and predictive benefit of extended endocrine therapy with a higher odds ratio associated with higher recurrence risk. Our study shows notable differences in BCI findings when stratifying patients by race. However, our sample size is relatively small, and we lack sufficient data from patients representing other races such as Hispanic and Black. Future studies may expand the sample size and adjust for known breast cancer risk factors. The goal is to identify trends that may improve our usage of the BCI as a tool to effectively guide hormone therapy recommendations in patients with early-stage HR+ breast cancer. Research Sponsor: U.S. National Institutes of Health.

<table>
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<th>BCI Risk (%)</th>
<th>Predictive Benefit (Yes)</th>
<th>OR</th>
<th>p-value</th>
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<tr>
<td>Low (&lt; 5)</td>
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<td>5</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>8</td>
<td>3.84</td>
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<tr>
<td>Mid (5-10)</td>
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<td>(p = 0.04)</td>
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<tr>
<td>High (≥10)</td>
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<td>9.16</td>
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<td></td>
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<td>(p &lt; 0.001)</td>
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<td>Race</td>
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<td>Other Asian or Pacific Islander</td>
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</table>
Cardiac safety and efficacy for patients with early-stage breast cancer treated with pegylated liposomal doxorubicin (PLD) or doxorubicin.

Lichen Tang, Min He, Jiong Wu, Zhonghua Wang, Guangyu Liu, Keda Yu, Cuizhi Geng, Zhimin Fan, Rui Ling, Guangdong Qiao, Li Cai, Ting Luo, Feng Jin, Haibo Wang, Anqin Zhang, Hongwei Zhang, Xiaohua Zeng, Xiaojia Wang, Ming Jiang, Shao Zhimin; Department of Breast Surgery, Fudan University Shanghai Cancer Center; Cancer Institute, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Department of Breast Surgery, Fudan University Shanghai Cancer Center and Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; Department of Breast Surgery, Fudan University Shanghai Cancer Center and Key Laboratory of Breast Cancer in Shanghai, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Department of Breast Surgery, The First Hospital of Jilin University, Changchun City, Changchun, China; Xi'An Hospital, The Air Force Military Medical University, Xi'an, China; Yuhuangding Hospital of Yantai, Yantai, China; Harbin Medical University Cancer Hospital, Harbin, China; Breast Disease Center, West China Hospital of Sichuan University, Chengdu, China; Department of Breast Surgery, The First Hospital of China Medical University, Shenyang, China; The Affiliated Hospital of Qingdao University, Qingdao, China; Guangdong Women and Children Hospital, Guangzhou, China; Zhongshan Hospital, Fudan University, Shanghai, China; Chongqing University Cancer Hospital, Department of Breast Cancer Center, Chonqing, China; Department of Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences/Zhejiang Cancer Hospital, Institute of Cancer and Basic Medicine, Chinese Academy of Sciences, Hangzhou, China; The Central Hospital of Wuhan, Wuhan, China

Background: Anthracyclines play an important role in the treatment of breast cancer (BC) while cardiotoxicity, a serious side effect, limits the clinical application. Pegylated liposomal doxorubicin (PLD) is a new dosage form of doxorubicin encapsulated in liposomes, which can reduce the plasma free level of doxorubicin and drug to normal tissue delivery, thereby reducing cardiotoxicity. The aim of this study was to evaluate the cardiac safety and efficacy of PLD compared with doxorubicin as adjuvant therapy in breast cancer patients. Methods: This is an open-label, randomized trial involving patients with operable breast cancer who were at high risk of recurrence after radical surgery (NCT03949634). Patients were randomized (1:1) to receive adjuvant PLD or doxorubicin (A) and cyclophosphamide followed by taxanes + trastuzumab. The primary endpoint was cardiotoxicity, which was defined as congestive heart failure (CHF) with clinical symptoms, or no symptoms but with an abnormal left ventricular ejection fraction (LVEF). Secondary endpoints included 5-year disease-free survival (DFS) rate, 5-year overall survival (OS) rate and safety. Results: Between November 2017 and September 2019, 247 patients were randomized and received study treatment (PLD arm, 131; A arm, 116). The median age was 49 years (range, 26-67) in PLD arm and 48 years (range, 25-70) in A arm. The pathological stages were 18.3% stage I, 58.0% stage II, and 22.1% stage III in PLD arm, while those of A arm were 20.7% stage I, 59.5% stage II, and 19.8% stage III. The median follow-up time was 43.0 months. The incidence of abnormal LVEF was 0 in the PLD arm and 1.7% the A arm (P = 0.220). The incidence of CHF was 0 in the PLD arm and 0.9% the A arm (P = 0.470). Survival data analysis is immature. The exploratory analysis of cardiac-related biomarkers showed that the incidence of high-sensitivity cardiac troponin-T (hs-cTnT) was lower in PLD arm than in A arm (3.8% vs. 30.2%, P < 0.001). Grade 3/4 adverse events (AEs) occurred in 42.7% patients in PLD arm and in 61.2% patients in A arm. The most common grade 3/4 AEs in PLD arm and A arm included neutropenia (34.4% vs. 55.2%), leukopenia (30.5% vs. 39.7%), and hand-foot syndrome (4.6% vs. 0.0%). Conclusions: Hs-cTnT elevation may have a role in the AE prediction of anthracycline. PLD usage may present lower incidence of cardiotoxicity than doxorubicin in the adjuvant treatment of patients with early-stage breast cancer. Clinical trial information: NCT03949634. Research Sponsor: CSPC Ouyi Pharmaceutical Co., Ltd.
Influence of adherence to adjuvant endocrine therapy in early breast cancer: Results from a large German real-world claims data analysis.

Dominik Dannehl, Tobias Engler, Tjeerd Dijkstra, Raphael Gutsfeld, Alexandra von Au, Markus Hahn, Sabine Hawighorst-Knapstein, Ariane Chaudhuri, Markus Wallwiener, Armin Bauer, Sara Brucker, Stephanie Wallwiener, Andreas Daniel Hartkopf; Department of Women’s Health, Tuebingen University Hospital, Tuebingen, Baden-Wuerttemberg, Germany; Department of Obstetrics and Gynaecology, University of Heidelberg, Heidelberg, Baden-Wuerttemberg, Germany; AOK Baden-Wuerttemberg, Stuttgart, Baden-Wuerttemberg, Germany; Department of Gynecology and Obstetrics, Ulm University Hospital, Ulm, Germany

Background: In hormone-receptor positive (HR+) early breast cancer (EBC) adjuvant endocrine therapy (ET) significantly reduces recurrence and mortality. The most common way to estimate therapy adherence is the use of patient reported outcome measures. Yet, this method is inaccurate due to the social-desirability bias. We therefore aimed to analyze adherence to ET over the first 5 years of treatment by using claims data from a large German health insurance provider (AOK Baden-Wuerttemberg).

Methods: Female patients diagnosed with HR+ EBC between July 1st 2010 and December 31st 2019 were included into the analysis. Adherence to ET was defined as the ratio of the summed number of pills of filled prescriptions for ET (either aromatase inhibitors or tamoxifen) and the duration of endocrine therapy in days (from the start of the first prescription after completion of surgery and chemotherapy, if applicable). ET administration was observed over 5 years. High/low adherence was defined as a ratio between 0.8 – 1 and 0 – 0.8, respectively. ET duration was divided into yearly intervals and adherence was calculated as above. Continuous high/low adherence was then defined as an adherence between 0.8 – 1 and 0 – 0.8 in each year. Distant recurrence-free survival (DRFS) was calculated from the day of the first diagnosis of EBC until onset of distant metastatic disease. Overall survival (OS) was defined as the period between first diagnosis of EBC until death. Results: In total, 20998 patients were included. 17006 patients (81%) were HR+. Regarding overall adherence during the first 5 years, average adherence was 0.81 ± 0.26, with 72% of all HR+ patients showing high adherence to ET. Of 17006 HR+ EBC patients, 8363 (49%) showed a continuous high adherence to ET and 1731 (10%) showed a continuous low adherence to ET over 5 consecutive years. Continuous adherence to endocrine therapy had a significant impact on DRFS (HR: 0.61; 95% CI: 0.52 - 0.71; p < 0.0001) and OS (HR: 0.52; 95% CI: 0.46 -0.59; p < 0.0001). The 10-year OS rate was 79% / 64% for patients with continuous high / low adherence to endocrine therapy. Conclusions: As measured by the number of prescribed pills, adherence during the first 5 years of endocrine therapy was higher than expected by literature. Continuous adherence to ET over 5 years has a significant impact on OS and DRFS. Future research should focus on identifying factors that influence therapy adherence in HR+ EBC patients. Research Sponsor: AOK Baden-Wuerttemberg.

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Beneficial effect of repeated participation in breast cancer screening upon survival.

Robert A. Smith, Stephen W Duffy, Amy Ming-Fang Yen, László Tabár, Abbie Ting-Yu Lin, Sam Li-Sheng Chen, Chen-Yang Hsu, Peter Dean, Tony Hsiu-Hsi Chen; American Cancer Society, Atlanta, GA; Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; School of Oral Hygiene, College of Oral Medicine, Taipei Medical University, Taipei City, Taiwan; Department of Mammography, Falun Central Hospital, Falun, Sweden; Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; Master of Public Health Program, College of Public Health, National Taiwan University,, Taipei, Taiwan; University of Turku, Turku, Finland

**Background:** The benefit of mammography screening in reducing population mortality from breast cancer is well established. However, the effect of repeated participation at scheduled screens on case survival is less well documented. **Methods:** In this retrospective analysis of breast cancer survival, we analyzed incidence and survival data on 37,079 women ages 40-69 from nine Swedish counties who had between one and five invitations to mammography screening and were diagnosed with breast cancer between 1992 and 2016. Of these, 4,564 subsequently died of breast cancer. For each breast cancer diagnosed in each county’s period of observation, we obtained data on previous screening history, and subsequent death (or not) from breast cancer. Formal comparisons of survival with respect to numbers of screening exams attended prior to a diagnosis of breast cancer were carried out using Cox proportional hazards regression with time-varying covariates, ie, cumulative numbers of screens, yielding hazard ratios and 95% confidence intervals (CI). We corrected for potential self-selection using the method of Duffy et al, which gives a corrected estimate based on the proportion of participants, the uncorrected estimate, and the relative risk of breast cancer death for non-participants compared to an uninvited population. **Results:** Depending on number of invitations, 58-73% (average 65%) participated in all scheduled screens, and 73-96% (average 91%) participated in at least one examination. There was successively better survival among women with increasing numbers of screening exams. For a woman with five previous screening invitations who participated in all five screening exams, the hazard ratio was 0.28 (95% CI 0.25-0.33, p<0.0001), a 72% risk of dying from breast cancer, compared to a woman attending none. Following a conservative adjustment for potential self-selection factors, the hazard ratio was 0.34 (95% CI 0.26-0.43, p<0.0001). **Conclusions:** For those women who develop breast cancer, regular prior participation in mammography screening confers significantly better survival. Most women will not develop breast cancer in their lifetime. These results indicate that for those who do, regular participation in screening considerably improves the probability of surviving it. The distinction between the general, population benefit of mammography screening, and the benefit of regular participation in mammography screening should be clearly articulated in breast cancer screening messaging and decision aids. **Research Sponsor:** American Cancer Society.

<table>
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<tr>
<th>Number of screens participated in</th>
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<th>Adjusted</th>
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<td>0</td>
<td>1.00 (-)</td>
<td>1.00 (-)</td>
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</tr>
<tr>
<td>1</td>
<td>0.71 (0.57-0.89)</td>
<td>0.87 (0.67-1.12)</td>
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<tr>
<td>2</td>
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<td>0.61 (0.45-0.83)</td>
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</tr>
<tr>
<td>3</td>
<td>0.37 (0.30-0.46)</td>
<td>0.45 (0.34-0.60)</td>
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<tr>
<td>4</td>
<td>0.37 (0.31-0.43)</td>
<td>0.45 (0.35-0.58)</td>
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<td>5</td>
<td>0.29 (0.25-0.33)</td>
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</table>

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State-of-the-art management of HER2-negative early breast cancer: Treatment patterns among healthcare professionals and concordance with expert recommendations.

Marie N. Becker, Jame Abraham, Kevin Kalinsky, Laura Spring, Tiffany A. Traina, Timothy A. Quill, Denise A. Yardley; Clinical Care Options, Reston, VA; Department of Hematology and Medical Oncology, Taussig cancer institute, Cleveland Clinic, Cleveland, OH; Winship Cancer Center of Emory University, Atlanta, GA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN

Background: The management of high-risk HER2-negative early-stage breast cancer (EBC) has recently evolved with the addition of newer agents including abemaciclib, olaparib, and pembrolizumab as (neo) adjuvant therapy options for appropriate patients. To aid healthcare professionals (HCPs) in the recommended implementation of these agents, we developed an online treatment decision support tool providing case-specific treatment guidance from 5 breast cancer experts. Here, we report an analysis of cases entered into the tool by HCPs, comparing their planned treatment with expert recommendations.

Methods: Expert therapy recommendations for 10 case scenarios in high-risk HER2-negative EBC based on 3 pivotal clinical trials (KEYNOTE-522, OlympiA, and monarchE) were obtained in March 2022. Patient and disease characteristics included hormone receptor (HR) status, BRCA mutational status, lymph node positivity, presence of residual disease after resection, and additional criteria based on the 3 practice-changing trials. HCPs entered specific patient and disease factors into the tool along with their intended treatment plan and were shown 5 individual expert treatment recommendations for the unique case scenario. Results: From June 2022 to January 2023, 547 HCPs entered 982 patient case scenarios into the tool. A comparison of treatment recommendations by experts and HCPs showed divergence for several case scenarios. For patients with high-risk HR-positive/HER2-negative EBC and no BRCA mutation, all 5 experts recommended adjuvant abemaciclib plus endocrine therapy. By contrast, 64% of HCPs’ therapy choices were discordant with the experts, with 49% choosing chemotherapy followed by endocrine therapy. For patients with triple-negative breast cancer (TNBC) who received neoadjuvant chemotherapy and have no residual disease, all 5 experts recommended observation, whereas 36% of HCPs recommended additional adjuvant therapy. In the setting of BRCA-mutated TNBC with residual disease after neoadjuvant pembrolizumab plus chemotherapy, 4 of 5 experts recommended adjuvant pembrolizumab plus olaparib, but just 33% of HCPs chose this combination. One third of HCPs who initially selected treatment options that diverged from expert recommendations or who were uncertain about treatment choice intend to change their therapy selection to align with the experts. Conclusions: Analysis of data from this tool suggests differences in clinical practice between experts and HCPs for multiple case scenarios of high-risk EBC, including examples of potential overtreatment. Moreover, our data demonstrate that this decision support tool may lead to better alignment of HCP treatment choices with experts, with the potential to improve clinical management of patients. Research Sponsor: None.
SEER analysis of 9-year breast cancer specific mortality (BCSM) in patients (pts) with invasive lobular breast cancer (ILC) assessed by the 21-gene Breast Recurrence Score (RS) assay.

Charles E. Geyer, John Bennett, Gong Tang, Jennifer M. Racz, Christy Ann Russell, Jung S. Byun, Julia Foldi, Frederick L. Baehner, Valentina I. Petkov; UPMC Hillman Cancer Center, Pittsburgh, PA; Genomic Health Inc, an Exact Sciences Corporation, Redwood City, CA; NSABP, and University of Pittsburgh, Pittsburgh, PA; Exact Sciences Corporation, Madison, WI; NIH, Bethesda, MD; University of Pittsburgh Medical Center Cancer Center, New Haven, CT; Exact Sciences, Redwood City, CA; National Cancer Institute, Rockville, MD

Background: Linking of the results of the 21-gene Breast Recurrence Score (RS) commercial assay to SEER registries provides opportunity to assess real world prognostic performance of the assay in important subgroups of early breast cancer (BC). ILC is less common than invasive ductal carcinoma (IDC) and the performance of the RS assay in ILC is of interest. The relationship between RS results and 5-year BCSM in patients with ILC was reported based on a linkage in 2015 at this meeting in 2017. Here we present a comparison of 9-year BCSM of ILC vs IDC from a linkage update in 2019. These results will be updated further based on a new linkage of RS data to be completed in April 2023.

Methods: Eligible pts had 0-3 axillary nodes at initial surgery, were hormone receptor positive and HER2-negative with a RS result, had no prior malignancy, and were diagnosed between January 2004 and December 2012. Pts with ICD-O-3 code 8520 were categorized as ILC and those with code 8500 as IDC. 9-year BCSM of both cohorts was estimated using actuarial methods. Multivariable Cox proportional hazards models characterized association between RS results and BCSM.

Results: Of 89818 pts, 9835 (11.0%) had ILC and 64669 (72.0%) had IDC. Among pts with ILC, median age was 60 years; 12.5% were N1 and 28.4%, 63.7% and 7.9% were grade 1, 2 and 3. Median follow-up was 84 months. Chemotherapy (CT) use and BCSM increased with increasing RS result in both cohorts. After adjusting for age, race, tumor grade, tumor size, nodal status, and histologic subtype, the RS result was independently associated with BCSM ($p < .001$) in both ILC and IDC.

Conclusions: In this linked SEER analysis of pts with ILC or IDC, the RS results were prognostic for 9-year BCSM, regardless of nodal status.

<table>
<thead>
<tr>
<th>Histologic subtype</th>
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<th>Node-positive</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>% CT use</td>
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<tr>
<td>IDC</td>
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<tr>
<td>0-15</td>
<td>24265</td>
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<td>16-20</td>
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Impact of neoadjuvant chemo-immunotherapy on surgical outcomes and time to radiation in triple negative breast cancer.

Sara P. Myers, Srinivasa Sevilimedu Veeravalli, V. Morgan Jones, Nour Abuhadra, Giacomo Montagna, George Plitas, Monica Morrow, Stephanie Downs-Canner; Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; Biostatistics Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY

**Background:** The impact of preoperative chemo-immunotherapy on surgical complications and timing of adjuvant therapy is not well understood. We examined the association between neoadjuvant pembrolizumab plus chemotherapy (NAC+P) compared to neoadjuvant chemotherapy alone (NAC) and treatment delays and postoperative complications in triple negative breast cancer (TNBC). The effect of immune-related adverse events (irAEs) on these outcomes was also compared. **Methods:** 143 women with stage II-III TNBC treated with NAC+P based on the KEYNOTE 522 (KN522) regimen from 8/2021-9/2022 were compared to 287 consecutive patients who received NAC prior to 7/2021. Baseline characteristics, time to treatments, and surgical complications were compared between KN522 and non-KN522, and among KN522 with/without irAEs using two-sample non-parametric tests. Linear regression evaluated association of irAEs with time to surgery and radiation. Conditional logistic regression identified factors associated with surgical complications among KN522 patients. **Results:** Age, BMI, race, ASA class, and mastectomy rates were similar among KN522 and non-KN522 patients. Interval from end of neoadjuvant treatment until surgery was one day longer for patients receiving NAC+P (median 32 days (IQR 27, 43) vs. 31 days (26, 37) non-KN522, p = 0.035). Time to radiation did not differ (p = 0.2). Postoperative complications occurred in 26 (9%) non-KN522 vs 12 (8.4%) of KN522 patients (p = 0.7) (Table). 55/144 (38%) of KN522 patients experienced 74 irAE; 42 (76%) required treatment. Pembrolizumab was held in 21 (38%) and discontinued permanently in 17 (31%). One KN522 patient experienced a fatal irAE (pneumonitis). Older age (coeff. 0.38, 95% CI 0.06-0.70, p = 0.02) and ASA class 4 (coeff. 53, 95% CI 14-92, p = 0.009) were associated with delays to surgery but irAE was not (p = 0.070). Neither presence of irAE (coeff. 6.8, 95% CI -0.74-14, p = 0.081) or number of irAEs (coeff. 4.1, 95% CI -1.2-9.3, p = 0.13) were associated with time to radiation. IrAEs were not associated with surgical complications (p = 0.5). **Conclusions:** Postoperative complications or delays to surgery or adjuvant radiation were similar in patients treated with NAC+P compared to NAC. IrAEs were not associated with delays to surgery or adjuvant radiation or postoperative complications. **Research Sponsor:** None.

<table>
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<th>Complication*</th>
<th>KN522 n (%); (N = 143)</th>
<th>Non-KN522 n (%); (N = 287)</th>
<th>KN522 n (%); (N = 143)</th>
<th>Non-KN522 n (%); (N = 287)</th>
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<td>Complication*</td>
<td>KN522 n (%); (N = 143)</td>
<td>Non-KN522 n (%); (N = 287)</td>
<td>KN522 n (%); (N = 143)</td>
<td>Non-KN522 n (%); (N = 287)</td>
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<td>3 (1%)</td>
<td>Antibiotics + bedside procedure</td>
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<td>Infection/abscess</td>
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*p = value 0.7  *p-value 0.4.
Detection of homologous recombination deficiency (HRD) using a novel genomic and epigenomic liquid biopsy assay in patients with breast cancer.

Catalin Barbacioru, Jennifer Yen, Denis Tolkunov, Pegah Safabakhsh, Hao Wang, Andrew Gross, Brooke Overstreet, Colby Jenkins, Leylah Drusbosky, Lesli Ann Kiedrowski, Craig Eagle, Han-Yu Chuang; Guardant Health, Redwood City, CA; Guardant Health, Inc., Redwood City, CA; Guardant Health, Inc., Burlingame, CA

Background: Homologous recombination and repair (HRR) deficiency (HRD) is characterized by genomic instability associated with dysfunction in BRCA1/2 or other HRR genes. Patients with breast cancer harboring an HRD phenotype with or without HRR mutations have derived clinical benefit from PARPi therapy. We have previously shown that GuardantINFINITY, a novel genomic and epigenomic liquid biopsy assay, can identify HRR SNVs, indels, rearrangements, copy number loss, reversions, and BRCA1 promoter methylation for patient selection and resistance monitoring, a major challenge for PARPi treatment. Here, we present a method of predicting HRD status by cfDNA using GuardantINFINITY in patients with advanced breast cancer.

Methods: We developed a probabilistic genomic model to predict HRD status, inferred from genome-wide somatic SNV, indel, and CNV signatures indicative of BRCA1/2 deficiency, including large-scale state transitions (LST), whole-genome tumor loss of heterozygosity (LOH), telomeric allelic imbalance (TAI). A second probabilistic model, based on targeted measurements of genomic and epigenetic changes was learned from a subset of clinical samples to enhance the genomic model. The model was trained and tested on a cohort of over 12,000 GuardantOMNI and GuardantINFINITY clinical breast cancer samples to assess the sensitivity of accurately detecting deficiency in select HRR-genes (BRCA1/2, PALB2, RAD51D). The aggregated predictive model was validated on an independent cohort of breast cancer samples. Results: The model based on genomic and epigenetic signals identified HRR-gene deficiency in a breast cancer cohort with a estimated 95% LoD of 22.5% tumor fraction and an AUC of 0.75 across all tumor fractions, an improvement in sensitivity over when only the genomic model is used (AUC of 0.7, 95% LoD of 28%). Specificity remained high for both models (100%, n = 83) in cancer free samples. Application of this model in a cohort of 1,101 patients with unselected breast cancer identified 390 patients with an HRD phenotype, of whom 192 patients had a known HRR-gene mutation. Of the 201 patients with a known pathogenic mutation in an HRR gene, 49 also had co-occurring LoH in the same gene, indicating biallelic loss. Conclusions: In this analysis, we demonstrate that a probabilistic model of genomic and methylation predictors can detect HRD status in patients with breast cancer from cfDNA using GuardantINFINITY. Additional analytical and clinical studies to further evaluate this model are ongoing. With HRD prediction, GuardantINFINITY provides a comprehensive minimally-invasive solution for PARPi and DNA damage treatment selection, longitudinal monitoring, and an exploratory platform for investigating epigenetic signals that may underpin resistance. Research Sponsor: Guardant Health.
Background: Male breast cancer (MBC) is a rare disease. Research on trends and survival outcomes in systemic treatment for MBC is limited. This study aims to describe trends and survival outcomes of different systemic treatments in hormone receptor-positive (HR+) early MBC and to assess the factors related to treatment selection.

Methods: We identified stage I-III HR+ invasive MBC patients who have undergone surgery and systemic therapy diagnosed during 2004-2014 from the National Cancer Database (NCDB). Treatment groups include: endocrine therapy (ET), chemotherapy (CT), combination therapy (ET+CT), and None. Using Cochran-Armitage trend tests to describe the temporal trends of different treatments. Performing propensity score models to evaluate overall survival. Conducting a logistic regression to analyze factors associated with ET+CT.

Results: Among 6217 patients included (median follow-up 50.1 months), 1290 (20.7%) patients received no systemic therapy (None), 705 (11.3%) patients only received CT, 2358 (37.9%) patients only received ET, and 1864 (30.0%) patients received ET+CT. From 2004 to 2013, there was a significant increase in the use of ET (P(trend) < .001), which was accompanied by a decrease in CT and no treatment (all P(trend) < .001). And the use of ET+CT showed no significant change. After using overlap weighting (OW) to control confounders, multivariable cox regression analysis showed that ET+CT was associated with improved survival compared with ET (hazard ratio [HR], 0.46; P < .001). Sensitivity analyses (including the inverse probability of treatment weighting (IPTW) (HR, 0.49; P < .001), IPTW with stabilized weight (HR, 0.49; P < .001), propensity score matching (PSM) (HR, 0.51; P < .001), PS regression adjustment (HR, 0.47; P < .001), and PS stratification (HR 0.44; P < .001)) and exploratory subgroup analyses (except for well-differentiated, stage I, and breast conservation + radiotherapy subgroups) indicated similar outcome. Factors associated with receiving ET+CT include younger age, private insurance, Charlson Comorbidity Index was 0, poorer differentiation, higher stage, mastectomy and radiotherapy, estrogen receptor-positive and progesterone receptor-negative, and HER2-positive.

Conclusions: ET+CT was associated with improved survival compared with ET in HR+ early MBC patients, except for some low-risk subgroups. Research Sponsor: None.
Decision value of the circulating tumor DNA on the adjuvant anti-Her2 regimens in patients with Her2-positive breast cancer treated with neoadjuvant therapy.

Po-Han Lin, Li-Wei Tsai, Chiao Lo, Sung-Hsin Kuo, Chiun-Sheng Huang; National Taiwan University Hospital, Taipei City, Taiwan; National Taiwan University Hospital, Taipei, Taiwan; National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taipei, Taiwan

Background: A significant proportion of patients with early-stage Her2-positive breast cancer are treated with neoadjuvant therapy (NAT). Previous studies suggested the presence of circulating tumor DNA (ctDNA(+)) after NAT was a significant predictor for recurrence in early-stage Her2-positive breast cancer. However, it is unknown whether the ctDNA(+) was able to guide adjuvant anti-Her2 regimen for patients with early-stage Her2-positive breast cancer? Methods: We enrolled 117 patients who had Her2-positive breast cancer and received NAT. CtDNA was collected before and after NAT as well as detected by Oncomine breast cell-free DNA assay. Adjuvant anti-Her2 regimens were classified as T-DM1 and non-T-DM1. Recurrence-free survival (RFS) was estimated by Kaplan-Meier method and hazard ratio (HR) with 95% confidence interval (CI) was analyzed by Cox proportional hazards regression model. Results: Of the 117 patients enrolled, there were 18 patients receiving adjuvant T-DM1 and 99 receiving trastuzumab (N = 70) or trastuzumab plus pertuzumab (N = 29). CtDNA(+) was observed in 79 patients before NAT while 32 patients remained ctDNA(+) after NAT. Multivariate Cox regression model showed that ctDNA(+) after NAT (HR 3.497 95% CI 1.364-8.964, p = 0.009) was an independently poor factor that predicted recurrence, after adjustment with clinical and pathologic parameters. Non-pCR was associated with an inferior trend of survival but not a statistically significant factor of recurrence. Patients who received adjuvant T-DM1 had a reduced risk of recurrence (HR 0.118, 95% CI 0.015-0.931, p = 0.043) in the multivariate analysis. Further analysis of the prognostic value of adjuvant T-DM1 therapy in context with and without ctDNA, we divided patients into 4 subgroups: ctDNA(-)/non-T-DM1, ctDNA(-)/T-DM1, ctDNA(+)/non-T-DM1 and ctDNA(+)/T-DM1. Our data revealed that patients with ctDNA(+)/T-DM1 had a significantly better RFS than those with ctDNA(+)/non-T-DM1 (p = 0.019). The 5-year RFS was similar between patients with ctDNA (+)/T-DM1 and those with ctDNA(-) after NAT. Conclusions: The presence of ctDNA in patients with early-stage Her2-positive breast cancer after NAT was independently associated with disease recurrence; however, ctDNA(+) after NAT became inconsiderable when patients were treated with adjuvant T-DM1 therapy, which represented ctDNA(+) as an important factor determining adjuvant anti-Her2 regimen. Research Sponsor: Yonglin Foundation.
Utility of Ki67 in guiding adjuvant abemaciclib therapy for patients with hormone receptor (HR)-positive, early breast cancer (EBC).

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Background: The monarchE trial found that the addition of adjuvant abemaciclib to endocrine therapy in pts with lymph node (LN)+, HR+ EBC improved invasive disease-free survival in two pt cohorts: (1) ≥ 4 +LNs or 1-3 +LNs and Grade 3 disease or tumor ≥ 5 centimeters and (2) 1-3 +LNs and Ki67 ≥ 20%. The FDA approved adjuvant abemaciclib only in pts with HR+, HER2-negative, LN+ EBC with Ki67 ≥ 20%. The role of Ki67 as a predictive biomarker in this setting is unclear. ASCO guidelines recommend offering abemaciclib to pts who meet eligibility for either cohort and not restricting inclusion by Ki67. The objectives of this study were to (1) determine the association between Ki67 and the 21-gene recurrence score (RS), an established prognostic and predictive biomarker, using Ki67 cutoff ≥ 20% and (2) compare eligibility for adjuvant abemaciclib by FDA versus ASCO criteria.

Methods: Women with HR+, HER2-negative EBC with 1-3 +LNs, diagnosed between 2018 and 2019, and who had available information on Ki67 and RS in the National Cancer Database were identified. Pts were categorized into Ki67 low (< 20%) or high (≥ 20%) based on cutoff used in the monarchE and stratified by RS of low-intermediate (0-25) or high (26-100). Stratified agreement between Ki67 and RS were assessed using the proportion of agreement and Kappa statistic. McNemar’s test was used to compare proportion of pts eligible for abemaciclib by FDA versus ASCO criteria.

Results: 50,222 eligible women were included. 63.9% (n = 32,082) had Ki67 < 20% and 36.1% (n = 18,140) Ki67 ≥ 20%. There was fair agreement (Kappa 0.21-0.40) between Ki67 and RS, which was statistically significant (Kappa = 0.272, p < 0.001). Overall, using the FDA criteria for abemaciclib, 36.1% (n = 18,140) of patients would be eligible while based on ASCO criteria, 39.9% (n = 20,061) could be offered adjuvant abemaciclib (p < 0.001). Among the 20,061 patients eligible for abemaciclib based on ASCO criteria, 57.4% (n = 11,513) were eligible due to Ki67 ≥ 20% alone, 9.6% (n = 1,921) due to Grade 3 alone, while 33.0% (n = 6,627) satisfied both Ki67 ≥ 20% and Grade 3 criteria. There were 33,789 patients who were post-menopausal with RS 0-25 and would be spared chemotherapy, yet 32.1% (n = 10,856) would be eligible for adjuvant abemaciclib based on FDA or ASCO criteria.

Conclusions: There was only fair agreement between Ki67 and RS in patients with 1-3 +LNs on Ki67 cutoff of 20%. Among patients with LN+ EBC, more patients would be offered abemaciclib using ASCO criteria compared to FDA criteria. Most were eligible for abemaciclib based on Ki67 alone, suggesting that Ki67 may provide additional information beyond tumor grade. In postmenopausal women with 1-3 +LNs, about 30% may be spared adjuvant chemotherapy based on the RS but still be sufficiently high risk to be considered for adjuvant abemaciclib. Research Sponsor: None.
Influence of ovarian function suppression on quality of life in breast cancer survivors during adjuvant endocrine therapy.

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**Background:** Adding ovarian function suppression to adjuvant endocrine therapy (AET) lowers the disease recurrence rates among premenopausal women with hormone receptor-positive (HR+) early breast cancer (EBC). However, a detrimental effect on endocrine symptoms burden (ESB) is expected. Therefore, this study aimed to investigate differences in Quality of life (QoL) and endocrine symptoms in premenopausal women prescribed AET, with/without gonadotropin-releasing hormone agonist (GnRH).

**Methods:** This cross-sectional study included women, with HR+ EBC, premenopausal at diagnosis, treated with AET for more than 3 months, with and without GnRH. The research was conducted with institutional Ethics Committee approval at the University Hospital Centre Zagreb, General Hospital Sibenik, and with online survey. A validated instrument, the Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES), was used. The collected data were analysed using SPSS v. 29 (p=0.05).

**Results:** Overall, 314 eligible BC survivors with a median age of 45 years (22-65) and a median duration of AET of 2 years (3 months -12 years) responded to FACT-ES and were included in the analysis. Altogether 45.2% (n=142) of participants were prescribed tamoxifen (TAM), 25.8% (n=81) GnRH+TAM, and 29% (n=91) GnRH+aromatase inhibitor (AI); exemestane (9%), letrozole (13.6%) and anastrozole (6.4%). The total QoL (FACT-ES) score was higher in patients treated with TAM as opposed to patients treated with AI+GnRH (p=0.01). Adding GnRH to TAM did not significantly change QoL when compared to TAM alone or AI+GnRH. In addition, patients on AI+GnRH had lower physical well-being (PWB) score than patients on TAM-GnRH (p=0.03) or TAM alone (p=0.05) and lower endocrine subscale score (ESS-19) than patients on TAM (p=0.01), indicating more endocrine symptoms in premenopausal women treated with AI+GnRH. Among patients treated with AI+GnRH letrozole had lower PWB (p=0.03) and ESS-19 score (p=0.01) than exemestane.

**Conclusions:** This study showed that GnRH+AI in premenopausal women with HR+ EBC results in greater ESB and lower QoL compared to patients treated with TAM or GnRH+TAM. Therefore, interventions helping decrease the ESB in patients treated with AI+GnRH should be explored and developed to help patients adhere to and persist in AET.

<table>
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<tr>
<th>Subscale score - mean (SD)</th>
<th>TAM</th>
<th>GnRH+TAM</th>
<th>GnRH+AI</th>
<th><em>p</em>-value</th>
<th>Tukey HSD post-hoc test</th>
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<td>PWB</td>
<td>21.15 (6.30)</td>
<td>21.62 (5.21)</td>
<td>19.23 (6.21)</td>
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<td>GnRH+TAM – GnRH+AI, p=0.03, TAM – GnRH+AI, p=0.05</td>
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<td>SWB</td>
<td>21.26 (5.88)</td>
<td>21.32 (5.10)</td>
<td>20.61 (5.64)</td>
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<td>EWB</td>
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<td>18.06 (4.30)</td>
<td>16.91 (5)</td>
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<td>FWB</td>
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<td>18.35 (4.47)</td>
<td>17.09 (4.65)</td>
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<tr>
<td>ESS-19</td>
<td>54.50</td>
<td>52.43 (11)</td>
<td>49.75</td>
<td>0.01</td>
<td>TAM - GnRH+AI, p=0.01</td>
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<td>FACT-ES</td>
<td>132.91</td>
<td>131.78</td>
<td>123.39</td>
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<td>TAM - GnRH+AI, p=0.01</td>
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</table>

*One-way ANOVA.
Social well-being (SW), emotional well-being (EWB), functional well-being (FWB).

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Background: Primary squamous cell carcinoma (SCC) of the breast is a rare disease, accounting for about 0.1% of all breast cancers. We aimed to determine the clinical features and prognosis of breast SCC, and the effect of radiotherapy by biological subtypes using the Japanese Breast Cancer Registry.

Methods: We conducted a matched-pair analysis of 350,977 breast cancer patients with SCC or invasive ductal cancer (IDC) in the Japanese Breast Cancer Registry between 2004 and 2014. Inclusion criteria were female breast cancer patients who underwent surgery with stage I–III diseases, SCC or IDC, and age ≥ 18. Patients who received preoperative radiotherapy were excluded. We performed 1:1 SCC-IDC exact matching analysis by predominant subtypes in SCC: ER(-) and PgR(-)/HER2(-) or ER(+) and/or PgR(+)HER2(-). Overall survival (OS), breast cancer-specific survival (BCSS), recurrence-free survival (RFS), and first locoregional or distant metastasis recurrence incidence were compared between IDC and SCC by Kaplan-Meier methods and log-rank test. In-field area recurrence was compared between those who received radiotherapy and those who did not.

Results: We included 452 SCC and 182,707 IDC patients for the analysis. SCC patients were more likely to present with advanced stage disease compared to those with IDC. Among SCC patients, 59% was ER(-)/PgR(-)/HER2(-), 19% was ER(+)/PgR(+)HER2(-), 8% was ER(-)/PgR(-)/HER2(+), 2% was ER(+)/PgR(+)/HER2(+), and 12% was data missing. Ten-year OS, BCSS, and RFS rates were 70%, 80%, and 66% in SCC, and 88%, 93%, and 81% in IDC, respectively, and SCC carried a significantly worse prognosis than IDC (all P < 0.001). For exact-matched analysis, 10-year BCSS of ER(-)/PgR(-)/HER2(-) SCC patients was significantly worse than IDC (P = 0.02), whereas there were no significant differences between SCC and IDC of ER(+)/PgR(+)HER2(-) patients in OS, BCSS, and RFS. Among patients who received radiotherapy, no difference was found in in-field area recurrence between SCC and IDC in either ER(-)/PgR(-)/HER2(-) or ER(+)PgR(+)/HER2(-) subtype. Conclusions: SCC of the breast was often diagnosed in an advanced stage and had a worse prognosis than IDC. More than half of them were triple-negative subtype. In the triple-negative subtype, SCC was an independent poor prognostic factor. No significant differences in in-field area recurrence after radiotherapy between SCC and IDC suggested that the effect of radiotherapy on local control for SCC was similar to IDC. Research Sponsor: None.
Background: The incidence of young Asian women with breast cancer has been increasing but these patients are underrepresented in global data. We analyzed the epidemiology and outcomes of the young Asian patients with breast cancer in different subtypes with clinically unmet need. Methods: Female patients of age 20 years or older diagnosed with early breast cancer of stage I, II, or III from the prospective cohort of the Asian Breast Cancer Cooperative Group (ABCCG) were analyzed. For comparison, data of patients with early breast cancer from Surveillance, Epidemiology, and End Results Program (SEER) cancer registry was used. The patients were divided into three age groups: young (below 40 years), alleged premenopausal mid-age (40-49 years), and alleged postmenopausal elderly (50 years and older). Multivariable Cox proportional-hazard models for survivals were adjusted with age, subtypes consisting of hormone receptor (HR) and human epithelial growth factor receptor 2 (HER2) status, histologic grade, T stage, nodal status, and countries. Patients diagnosed in 2000–2010 were censored at 6 years for comparability with SEER database. Results: Total 45,021 patients with breast cancer from Asian countries, 496,332 of SEER Whites and 18,279 from SEER non-Whites were included. The median age at diagnosis was younger in Asians compared to SEER Whites and non-Whites (51, 62, 58 years, respectively). Among subtypes, HR-positive and HER2-negative breast cancer was more frequent among SEER Whites and SEER non-Whites, compared to Asians (75.89%, 73.38% vs. 65.75%, respectively). In the young group, HR-positive and HER2-negative breast cancer was prevalent in Asians and SEER non-Whites, compared to SEER Whites (61.2% and 59.8% vs. 54.7%, respectively). In the elderly group, the proportion of HR-positive breast cancer increased in SEER Whites, while that of triple-negative breast cancer (TNBC) increased in Asians. Elderly group showed the worst survival in all subtypes and in all populations. In Asian population, the mid-age group of the patients with HR-positive and HER2-negative breast cancer showed significantly superior overall survival (OS) than the young group (6 year OS 96.6% vs. 94.4%; hazard ratio 0.62, 95% confidence interval 0.50-0.76; p<0.001). Similarly, young patients in SEER Whites also showed early decline of survival curve compared those in mid-age group (89.1% vs. 94.0%, p<0.001), while young patients of SEER non-Whites showed equivalent prognosis to those in mid-age group (92.4% vs. 95.0%, p=0.118). Conclusions: Young Asian breast cancer patients diagnosed with HR-positive and HER2-negative subtypes, but not HER2-positive or TNBC subtypes, are more likely to have worse survival outcomes than those in mid-age. Further studies on young patients with breast cancer are needed for tailored treatments among different subtypes and ethnic groups. Research Sponsor: None.
Association of human epidermal growth factor receptor 2 expression with 21-gene recurrence score and survival among patients with estrogen receptor–positive breast cancer.

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**Background:** Trastuzumab-deruxtecan was recently shown to improve survival for metastatic human epidermal growth factor receptor 2 (HER2)-low breast cancer. HER2-negative breast cancer has been redefined as a group of heterogeneous entities. However, HER2-low status is not considered as a prognostic factor among patients with nonmetastatic breast cancer, and the role of HER2 expression levels in the setting of 21-gene recurrence score (RS) remains unclear. We performed an observational cohort study using a national oncology database to evaluate the association of HER2 expression levels with RS and survival among patients with estrogen receptor (ER)-positive breast cancer. **Methods:** The National Cancer Database was queried for women diagnosed between 2006 and 2018 with ER-positive, pT1-3N0-1aM0 breast cancer who received surgery followed by adjuvant endocrine therapy with or without chemotherapy. HER2 expression levels were stratified by 3 groups: HER2-0 (immunohistochemistry [IHC] 0), HER2-1 (IHC +1), and HER2-2 (IHC +2 and in situ hybridization [ISH] negative). Logistic and Cox multivariable analysis (MVA) were used to identify factors associated with high RS (26 or higher) and overall survival (OS), respectively. Interaction term was analyzed to evaluate any heterogeneous associations in survival outcomes between HER2 levels and RS. Subgroup analysis was performed by repeating Cox MVA stratified by RS. Holm-Bonferroni correction was used to adjust for multiple comparisons, with p value less than 0.05 considered as statistically significant. **Results:** Among 108,973 women, 31,738 (29.1%), 52,839 (48.5%), and 24,396 (22.4%) patients had HER2-0, HER2-1, and HER2-2, respectively. Logistic MVA showed that, compared to HER2-0, HER2-2 was associated with higher RS (adjusted odds ratio [aOR] 1.09, 95% confidence interval 1.04-1.15, p < 0.001), but HER2-1 was not (aOR 0.96, 95% CI 0.91-1.00, p = 0.05). Cox MVA showed that both HER2-1 (adjusted hazards ratio [aHR] 1.03, 95% CI 0.97-1.10, p = 0.34) and HER2-2 (aHR 1.06, 95% CI 0.98-1.14, p = 0.14) were not associated with OS. There was an interaction between HER2 expression levels and RS (interaction p = 0.03). Among those with RS < 26, compared to HER2-0, HER2-2 was associated with worse OS (aHR 1.10, 95% CI 1.01-1.20, p = 0.02), but HER2-1 was not (aHR 1.04, 95% CI 0.97-1.12, p = 0.24). Among those with RS 26 or higher, both HER2-1 (aHR 1.00, 95% CI 0.88-1.13, p = 0.98) and HER2-2 (aHR 0.94, 95% CI 0.82-1.09, p = 0.41) were not associated with OS. **Conclusions:** To our knowledge, this is the largest study using nationwide oncology database to suggest that, when compared to HER2-0, HER2-2 was associated with higher RS and poor survival among patients with RS < 26. Further studies would be warranted to evaluate the role of HER2 expression levels for risk stratification to tailor interventions. Research Sponsor: U.S. National Institutes of Health.
Impact of race on BluePrint genomic subtyping in HER2+ breast cancer.

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Background: Breast cancer (BC) is the leading cause of cancer-related deaths in Black women, who are 41% more likely to die than White women. We’ve recently reported that Black women have a significantly greater proportion of hormone receptor-positive (HR+) tumors further classified as Basal-Type with BluePrint genomic subtyping, which may contribute to their worse outcomes. Here, we evaluated whether there were differences in tumor genomics among patients with clinically assessed HER2+ (cHER2) tumors between Black and White women. Methods: This study includes 204 women with stage I-III cHER2 BC who received BluePrint testing and are participants of the BEST study (5R01CA204819) at Vanderbilt University Medical Center or FLEX study (NCT03053193). Patients were treated per NCCN guidelines based on immunohistochemistry (IHC)/FISH classification. cHER2 tumors were further classified by BluePrint, an 80-gene molecular subtyping test, as Luminal-Type (gLuminal), HER2-Type (gHER2), or Basal-Type (gBasal). White women within FLEX were matched by age, tumor and node status and included as a reference group. A two-tailed proportional z-test was used to assess BluePrint subtype differences. Limma R package was used for differential gene expression analysis (DGEA) of whole transcriptome data. Significant differentially expressed genes had an adjusted p-value < 0.05 and absolute log2 fold change > 1. Results: Of 102 Black women with cHER2 tumors, 59 had gHER2, 34 had gLuminal and 9 had gBasal tumors, and of 102 White women, 63 had gHER2, 28 had gLuminal and 11 had gBasal tumors. There were no significant differences in the frequency of BluePrint subtypes or in gene expression by race among cHER2 tumors. All gHER2 tumors had upregulated HER2 signaling compared to upregulated estrogen signaling genes in gLuminal tumors, and upregulated genes characteristic of metastasis and triple negative tumors in gBasal tumors. Among patients with available neoadjuvant treatment response data, 57.1% (16/28) gHER2, 33.3% (2/6) gLuminal and 50.0% (3/6) gBasal achieved a pathologic complete response (pCR). Conclusions: Unlike HR+HER2- tumors, these data suggest that race may not influence the biology underlying cHER2 tumors. However, there was genomic heterogeneity among cHER2 tumors identified by BluePrint, independent of race. Overall, the rate of BluePrint classification among cHER2 tumors was comparable to NBRST and APHINITY, which demonstrated distinct treatment response and outcome based on BluePrint genomic subtype. In this study, DGEA suggests gHER2 tumors exhibit extensive HER2 signaling and may benefit most from HER2-targeted therapy. Although limited by sample size, rates of pCR to neoadjuvant therapy appear greater in gHER2 than non-HER2 tumors (gLuminal, gBasal). gBasal tumors may harbor more aggressive tumor characteristics, which has important clinical implications for optimizing treatment and improving outcomes in these patients.

Research Sponsor: U.S. National Institutes of Health; Agendia.
Lipidomic signature from plasma to detect localised breast cancer.

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Background: An effective and accurate blood test to detect localised breast cancer may increase the screening detection rate and improve patient outcomes. We have previously reported a series of lipidomic studies and derived a lipid signature from plasma enriched extracellular vesicles (EVs) that effectively distinguished people with localised breast cancer from cancer-free controls. Here we report on a significant refinement to the test methodology allowing the assessment of the lipid signature directly from plasma samples and its performance, with the aim of advancing the commercial viability of the test as we move towards clinical application. Methods: Lipids were extracted from enriched EVs from plasma samples donated by fasted people with localised breast cancer and control samples (n=793) and analysed by high resolution accurate mass liquid chromatography-mass spectrometry (LC-MS). Over 400 manually curated lipids were quantified. Following variable selection, a lipid signature capable of distinguishing breast cancer samples from controls was derived. The lipid signature was modelled on each of the cohorts using leave-one-out internal cross-validation. Next, we analysed the lipids in cancer and control (n=256) plasma samples corresponding to patients from Cohorts 3 and 4 previously used for EV preparations, and applied the signature derived using EVs on plasma lipidomic data. Results: EV samples of people with breast cancer were distinguished from controls with an area under the curve (AUC) of 0.77-0.89 across 4 cohorts. When the lipid signature was assessed directly from plasma the test achieved a comparable AUC of 0.84. Assessing the markers directly from plasma samples would make the test more scalable, higher throughput and easier to perform. Conclusions: Our study demonstrated the high performance of a lipid biomarker signature derived from plasma enriched EVs for early detection of localised breast cancer. Our results suggest that the lipidomic signature could potentially be assessed directly from plasma samples instead of EVs reducing the test complexity. Ongoing studies will optimise the plasma lipidomic signature and prospectively compare the test against mammographic and pathological diagnoses. Research Sponsor: BCAL Diagnostics Limited.

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AUC | 0.89 | 0.77 | 0.88 | 0.88 | 0.88 | 0.84 |
Correlation of gene signatures of Kaiso and LC3A/B protein expression with distinct tumor ecosystems and to predict response to breast cancer therapy.

Sandeep K. Singhal, Kevin Gardner; Department of Pathology, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND; Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY

Background: The multifunctional transcriptional repressor, Kaiso, is a member of the BTB/POZ (Broad complex, Tramtrak, Bric `aBrac/Pox zinc finger) family of zinc finger proteins. Kaiso protein levels in both the nucleus and the cytoplasm have each been shown to be highly sensitive and independent predictors of overall breast cancer survival. Through the use of gene signatures and/or gene modules developed through the analysis of RNA-seq data from breast cancer patients following biomarker stratification by either nuclear Kaiso, cytoplasmic Kaiso, or the Kaiso’s functional downstream target LC3A/B, we demonstrate the utility of Kaiso and LC3A/B derived signatures as predictors of treatment outcome. Methods: We used a machine Learning approach to assess a cohort of racially diverse 555 BC patients who underwent surgery for their primary BC in Greenville, NC and develop proteomics-based genomics (PbG) signatures. The cross-validated logistic regression modeling using publicly available gene expression data compiled from neoadjuvant clinical trials (N=996, JCO:30(16):1996-2004). Results: Kaiso and LC3A/B derived gene modules show accuracy in predicting pathological complete response (pCR, AUC = 0.728, 95% CI: 0.689-0.764). Moreover, predictive estimates of distant metastasis-free survival utilizing Kaiso and LC3A/B derived gene modules are also significant (overall DMFS, AUC= 0.737, 95% CI: 0.665-0.819) and (DMFS of non-pCR patients AUC= 0.71, 95% CI: 0.633-0.773). We then validate these findings in an independent, racially diverse breast cancer cohort receiving neoadjuvant treatment (N=443). Gene modules based on Kaiso and LC3A/B were also highly predictive in this independent cohort (total cohort pCR, AUC= 0.775, 95% CI: 0.687-0.838; pCR NHW (N=257), AUC= 0.762, 95% CI: 0.659-0.855; pCR Hispanic (N=125), AUC= 0.725, 95% CI: 0.493-0.873; and pCR NHB (N=42), AUC= 0.681, 95% CI:0.405-0.904). Conclusions: Combined analysis by multiplex immunofluorescence and deconvolution of gene expression data show that the protein expression of Kaiso and LC3A/B in tumors are associated with distinct tumor ecosystems where high levels cytoplasmic Kaiso are linked to an immune-suppressed tumor microenvironment. Research Sponsor: U.S. National Institutes of Health.
Association of anthracyclines induced cardiotoxicity (AIC) in patients with early breast cancer (eBC) with germline BRCA1/2 (gBRCA1/2) mutation: BRCAN study.

Juan José Serrano Domingo, David Cordero, Miriam Menacho, Jose Manuel del Rey, Jesús Chamorro, Diana I. Rosero, Pilar Sotoca, Laura del Campo, Gonzalo Alonso, Cristina Saavedra Serrano, María Fernández-Abad, Maria Gion Cortes, Eva M. Guerra, Noelia Martínez-Jañez, Elena Lopez-Miranda, Elena Maria Vida Navas, Raquel Fuentes Mateos, CARMEN GUILLEN PONCE, María Teresa Salazar, Alfonso Cortés Salgado; Medical Oncology Department, Ramón y Cajal University Hospital, Madrid, Spain; Cardiology Department, Ramón y Cajal University Hospital, Madrid, Spain; Biochemistry Department, Ramón y Cajal University Hospital, Madrid, Spain; Clinical Biostatistics Unit, Ramón y Cajal University Hospital, Madrid, Spain; Cardiology Department, Hospital Universitario de Navarra, Navarra, Spain; Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain

Background: BRCA1/2 genes play a critical role in genome stability and DNA repair in human cells, including cardiomyocytes. In animal models, loss of cardiomyocyte-specific BRCA1/2 is associated with DNA damage, apoptosis, cardiac dysfunction, and cardiac mortality following anthracyclines (A) exposure. However, whether these preclinical findings translate to humans still remains unclear. We conducted the BRCAN study to assess the impact of gBRCA1/2 status on AIC in a cohort of patients with eBC.

Methods: This is a single center retrospective/prospective study including patients diagnosed with HER2-negative eBC treated with A based chemotherapy in the neo/adjuvant setting, known gBRCA1/2 status, left ventricular ejection fraction (LVEF) ≥ 50% at baseline and no previous significant cardiovascular events. During follow-up, we performed myocardial dysfunction blood biomarkers (MDBB), cardiac ultrasound and quality of life questionnaires (QoL). Primary objective was to assess the absolute LVEF change from baseline in BRCA1/2 mutation carriers (gBRCA1/2mut) versus non-carriers (gBRCA1/2wt). Secondary objectives were comparing MDBB and QoL in these groups. Results: 137 patients with eBC were included in the study (103 gBRCA1/2wt and 34 gBRCA1/2mut). Patients' characteristics were similar between both groups in terms of age, baseline LVEF, radiotherapy (RT) on left side, total A accumulative dose, time from A exposure, antihypertensive or hypolipidemic agents use and smoking habit. Compared to baseline, LVEF % reduction was -4.7 [-12.0, 0.0] versus -9.5 [-18.0, -5.0] in gBRCA1/2wt and gBRCA1/2mut, respectively (p=0.027). To correct for confounding, we fit a regression model for the variables smoking habit, antihypertensive and hypolipidemic agents use and smoking habit. Compared to baseline, LVEF % reduction was -4.7 [-12.0, 0.0] versus -9.5 [-18.0, -5.0] in gBRCA1/2wt and gBRCA1/2mut, respectively (p=0.027). To correct for confounding, we fit a regression model for the variables smoking habit, antihypertensive and hypolipidemic agents use and smoking habit. On average, LVEF % reduction in gBRCA1/2mut group was -4.5 [-8.6, -0.4, p=0.032] compared to gBRCA1/2wt. No differences between MDBB (protein C-reactive, hsTn, NT-ProBNP, D-Dimer, ST-2 or Galectine-3) and QoL (MLHFQ and EQ5-D index) were detected between groups.

Conclusions: Our data suggest that gBRCA1/2mut patients could represent a high risk population for AIC. A baseline comprehensive cardiovascular risk assessment and a closer follow-up should be recommended in these patients. Further research is needed on order to identify early predictive biomarkers for AIC. Research Sponsor: Instituto Ramón y Cajal de Investigación Sanitaria.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>gBRCA1/2wt</th>
<th>gBRCA1/2mut</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age*</td>
<td>49.1 (29.3)</td>
<td>43.2 (10.2)</td>
<td>0.126</td>
</tr>
<tr>
<td>RT on left side</td>
<td>42 (40.8%)</td>
<td>10 (29.4%)</td>
<td>0.118</td>
</tr>
<tr>
<td>Total dose Adriamycin*</td>
<td>237.4 (41.5)</td>
<td>250.8 (35.8)</td>
<td>0.109</td>
</tr>
<tr>
<td>Total dose epirubicin**</td>
<td>325 (77.9)</td>
<td>400 (124.9)</td>
<td>0.148</td>
</tr>
<tr>
<td>Exposition time (years)*</td>
<td>7.5 (4.6)</td>
<td>8.3 (5.2)</td>
<td>0.203</td>
</tr>
<tr>
<td>Initial LVEF (%)</td>
<td>68.5 (6.7)</td>
<td>68.9 (8.3)</td>
<td>0.380</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>14 (13.6)</td>
<td>1 (2.9)</td>
<td>0.109</td>
</tr>
<tr>
<td>Hypolipidemic</td>
<td>25 (24.3)</td>
<td>6 (17.6)</td>
<td>0.569</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>17 (17.2)</td>
<td>5 (14.7)</td>
<td>0.824</td>
</tr>
</tbody>
</table>

*Mean (standard deviation); **mg/m².
Comprehensive profiling of mutational signatures and machine learning and subtypes of homologous recombination deficiency.

Joonoh Lim, Seongyeol Park, Ryul Kim, Baek-Lok Oh, Sangmoon Lee, Jeong Seok Lee, Ji In Ryu, Jai Min Ryu, Se-Kyung Lee, Byung-Joo Chae, Jeongmin Lee, Ji-Yeon Kim, Yeon Hee Park, Young Seok Ju; Genome Insight Inc., San Diego, CA; Research Institute for Future Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Division of Breast and Endocrine Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University, School of Medicine, Seoul, South Korea; The Catholic University of Korea Seoul St. Mary’s Hospital, Seoul, South Korea; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Samsung Medical Center, Seoul, South Korea

**Background:** Recently, genomic features have proven effective at gene-agnostic detection of homologous recombination deficiency (HRD). However, it remains to be explored to what extent we can exploit genome analysis to assess HRD status. Here, we show that a machine learning (ML) classifier based on mutational signatures enables a robust detection and subtyping of HRD and outperforms a current state-of-the-art HRD classifier.

**Methods:** We whole-genome-sequenced (WGS) ~700 breast cancers and identified pathogenic variants in HR-related genes (*BRCA1/2, PALB2, CHEK2, RAD51B, ATM*, etc.). Mutational signatures of all variant types, single-base substitution (SBS), indel (ID), structural (SV) and copy-number variant (CN), were included as features. Biallelic inactivation in *BRCA1/2* by germline pathogenic variant and somatic loss-of-heterozygosity (LOH) was regarded as true HRD. We trained four different classifiers with *n*-fold cross validation and used averaged scores for prediction. In addition, we performed cluster analysis and subgroup analysis within the predicted HRD cases to unveil the heterogeneity of HRD.

**Results:** We identified a total 88 (12%) germline pathogenic variant carriers with somatic LOH, including 29 *BRCA1* (4%), 28 *BRCA2* (4%), 4 *PALB2* (0.6%), and 3 *RAD51B* (0.4%). Among them, 70 (80%) were classified as HRD positives. As expected, most *BRCA1* (28/29) and *BRCA2* (28/28) cases were HRD-positive. All the *PALB2* (4/4) and *RAD51B* (3/3) cases were also classified as HRD-positive, confirming their importance in HR. Inclusion of somatic *RAD51B* biallelic mutants (10; 1.4%) reached a statistical significance for the HRD enrichment (Fisher’s; P = 0.045). We identified a total 171 (24%) having at least one somatic pathogenic variant with LOH, including 57 *PTEN* (33%), 40 *CDK12* (23%), 17 *RAD51B* (10%), 17 *ARID1A* (10%), and 15 *BRIP1* (9%). 72 of these (42%) were classified as HRD-positive. Our classifier identified 12 (7%) more HRD cases than HRDetect (167 vs. 155; F1 = 0.99 vs. 0.95) using signature ID6, SV3 (or RS3), LST, and SBS3. Further, it correctly identified *BRCA1* (33/34) and *BRCA2* (27/28) somatic and germline biallelic mutants from each other (F1 = 0.97), based on RS3, ID6, RS1, and SBS3. Features of *RAD51B* were similar to *BRCA1*, and *PALB2* to *BRCA2*, but our classifier was able to distinguish *PALB2* from *BRCA2* using a combination of CN11, ID11, LOH, CN8, and SBS40 (F1 = -1). Total 112 (67%), 48 (29%), and 7 (4%) cases were identified as *BRCA1*-like, *BRCA2*-like, and *BRCA1/2*-like, among which 47 (28%) were monoallelic HR-gene mutants and 27 (16%) were wild types. Our results suggest that mutational signatures can identify ~40% (47/120) more HRD cases than using mutation profile alone.

**Conclusions:** We believe that the method developed here, using ML to detect and classify HRD, will benefit from larger WGS data and identify more patients who can benefit from HRD-related therapeutics. Research Sponsor: Genome Insight Inc.
ERBB2 mRNA expression to distinguish HER2-low/neg breast cancer prognosis.

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Background: Antibody-drug conjugates such as Trastuzumab deruxtecan significantly improved progression-free and overall survival for the HER2 low expression (HER2-low) breast cancer (BC) patients, pushing the research field of HER2-low to a new climax. In fact, the traditional immunohistochemistry (IHC) to identify the HER2-low or HER2-negative expression (HER2-neg) has been challenged, and it cannot predict the prognosis of HER2-low/neg patients well. Methods: Three pathologists evaluated the HER2 expression status of the subjects via IHC. More than two pathologists judged HER2 0-2 and FISH negative samples were included in this trial. ERBB2 mRNA level of formalin-fixed, paraffin-embedded BC post-surgery specimens were detected by MammaTyper quantitative real-time polymerase chain reaction (qRT-PCR) kit. The consistency of HER2 immunohistochemistry (IHC) and MammaTyper results were analyzed by interclass correlation coefficients (ICC). Differences in disease-free survival (DFS) were assessed by Kaplan Meier analysis. Results: 793 cases were included. The ICC value between IHC and MammaTyper, assessed for HER2-neg vs HER2-low is 0.28. With a median follow up of 2.5 years, there were 36 events in the whole subjects. In the whole subjects, MammaTyper successfully showed that the prognosis of HER2-low was significantly better than HER2-neg (P < 0.001, HR = 3.497, 95%CI,1.807-6.77), but IHC could not distinguished them (P = 0.1071, HR = 1.776, 95%CI, 0.9194-3.43). Although the follow-up time is short, HER2-low subjects also showed better prognosis than HER2-neg in TNBC subjects distinguished by MammaTyper (P = 0.0271, HR = 2.912, 95%CI,1.129-7.511), not by IHC (P = 0.1032, HR = 2.213, 95%CI, 0.8512-5.756). However, in 291 cases of IHC and MammaTyper detection discordancy group, IHC results showed that the prognosis of HER2-low was worse, which was contrary to the MammaTyper results and the results of the above overall test results, suggesting that IHC could not verily reflect the amount of HER2 expression in some samples, and the prognosis of HER2-low population might be more related to the mRNA expression of HER2. Conclusions: Compared with IHC/FISH, MammaTyper qRT-PCR assay may actually reflect the prognosis of HER2-neg/low, which is expected to become a diagnostic beacon for HER2-low target drugs. Research Sponsor: None.
Do HER2 low tumors have a distinct clinicopathologic phenotype?

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Background: Clinicopathologic features of breast cancer subtypes defined by hormone receptor (HR) and HER2 status differ. These analyses classified HER2 IHC <3+ with negative FISH as HER2-. With the recognition of the clinical relevance of HER2 low, there is debate as to whether this is a distinct subtype. We sought to determine if features of HER2 low tumors differ from HER2- and HER2+ after controlling for HR status. Methods: Patients undergoing upfront surgery from 1998 to 2010 were identified from a prospectively maintained institutional database. HER2 status was classified by IHC/FISH analysis as HER2-, HER2 low (IHC 1+ or 2+ with negative FISH), and HER2+ (IHC 3+ or FISH +) and stratified by HR status. Univariable (UVA) and multivariable multinomial logistic regression analysis (MVA) were performed to determine associations among variables and subtypes.

Results: 11,323 tumors from 11,072 patients were included. 5,104 (45%) were HER2 low, 41.2% were HER2- and 13.6% were HER2+. On MVA stratified by HER2 status only, compared to HER2- tumors, HER2 low was associated with LVI (OR 1.2 [95% CI 1.06-1.36]; p=.003), multifocality (OR 1.26 [95% CI, 1.12-1.42]; p<.001), nodal micrometastasis (OR 1.15 [95% CI, 1.02-1.31]; p=.024), and lower rates of <3 positive nodes (OR 0.77 [95% CI, 0.66-0.90], p=.001). HER2+ was associated with younger age, high grade, multifocality, extensive intraductal component (EIC), and pN2/3 nodal stage. Clinicopathologic features stratified by HR and HER2 status are shown in the table. On UVA, in both HR+ and HR- tumors, age and multifocality were associated with HER2 low, and LVI, multifocality, and EIC with HER2+ compared to HER2- tumors. On MVA, no variables were independently associated with both HR+ and HR-/HER2 low tumors compared to HER2-. In contrast, HER2+ tumors regardless of HR status were significantly associated with multifocality and EIC. Conclusions: HER2 low breast cancer features seem to be driven by HR status and HER2 overexpression. We do not have enough evidence to support the interpretation of HER2 low as a distinct subtype. Research Sponsor: Memorial Sloan Kettering Cancer Center.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR+</th>
<th>HR-</th>
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<tbody>
<tr>
<td>Median age</td>
<td>58</td>
<td>53</td>
</tr>
<tr>
<td>(IQR)</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>LVI</td>
<td>968</td>
<td>53</td>
</tr>
<tr>
<td>(25)</td>
<td>440</td>
<td>61</td>
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<tr>
<td>High grade</td>
<td>1,666</td>
<td>765</td>
</tr>
<tr>
<td>(46)</td>
<td>815</td>
<td>0.14</td>
</tr>
<tr>
<td>Multifocal</td>
<td>961</td>
<td>756</td>
</tr>
<tr>
<td>(25)</td>
<td>444</td>
<td>506</td>
</tr>
<tr>
<td>EIC</td>
<td>347</td>
<td>477</td>
</tr>
<tr>
<td>(15)</td>
<td>171</td>
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<td>Nodal disease</td>
<td>2,304</td>
<td>463</td>
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<td>153</td>
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<tr>
<td>1-2+</td>
<td>668</td>
<td>15</td>
</tr>
<tr>
<td>≥ 3+</td>
<td>682</td>
<td>250</td>
</tr>
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</table>

p values from multinomial UVA.
Outcomes in premenopausal patients with HR+/HER2- breast cancer and lymph node micro-metastasis based on the 21-gene recurrence score.

Nadeem Bilani, Rima Patel, Amy Tiersten; Icahn School of Medicine at Mount Sinai Morningside-West, New York, NY; Icahn School of Medicine at Mount Sinai, New York, NY

Background: Postmenopausal patients with hormone receptor positive, HER2-negative (HR+/HER2-) early breast cancer (EBC) and 21-gene OncotypeDX (ODX) recurrence scores (RS) <26 do not benefit from chemoendocrine therapy (‘CET’) compared to endocrine monotherapy (‘E’). The TAILORx and RxPONDER trials demonstrated this was consistent in node-negative and node-positive disease, respectively. In premenopausal patients, however, guidelines for those with low RS diverge between disease involving 0 (pN0) vs. 1-3 (pN1a-c) lymph nodes. Additionally, treatment decisions are less clear for patients with micro-metastasis (pN1mi), who comprised only about 10% of patients in RxPONDER. This study used the National Cancer Database (NCDB) to assess treatment patterns and survival outcomes in premenopausal patients with EBC and lymph node micro-metastasis.

Methods: A cohort of patients aged <50, diagnosed between 2004-2019 with HR+/HER2- EBC and who underwent ODX testing, was recruited from the NCDB. (A) Firstly, we described demographic and clinical characteristics of a sub-cohort with micro-metastasis using univariate statistics. (B) We confirmed the prognostic value of ODX in this sub-cohort with multivariate Cox regression analysis of overall survival (OS). (C) We explored patterns of practice amongst the total cohort with ODX <26 with chi-squared testing for differences in CET use by nodal status. (D) To elucidate the predictive value of this assay, we performed Kaplan-Meier models comparing OS for those with RS <26 receiving E vs. CET, controlling granularly for nodal status: (i) pN1a-c, (ii) pN1mi, and (iii) pN0. Results: Of n=72,068 patients aged <50 with HR+/HER2- EBC and ODX data, 6.1% (n=4,402) had micro-metastasis. (A) The median age of this subgroup was 45 (IQR 41-47) years. Most tumors were grade II (n=2,472, 57.7%) with ductal histology (n=3,500, 80.3%). 73.4% of pN1mi cases had RS <26, while 26.6% had RS ≥26. (B) Multivariate Cox regression – adjusting for comorbidity, race and chemotherapy use – confirmed significance in this pN1mi cohort of RS ≥26 prognosticating poorer OS compared to RS 0-15 (HR 4.42, 95% CI 2.35-8.31, p<0.001). (C) 29.0% (n=1,033) of patients with pN1mi and ODX <26 underwent CET, greater than 15.2% (n=6,568) with pN0 and less than 47.3% (n=2,884) with pN1a-c staging (p<0.001). (D) A benefit in OS (p=0.017) was observed in cases with RS<26 and pN1a-c using CET (5-year OS: 99%) vs. E (5-year OS: 97.5%), but not in pN1mi (p=0.49) or pN0 (p=0.57) disease. Conclusions: The management of premenopausal patients with HR+/HER2- EBC, isolated micro-metastasis, and ODX <26 is unclear. Our large registry study found the addition of chemotherapy to endocrine therapy was associated with improved survival in cases with ODX<26 involving 1-3 lymph nodes, but not in node-negative or micro-metastatic disease. Prospective trials are needed to confirm these findings. Research Sponsor: None.
Clinical meaning of stromal tumor infiltrating lymphocytes (sTIL) in luminal early breast cancer.

Esmeralda García-Torralba, Alejandra Ivars-Rubio, Miguel Perez-Ramos, Esther Navarro Manzano, Noel Blaya-Boluda, Pilar de la Morena Barrio, Elisa Garcia-Garre, Gema Marin Zafra, Francisco Martinez-Diaz, Francisco Gomez Martinez, Javier Lopez-Robles, Beatriz Alvarez Abril, Elena Garcia Martinez, Francisco Ayala; Department of Hematology and Medical Oncology, Hospital Universitario Morales Meseguer, Murcia, Spain; Department of Pathology, Hospital Universitario Morales Meseguer, Murcia, Spain; Department of Pathology, University Hospital Reina Sofia, Murcia, Spain; Department of Hematology and Medical Oncology, Hospital G. Universitario Morales Meseguer, IMIB, Murcia, Spain

Background: Luminal breast cancer (BC) is associated with lower immune activation. Although stromal tumor infiltrating lymphocytes (sTIL) are a marker of better prognosis and response in hormone receptor (HR) negative tumors, sTIL predictive and prognostic implications are less clear in luminal BC. Further insights on the clinical correlations of immune microenvironment in luminal disease may facilitate therapeutic improvement and prognostic stratification in these patients. Methods: Observational and single-center cohort of 345 women with early luminal (HR positive, HER2 negative) BC (2012-2020) treated with chemotherapy. Pre-treatment sTIL were determined in the diagnostic biopsy following validated standard methods. The correlation between sTIL and other tumor characteristics were analyzed (Spearman’s Rho and Chi-squared tests). Association of sTIL with pathologic complete response (pCR) in patients treated with neoadjuvant chemotherapy (nCT) was evaluated with logistic regression models. Prognostic value of sTIL for overall (OS) or relapse free interval (RFI) was analyzed by Cox regression models. Results: Median age: 50 (range: 24-89); 48.1% premenopausal; 91.3% infiltrating ductal carcinoma; 30.1% grade 3; 87.2% progesterone receptor (PgR)+; 67.5% treated with nCT and 32.8% with adjuvant CT (aCT); 47.6% N0, 32.8% N1, 19.6% N2-3; median ki67: 30% (82.7% >10%). A 29% of patients showed sTIL=0%. Median sTIL infiltration was 5 (Q1-Q3 range [IQR], 0-10), with higher values in premenopausal (p=0.001), grade 3 (p=0.001), N+ (p<0.001) and luminal B tumors (defined as PgR- and/or grade 3 and/or Ki67>15%) (p=0.001). Ki67 was significantly correlated with sTIL (r:0.39; p=0.001). The percentage of sTIL was associated with pCR after nCT (OR: 1.045, 95%CI 1.02-1.07, p=0.001). No prognostic impact of sTIL for OS or RFI was found in luminal A tumors. In luminal B cases (n=286), any grade of lymphocytic infiltration (defined as sTIL >0%) was associated with a shorter RFI both in univariate (p=0.01) and multivariate Cox models (HR: 4.83, 95%CI 1.28-18.21, p=0.02), with a non-significant trend for poorer OS (p=0.06). Conclusions: In luminal BC, an increased level of sTIL is associated with luminal B subtype characteristics such as higher proliferation, higher tumor grade and nodal involvement. Lymphocytic infiltration has been found to be a predictor of pCR after nCT, but, in contrast with hormone receptor-negative BC, it is also associated with a poorer prognosis for recurrence and a trend towards worse overall survival in luminal B tumors. Research Sponsor: Instituto Salud Carlos III (Spain) (PI21/380); SEOM (Spanish Society of Medical Oncology).

Multivariate Cox model for RFI in luminal B breast cancer.

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
<th>Hazard ratio (HR)</th>
<th>95%CI HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size (mm)</td>
<td>0.023468</td>
<td>1.0237</td>
<td>1.011-1.037</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive nodes (number)</td>
<td>0.101474</td>
<td>1.1068</td>
<td>1.045-1.172</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PgR positive</td>
<td>-1.112061</td>
<td>0.3289</td>
<td>0.144-0.751</td>
<td>0.008</td>
</tr>
<tr>
<td>Ki67 (percentage)</td>
<td>0.009734</td>
<td>1.0098</td>
<td>0.990-0.992</td>
<td>0.277</td>
</tr>
<tr>
<td>sTIL &gt; 0%</td>
<td>1.575154</td>
<td>4.8315</td>
<td>1.282-18.211</td>
<td>0.019</td>
</tr>
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</table>
Phase II randomized window of opportunity trial evaluating cytotoxic and immunomodulatory effects of intratumoral INT230-6 in early stage breast cancer: The INVINCIBLE trial.

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Background: Most breast cancers are considered immunological cold and are therefore minimally responsive to immunotherapies. Local cytotoxic therapies can induce cell death, expose tumor antigens, provide adjuvants for anti-tumor immune priming, and potentially increase responsiveness to immunotherapies. We conducted a randomized, double blind, Phase 2 presurgical Window-Of-Opportunity trial for intratumoral (IT) INT230-6 (comprising VINblastine (VIN) Cisplatin (VIN)) evaluating clinical and Biological Effects in patients with early-stage operable Breast Cancer (the INVINCIBLE trialNCT04781725. The trial evaluated the immune response within the tumor and microenvironment in vivo after IT INT230-6 injections. Methods: Women with newly diagnosed and awaiting surgery for early-stage intermediate or high-grade ER+ T1-T2 invasive breast cancers were recruited to the trial. Participating patients were allocated (2:1) to IT injections of INT230-6 vs saline placebo, prior to resection. RNA profiling of the pre- (baseline biopsy) and post- treatment (surgical resection) tumours using the Ion AmpliSeq Transcriptome Human Gene Expression (Thermo Fisher Scientific) and DNA sequencing using a large (500 gene) comprehensive genomic profiling panel (OCAPlus,) was performed. Results: Significant tumor necrosis was observed in the majority of subjects injected with INT230-6. In the 60 pre-treatment biopsies profiled with OCAPlus, the genes most frequently mutated included PIK3CA (38%), TP53 (23%), CDH1 (22%) and TBX3 (17%). Frequent copy number changes were identified in CCND1 (23%), FGFR1 (18%), and CDH1 (17%). Gene expression analysis showed significant differential gene expression between the baseline biopsy and surgical specimens in patients treated with the drug. Pathway analysis identified genes associated with TCR signaling, macrophage markers, IL-18 signaling and B cell receptor signaling were significantly up-regulated in the post treatment samples. Conclusions: This is the first study evaluating the potential biologic effects of intratumoral cytotoxicity with INT230-6 and its role as a potential immune priming therapy in traditional immune quiescent ER+ breast cancers. Research Sponsor: INTENSITY.
Background: Guidelines recommend the use of genomic assays to aid decision making regarding the use of adjuvant chemotherapy (CT) for hormone receptor-positive, HER2-negative (HR+/HER2-) early breast cancer (EBC). Recently, the RSClin tool, which integrates the 21-gene recurrence score (RS) and clinicopathologic features, was developed to better estimate CT benefit. Here, we studied patients with RSClin/RS discordance to determine if patients (pts) should be treated according to RS or RSClin.

Methods: This was a retrospective cohort study of pts from the National Cancer Database who were diagnosed with HR+/HER2- node negative EBC from 2010-2020 who underwent RS testing and received adjuvant endocrine therapy with or without CT. Pts were classified as low RS (< 26) or high RS (≥ 26) and low (< 3%) versus high (≥ 3%) predicted CT benefit per RSClin. The primary outcome was overall survival (OS) benefit associated with CT administration for pts with discordant RS/RSClin, measured as hazard ratio (HR) for receipt of CT. Hazard ratios were adjusted for age and comorbidity index, and inverse probability of treatment weighting was performed for age, comorbidity index, race, ethnicity, and insurance status. Results: 262,748 pts with EBC were included, with a median follow-up of 58 months. Median age was 60 years; 82% were White, 7% Black, 5% Hispanic, and 4% Asian/Pacific Islander. Median tumor size was 1.5 cm, and median RS was 15. The 31,955 cases with concordant high RS/RSClin had an OS benefit with CT (HR: 0.71, 95% CI: 0.67 - 0.75, p < 0.001), while the 206,631 cases with concordant low RS/RSClin did not have a survival benefit (HR: 1.00, 95% CI: 0.95 - 1.04, p = 0.85, Table). High RS with low RSClin was seen in 435 cases – all with grade 1 tumors, with RS no greater than 28, and tumor size under 1.3cm. No significant CT benefit was seen in this small subset of pts (HR 1.57, 95% CI 0.75 – 3.26, p = 0.23). In 23,727 pts with low RS but high RSClin, a CT benefit was seen (HR 0.73, 95% CI 0.67 – 0.78, p < 0.001). These pts had high-intermediate RS (median 23, interquartile range 20 – 24) with other higher risk features. Similar results were seen in older (age ≥ 50) and younger (age < 50) subgroups – although no pts ≤ 50 were in the low RS/high RSClin group. Conclusions: RSClin may identify a small number of grade 1 tumors with high RS for which CT is not needed, and may help guide appropriate use of CT for EBC in the sizeable group with intermediate RS. Research Sponsor: U.S. National Institutes of Health.
Impact of HER2 low expression in the Oncotype DX RS in patients with operable hormone receptor positive early stage breast cancer.

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Background: Two thirds of breast carcinomas are human epidermal growth factor receptor 2 (HER2) low. To date, it is still unclear whether hormone receptor (HR) positive HER2 low tumors represent a distinct biological subtype. HER2 low status is not considered an independent predictive factor for benefit from adjuvant chemotherapy in HR positive early breast cancer. We aim to investigate the impact of HER2 low expression on the established predictive biomarker Oncotype DX RS in a cohort of patients with HR positive HER2 negative early breast cancer.

Methods: Retrospective study of patients with stage I-III HR positive HER2 negative breast cancer treated with upfront surgery between 2019-2022 at the Weill Cornell Breast Center and for whom Oncotype DX RS test was available. Patients were grouped to HER2-0 (immunohistochemistry (IHC) score of 0) or HER2 low (IHC score of 1+ or, 2+ with non-amplified in situ hybridization) expression. Clinicopathological characteristics and Oncotype DX RS were compared across the different categories of HER2 expression.

Results: Of 509 patients included, 37% and 63% were grouped as HER2-0 and HER2 low, respectively. Median age at diagnosis was 61 years [IQR 50-69]. Sixty-eight percent of patients were postmenopausal. Stage I, II and III corresponded to 76%, 23% and 1% of patients, respectively. Seven percent of patients had nodal involvement. Ductal carcinoma was the most common histological type (75%) followed by lobular carcinoma (17%). Most tumors had low-intermediate histological grade (81%) with a median Ki-67 of 10% [IQR 5-15]. No significant difference was observed in clinicopathological characteristics between the HER2-0 and HER2 low groups. The overall median Oncotype DX RS was 16 [IQR 11-21]. The median Oncotype DX RS based on a HER2 expression of 0, 1+ and 2+ was 15, 17 and 17, respectively. There was no statistically significant difference between the Oncotype DX RS score and HER2 expression, when comparing HER2-0 to HER2 low (p = 0.578), HER2-0 to HER2-1+ (p = 0.775) and HER2-0 to HER2-2+ (p = 0.157). In the pre-menopausal and lobular carcinoma subgroups, the median Oncotype DX RS was 15 [IQR 9-21] and 17 [IQR 12-22], respectively; and there was no statistically significant difference between the Oncotype DX RS score and HER2 expression (p > 0.05). Post-surgery, 87%, 66% and 13% of patients received endocrine therapy, chemotherapy and radiation therapy, respectively. Median follow up time was 16 months [IQR 8-34]. Disease recurrence was documented in 9 (2%) patients.

Conclusions: In this study, we found no differences in the Oncotype DX RS and the prognostic pathological features between the HER2-0 and HER2 low groups which is in line with previous retrospective studies. Survival analysis was limited by the median follow up. Further studies on the understanding of the biology of HER2-low and its clinical implications in early breast cancer are needed. Research Sponsor: None.
Somatic mutations in tumor-adjacent normal breast tissue in young women with high risk family history.

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Background: It’s incompletely understood why some women without germline breast cancer predisposing mutations develop early onset breast cancer. Breast cancer in young women is often more aggressive, with high histologic grade, worse prognosis, and higher risk of recurrence. We hypothesize that these women have somatic mutations in the normal breast tissue that contribute to breast cancer tumorigenesis. Methods: Whole exome sequencing (WES) data was analyzed from normal tissue adjacent to breast tumor and compared to matched peripheral blood (n=28). All patients were <50yo, had high risk family history as per NCCN guidelines, and had negative Ambry Genetics panel testing. FFPE sections were reviewed by two pathologists to identify normal breast tissue furthest away from tumor. WES was performed on Illumina HS4000 using 100-base pair paired-end reads. Samples were mapped to the human reference genome (vGRCh38). PCR duplicates were marked (Picard), and indel regions were adjusted (GATK). High-quality germline variants (HaplotypeCaller), somatic mutations (Mutect), and indels (IndelGenotyper) were called. Low-quality variants were filtered out. The classification and number of mutations per gene per sample were extracted and analyzed. Results: Majority of patients and samples were white (86%), median age 45, with invasive ductal carcinoma (86%), ER+/PR+/HER2- (100%). Median somatic variants per sample were 97 (range: 45-285), all single nucleotide variants, mostly missense mutations, C>T conversions were seen in 45% of mutations. This suggests cytidine deaminase (APOBEC) involvement. All samples had alterations in at least one of the top ten affected genes which include transcription factors in zinc finger family (listed below). Zinc finger proteins play a key role in tumorigenesis, cancer progression and metastasis in a variety of cancers. Upregulation of zinc finger proteins has been associated with worse prognosis in breast cancer. Conclusions: We describe novel somatic mutations in zinc finger proteins in normal breast tissue adjacent to tumor that may contribute to early onset breast cancer in patients with high risk family history. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.
Exploring HER2-low disease: Does it impact breast cancer survival?

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Background: HER-2 low has emerged as a potential new entity in breast cancer (BC). Data of this subset is still limited and prognostic results are controversial, suggesting HER2-low does not represent a distinct biological subtype. HER2-low account for up to 50% of BC, representing a potential therapeutic target with encouraging results in the metastatic setting. Hence, we pretend to analyze clinical characteristics of this subset to elucidate commented points. Methods: Confirmed HER2-negative BC patients (p) diagnosed between 2006-2017 were retrospectively reviewed in a single center study, in ICO-Badalona. HER2-positive and in situ carcinomas were excluded, and p were classified as HER2-low and HER2-0. The prevalence of HER2-low versus HER2-0 among p, originally scored as HER2-negative, was measured. Demographics and clinicopathological characteristics were examined and compared via medical charts/electronic health records. We aim to describe HER2-0/HER2-low populations, and explore its prognostic impact, using Kaplan-Meyer and Cox regression models. Results: From 1451 infiltrating HER2-negative BC p, 87% were hormone receptor (HR)-positive vs 13% triple negative (TNBC). Overall, 43% were HER2-0 and 57% HER2-low (61% IHC 1+ and 39% IHC 2+). Comparing HER2-0 vs HER2-low, the latest showed significant higher proportion of ER-positive (80% vs 91.7%, p = < 0.001) and PR-positive (69.3% vs 79.1%, p = < 0.001) cases, but there were no differences between HER2-low 1+ vs 2+. HER2-0 exhibited higher proportion of TNBC p (20% vs 8.3%, p = 0.001), grade III tumors (28.8% vs 23.5%, p = 0.036) and higher Ki67 median value (26.47% vs 23.88%, p = 0.041). No significant differences were observed in median age at diagnosis, menopausal status, clinical stage, clinical nodal status, histological subtype, time to recurrence, time to local recurrence and overall survival (OS). HER2-low presented longer time to distant recurrence (TDR) compared to HER2-0 (67.8 vs 54.1 months, p = 0.015) and better BC-related OS (19.2 vs 16.3 years, p = 0.033). However, in the multivariate analysis, considering HER2, ER, PR, histological grade and nodal status, PR showed the strongest association with longer TDR (HR: 0.69; 95%CI 0.54-0.89, p = 0.004); and positive nodal status was the strongest factor related to worse BC-related OS (HR: 2.97; CI 2.10-4.21, p = 0.000). No statistical differences in TDR and BC-related OS were observed between HER2 1+ vs 2+ populations. Conclusions: HER2-low was significantly associated to HR-positive disease whereas TNBC, histological grade III and higher Ki67% were more represented in HER2-0 group. Although HER2-0 was related to worse TDR and BC-related OS, these findings could be explained by the presence of an enriched population in worse prognostic features, as suggested by multivariate analysis. New therapies for HER2-0 disease are an unmet medical need.

Research Sponsor: None.

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Extracellular vesicle-derived non-coding RNAs to predict outcome in patients with triple-negative breast cancer (TNBC) with residual disease (RD).

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Background: TNBC patients with RD after neoadjuvant systemic therapy (NAST) have high risk of recurrence. Biomarkers to risk-stratify patients with RD could individualize adjuvant therapy and inform adjuvant therapy trials. We aim to investigate the impact of circulating extracellular vesicle (EV)-derived non-coding RNAs (exo-ncRNAs) on outcomes in TNBC patients with RD. Methods: The study population included 79 TNBC patients with RD post-NAST and available end-of-treatment plasma samples enrolled in an IRB-approved multisite prospective registry. EVs and their associated exo-ncRNAs were isolated by membrane affinity spin columns (Qiagen exoRNeasy). Exo-ncRNA was subjected to next-generation sequencing (Qiagen QIAseq miRNA library kit). N=47 served as a discovery cohort and N=32 served as validation cohort. With inclusion of transcripts expressed in ≥ 80% of samples, there were 1,123 normalized reads/sample. Hazard ratios and C-statistics for event-free survival (EFS) were computed for each exo-ncRNA. We report exo-ncRNAs that were significantly associated with EFS in both the discovery and validation cohorts. Results: Patient and tumor characteristics were balanced in discovery and validation cohorts. Three exo-ncRNAs were associated with increased recurrence risk in both the discovery dataset (miR-200a-3p, HR=1.39, 95%CI 1.01-1.89, P=0.04, C-stat=0.55; miR-203a-3p, HR=1.77, 95%CI 1.15-2.73, P=0.01, C-stat=0.59; and miR-7845-5p, HR=1.53, 95%CI 1.15-2.05, P=0.004, C-stat=0.62) and the validation dataset (miR-200a-3p, HR=1.83, 95%CI 1.24-2.72, P=0.003, C-stat=0.76; miR-203a-3p, HR=1.78, 95%CI 1.10-2.87, P=0.02, C-stat=0.67; and miR-7845-5p, HR=2.06, 95%CI 1.06-4.01, P=0.03, C-stat=0.52). Using the miRNA Target Prediction Database (miRDB), we identified 1,088, 1,352, and 387 predicted targets for miR-200a-3p, miR-203a-3p, and miR-7845-5p, respectively. Amongst 2,827 prediction events there were 2,526 unique target mRNAs. 2,235 mRNAs were targets for one candidate miRNAs, 281 mRNAs were predicted targets for two candidate miRNAs, and 10 mRNAs were predicted as targets for all three candidate miRNAs. Conclusions: The expression of miR-200a-3p, miR-203a-3p, and miR-7845-5p in plasma-derived EVs in TNBC patients with RD after NAST is associated with increased risk of recurrence. We identified ten mRNAs that are predicted targets of all three of these miRNAs. If validated in additional cohorts these exo-ncRNAs could be used in a liquid-biopsy assay to identify high-risk patients with RD who could benefit from adjuvant treatment intensification. Research Sponsor: Kansas Institute for Precision Medicine COBRE.
Differential genomic and transcriptomic analysis of invasive lobular and ductal carcinomas.

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Background: Invasive lobular carcinoma (ILC) is more aggressive than hormone receptor (HR)-positive invasive ductal carcinoma (IDC). However, in practice, ILC and IDC are often treated in a similar fashion with endocrine therapy and chemotherapy. Identifying novel biomarkers, genetic alterations, transcriptomic features, and tumor microenvironment (TME) variations could initiate the development of personalized treatment plans for patients with ILC. Methods: We collected ILC and luminal (non-basal/non-HER2) IDC samples from four datasets (TCGA, METABRIC, RATHER PMC4700448, and UQCCR PMC31263747) and performed differential expression and gene set enrichment analyses, revealing novel genomic, transcriptomic, and TME differences. Using methods from Bagaev et al., we quantified the activity of 29 functional gene expression signatures with single sample gene set enrichment analysis before clustering the samples into five TME subtypes; statistical significance was measured with the Mann-Whitney U test. Differential expression analysis of RNA-Seq data was completed using DESeq2. Further, we analyzed the frequency of specific biomarkers to identify potential therapeutic options. Mutations and biomarker enrichment were assessed using the chi-squared test. Results: We analyzed 1,735 samples (1,442 luminal IDCs and 293 ILCs). CDH1 mutations were more prevalent in ILC samples (56%) compared to IDC samples (6%). Of the 44% of ILC samples with wild-type CDH1, 90% had low CDH1 expression. Inference models showed differences in transcription factors expression between ILC and IDC. ILC had significantly higher expression of TFAP2B, SOCS2, NOSTRIN, THBS4, SCUBE2, and GDF9 and lower expression of CDCA4, PSMG1, LMOD1, and SLC7A5 (adj $p < 0.0001$ for all genes). Analysis of the TME showed that 44% of ILC samples were immune enriched with high PDL1, CTLA4, and LAG3 expression. In comparison, approximately 30% of ILC samples contained enhanced vascularization and expressed high VEGFA, PDGFRA, and PDGFRB. Finally, compared to luminal IDC, ILC tend to have a statistically significant higher TROP2 expression, similar to that seen in basal subtype. Conclusions: ILC and IDC expressed distinct genomic alterations, gene expression, transcriptomic features, TMEs, and biomarkers. These differences can be used as a blueprint to tailor ILC phenotype-specific interventional clinical trials. Research Sponsor: None.
Assessment of the differential profile of breast intratumoral bacteria in treatment responders and nonresponders.

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Background: Despite improvements in breast cancer therapy, many patients do not respond to treatment: the response rate varies between 31 and 80% [Walks et al., 2019]. The tumor microenvironment contains a microbiome which is both cancer type-specific and different to surrounding normal tissue [Nejman et al., 2020]. It plays an important role in tumour microenvironment crosstalk with tumor cells and has been implicated in disease pathogenesis, being recognised in the latest hallmarks of cancer [Hanahan et Weinberg, 2011]. It has also successfully predicted treatment response [Chen et al., 2022; Hermida et al., 2022]. Here, we use conventional microbiome analysis alongside our proprietary mechanistically-powered technology platform to compare the intratumoral bacteria between responders and non-responders. We hypothesise that there are significant differences between those groups regarding composition and mechanistic function of the bacteria. Methods: The tumor microbiome can be deduced from existing sequencing data of tumor biopsy samples. Using 34 tumor DNA samples from 5 breast cancer studies, we compared the intratumoral bacterial profiles of responders to non-responders of various treatments. We performed microbiome analysis in R, including alpha diversity, compositional abundance profiles, and PERMANOVA (permutational analysis of variance). Additionally, BioCortex CarbonMirror version dated 2023-02-14 was used to infer mechanistic links between bacterial species and the up- and downregulation of genes implicated in the hallmarks of cancer. Results: The results show significant differences in diversity and compositional profile between responders and non-responders: Non-responders have significantly higher alpha diversity ($p<0.05$) and a higher proportion of Proteobacteria. PERMANOVA analysis revealed that while responders are more likely to have commensal bacteria, non-responder tumour microbiomes are more likely to harbor pathogenic species such as *Mycoplasmosis fermentans*. Mechanistic analysis showed that for all responders the tumor microbiome is consistently promoting tumor suppressor genes and downregulating proto-oncogenes. In non-responders, however, the tumor microbiome is upregulating and downregulating both with unclear consistency. Conclusions: Our results show microbiome differences between responders and non-responders which were mechanistically implicated in tumor pathogenesis. Further analysis divided by the hallmarks of cancer is required to fully understand the non-responder microbiome links. The reported findings could make the tumor microbiome a useful biomarker aiding patient stratification for both prognosis and treatment choice. They also highlight a potentially meaningful mechanistic link between tumour microenvironment and treatment response that could be leveraged as a novel therapeutic avenue. Research Sponsor: BioCortex Ltd.
Characteristics associated with spatially resolved immune landscapes in triple-negative breast cancer in the FinXX trial and Mayo Clinic cohort.

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Background: Several studies have established the crucial role of preexisting immune response measured by tumor-infiltrating lymphocytes (TILs) in triple-negative breast cancer (TNBC). Emerging studies showed that not only the number of TILs but also the location of TILs is as critical. There are 3 distinct immune landscapes described based on the locations of TILs, namely immune enriched (IN), immune excluded (IE), and immune desert (ID), which are associated with outcomes in TNBC treated with immune-checkpoint inhibitors. Here we evaluated characteristics associated with each immune landscape. Methods: NanoString IO360, Digital Spatial Profiling (DSP), and CosMx, a spatial multi-omics single-cell imaging platform, were used. DSP was used to quantify 39 immune-related proteins in stromal and tumor-enriched segments from 44 TNBC samples from the FinXX trial (NCT00114816) and 276 samples from the Mayo Clinic (MC) TNBC cohort (Leon-Ferre BCRT 2018). CosMx was performed in 75 samples from the MC TNBC cohort. First, tumors with TIL quantified by H&E ≥ 30% were classified as ID. The rest of the tumors were categorized according to the intratumoral CD8 protein expression by DSP, with IE having intratumoral CD8 in the lower median and IN having intratumoral CD8 in the upper median. Differential expression listed as log fold change (FC) was estimated from the linear mixed model with significance defined as two-sided p < 0.05. Results: Using DSP in the FinXX trial, intratumoral and stromal higher HLA-DR (FC 1.68, p = 0.001), B2M (FC 0.8, p = 0.005), CD4 (FC 0.74, p = 0.01), and CD40 (FC 1.56, p = 0.001) were associated with IN compared to ID. When comparing IE and IN, higher intratumoral CD11c (FC 0.97, p = 0.01) and stromal CD4 (FC 0.89, p = 0.047), CD20 (FC 0.85, p = 0.016), CD40 (FC 0.95, p = 0.045), and CD27 (FC 0.84, p = 0.024) were associated with IN. Similar findings were observed in the MC cohort. Moreover, intratumoral NY-ESO-1 expression (FC 0.55, p = 0.03) was associated with IN. Using GSEA with IO360 in the FinXX trial, PI3K-Akt signaling was associated with ID compared to IN (p = 0.01). We further evaluated the differential gene expression in a spatially resolved manner using CosMx with single-cell sequencing in the MC cohort. Expressions of MHC class I and class II in tumor cells, including HLA-A, HLA-B, HLA-C, HLA-DRA, HLA-DRB1, HLA-DPA1, and HLA-E, were associated with IN compared to ID and IE. Conclusions: Using an in-depth analysis with spatially defined context, we identified characteristics associated with distinct immune landscapes in TNBC. Our study highlights the potential future implications of intratumoral MHC expression, CD40, and PI3K-AKT as biomarkers and therapeutic targets. Clinical trial information: NCT00114816. Research Sponsor: Breast Cancer Research Foundation.
The somatic mutation profile of breast cancer in Uganda.

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Background: Breast cancer, the most common cancer in sub-Saharan Africa (SSA), is characterized by poor survival compared with resource-rich regions. A variety of factors are responsible for this disparity and include late stage at presentation, limited diagnostic and therapeutic options, and potentially biologically more aggressive disease. The application of next generation sequencing to cancer specimens in resource-rich regions has identified new molecular mechanisms. However, such molecular testing has generally not been applied to tumors from SSA where the aggressive nature and younger age of women with breast cancer argues for the potential for novel pathogenic mechanisms. Here, we describe the somatic mutation profile of breast cancer in Uganda.

Methods: We enrolled 100 consecutive women with a new diagnosis of invasive breast cancer at the Uganda Cancer Institute (UCI) in Kampala - the primary cancer center of Uganda and neighboring countries. Histopathologic classification was performed at the UCI and revaluated in a blinded fashion at the Fred Hutchinson Cancer Center (Seattle, WA). Demographic and clinical data were obtained. A biopsy specimen of the tumor tissue was obtained, snap frozen, processed using standard protocols to obtain DNA, and sequenced using the clinically-validated UW-OncoPlex assay, identifying all classes of variants and mutations.

Results: We analyzed data from 100 women with a histologically-confirmed diagnosis of breast cancer between the ages of 35 and 65 - the vast majority of whom presented with either stage 3 or stage 4 (92%). All 100 tumor specimens were successfully sequenced, with 96 (96%) demonstrating somatic mutations. The most commonly altered gene was TP53, with mutations in 65% of patients, with identified variant classes including truncations (18), missense (19), and copy loss (33). PIK3CA mutations were identified in 36% of patients, while copy gain or amplification were identified in MYC (50%), CCND1 (31%), FGFR1 (26%), EGFR (9%), and ERRB2 (24%). Nearly half of the women had either a mutation in BRCA1 (24%) or BRCA2 (24%); 6 (6%) of the tumors expressed mutations in both BRCA1 and BRCA2.

Conclusions: We identified a diverse landscape of somatic mutations - the prevalence of BRCA1, BRCA2, and PIK3CA mutations are considerably higher than in other documented populations. A better understanding of the mutational profile can provide biological insights, inform prognosis, and serve as a predictive biomarker. As mutations in BRCA1/2 and PIK3CA can potentially be treated with targeted therapies (e.g. PARP inhibitor, PI3K inhibitor), such data can inform policymakers, allow for inclusion of these therapeutics in the formulary and in the WHO Model List of Essential Medicines, and reduce health disparities. Notably, all cases were successfully sequenced, with 96% of cases demonstrated somatic mutations, even without employing specific enrichment strategies commonly used in high-income countries. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology; GSK Open Africa Lab.
Phase II study on feasibility of sentinel lymph node biopsy for ycNO patients treated with primary chemotherapy in cT1-3N1M0 breast cancer (SHARE study).

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Background: Sentinel lymph node biopsy (SLNB)-guided axillary management is still debated for clinically node-positive breast cancer (BC) patients treated with neoadjuvant chemotherapy (NAC). Several phase II studies demonstrated high false-negative rates (FNR) in ycNO BC, but precise diagnostic imaging for nodal involvement may reduce FNR. To explore ideal imaging and lymphatic mapping, the Japanese Society for Sentinel Node Navigation Surgery conducted a prospective non-randomized phase 2 study (SHARE study, UMIN000030558). Methods: Clinical T1-3N1M0 BC was eligible under multimodal imaging of breast ultrasound, CT and/or MR mammography. Nodal metastasis was histologically confirmed. Standard regimen for NAC was performed by physician’s choice. In case of ycNO BC, SLNB was planned and lymphatic mapping depended on each institutional practice. The primary endpoint is FNR of SLNB and secondary endpoints are the identification rate and outcome of ycNO BC patients at 2 years after surgery. Moreover, in cases of pN0(sn), pN0(i+)(sn) and pN1mi(sn), SLNB followed by lymph node sampling had been allowed instead of axillary lymph node dissection. Based on an estimated FNR of 5%, 224 patients were needed to give 80% power to reject the null hypothesis that the threshold of FNR is 15% with a one-sided type I error rate of 5%. Results: Between February 2018 and May 2021, 185 patients from 19 institutes were registered. After 27 ineligible cases of protocol deviation, non-ycNO or withdrawal of SLNB were excluded, 158 ycNO cases underwent SLNB and sentinel lymph nodes were detected in 153 cases. Among them, 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. Finally, 61 cases had positive nodes, which included 7 false-negative cases. FNR was 11.5% (90% confidence interval, 5.5% and 20.5%). The identification rate was 96.8% and the accuracy rate was 95.4%. Before NAC, multimodal imaging was performed in 148 cases (96.7%) and 1 nodal metastasis was detected in 62 cases (40.5%). 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. If isolated tumor cells in lymph nodes had been defined as pathologically negative even after NAC, the FNR was 7.1%. Conclusions: Multimodal imaging could not improve FNR in ycNO BC. However, SLNB-guided axillary management should be considered when one positive-node is clinically converted to ycNO after NAC. We will report the outcome of ycNO BC cases next year. Clinical trial information: UMIN000030558. Research Sponsor: The Japanese Society for Sentinel Node Navigation Surgery.

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Background: Breast cancer tumor phenotype has prognostic value with triple negative (TN) cancers having higher rates of distant metastases early. While tumor phenotypes are prognostic, published data demonstrates that the choice of local therapy does not affect this predisposition or affect survival. This study was performed to determine whether mastectomy is being performed more frequently for TN or HER2+ phenotypes, relative to hormone receptor positive (HR+) phenotypes despite the lack of benefit this should provide. Methods: Data from the National Cancer Database (NCDB) was analyzed from 2010 through 2019 to assess mastectomy trends and associations with patient and tumor characteristics. Women with invasive breast cancer were included. Women with Stage IV disease were excluded. Patients were categorized as mastectomy or breast conservation surgery. Patient and tumor characteristics were compared across groups using chi-square and Wilcoxon rank sum tests, and a multivariable logistic regression model was fit to assess the association between mastectomy and tumor phenotype controlling for patient and tumor characteristics. Results: 543,590 patients were evaluated. 173,380 (31.9%) patients underwent mastectomy, and 370,210 (68.1%) patients underwent breast conservation surgery. Mean age at diagnosis was 56. There were 425,174 HR+, 64,960 HER2+, and 53,456 TN tumors. The proportion of patients undergoing mastectomy peaked in 2013 at 36.14% before declining. Compared to HR+, HER2+ patients were more likely to undergo mastectomy, OR 1.39, p < 0.0001 (95% CI 1.35–1.43); however, there was no significant difference in mastectomy between HR+ patients and TN patients. Compared to whites, black patients were less likely to undergo mastectomy, OR 0.71, p < 0.0001 (95% CI 0.69–0.74), and individuals of Hispanic ethnicity less likely to undergo mastectomy, OR 0.92, p < 0.0001 (95% CI 0.89–0.95). Compared to private insurance, Medicare had a greater association with mastectomy, OR 1.2, p < 0.0001 (95% CI 1.18–1.23). There was no significant difference between other forms of insurance (Medicaid, other government insurance, no insurance) and private insurance. Education and income were not associated with different frequencies of mastectomy. Patients with higher comorbidity scores were more likely to undergo mastectomy. Conclusions: Mastectomy rates have been declining since 2013 at CoC centers. While TN breast cancer is not associated with increased mastectomy percent, mastectomy continues to be performed more frequently for HER2+ positive phenotype when adjusting for tumor and patient characteristics. These data suggest a need for education about HER2 positive phenotype due to a possible lack of understanding about the why such tumors pose a risk, and the role of local therapy in treating them. Research Sponsor: Fox Chase Cancer Center.
Racial/ethnic and socioeconomic differences in breast cancer surgery performed and delayed surgical treatment: Mediating impact on mortality.

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Background: Breast cancer is the most common malignancy affecting women of all racial and ethnic backgrounds in the United States (US). Although Socioeconomic status (SES), race/ethnicity, and surgical type/delays are associated with breast cancer mortality outcomes, studies on these associations have been contrasting. This study examined the racial/ethnic and SES differences in surgical treatment types and delays. Also, we quantified the extent to which these differences explained the racial/ethnic disparities in breast cancer mortality. Methods: We studied 290,066 women 40+ years old diagnosed with breast cancer between 2010 and 2017 identified from the Surveillance, Epidemiology, and End Results database. We performed logistic regression models to examine the association of SES and race/ethnicity with surgical treatment type and delays. We performed mediation analysis models to quantify the extent to which mortality differences were mediated by treatment, sociodemographic, and clinicopathologic factors. The study subjects were de-identified, and there was no patient contact; thus, the study was exempted from an Institutional Review Board’s (IRB) approval. A p-value less than 0.05 indicated significant associations for the descriptive statistics, logistic and Cox proportional hazard regressions, and mediation analysis. We used Stata 17 to perform the analyses. Results: Non-Hispanic (NH) Black [Odds ratio (OR) = 1.16, 95% CI: 1.13-1.19] and Hispanic women [OR = 1.27, 95% CI: 1.24-1.31] were significantly more likely to undergo mastectomy compared to NH White women. Similarly, NH Black and Hispanic women had higher odds of delayed surgical treatment than NH Whites. Patients in the highest SES quintile, compared to those in lowest the lowest, were less likely to experience breast cancer-specific mortality (BCSM). Variations in treatment, SES, and clinicopathological factors significantly explained 70% of the excess BCSM among NH Blacks compared to their NH White counterparts. Conclusions: In conclusion, health disparity continues to be a major societal concern in the US. It affects people of all ages, socioeconomic classes, and ethnic/racial backgrounds. The findings of this study showed that racial and ethnic minorities, the majority of whom have a lower socioeconomic position, are significantly disadvantaged regarding the evaluation, quality, cost, and duration of medical care. Future studies can assess the multifactorial effects of sociodemographic factors like SES, access to health care assessment, and educational background amidst other variables as a multidimensional predictor of treatment delay and overall survival of breast cancer and other health issues among minoritized populations. Research Sponsor: None.
Disease outcomes by race in patients with high-risk triple negative breast cancer with residual disease after neoadjuvant chemotherapy: A post-hoc analysis of the EA1131 randomized clinical trial.

Olga Kantor, Lisa A. Newman, Lauren K Anderson, Charity Glass, Erica L. Mayer, Esther R. Ogayo, Mariana Chavez-MacGregor, Rachel A. Freedman, Tari A. King, Elizabeth A. Mittendorf; Brigham and Women's Hospital, Boston, MA; Weill Cornell, Detroit, MI; Dana-Farber Cancer Institute, Boston, MA; MD Anderson Cancer Center, Houston, TX; Division of Breast Surgery, Department of Surgery, BWH, Breast Oncology Program, Dana-Farber/Brigham and Women’s Cancer Center, Boston, MA

Background: Black women with breast cancer have the highest breast cancer mortality (BCM) rates of any racial and ethnic group. The higher burden of triple negative breast cancer (TNBC) in Black women contributes to disparities in BCM, but the extent to which disparate outcomes exist in patients with similar tumor biology is uncertain. The objective of this study was to examine racial differences in disease outcomes and BCM between Black and White patients in a clinical trial population of high-risk TNBC with residual disease after neoadjuvant chemotherapy (NAC). Methods: From 2015-2021, the ECOG-ACRIN EA1131 clinical trial randomized 415 clinical stage II-III TNBC patients with residual disease after NAC to either adjuvant capecitabine or platinum. For this analysis, 366 patients with known self-reported Black or White race and follow-up data were included. The aim of this unplanned exploratory analysis was to examine locoregional recurrence (LRR), distant recurrence (DR), and BCM by race using Kaplan-Meier curves for unadjusted estimates and Cox modeling for adjusted analyses. Results: Racial distribution of the analysis population included 66 (18.0%) Black and 300 (82.0%) White patients. 239 (65.3%) patients presented with clinical stage II and 127 (34.7%) with stage III disease. All patients had residual pathological disease after NAC: 86 (23.5%) stage I, 176 (48.1%) stage II, and 102 (27.9%) stage III (n=2 unknown). Median age was 49 years in Black and 54 years in White patients, p=0.003. Disease presentation, response to chemotherapy, and treatment arm were similar by race. Median follow up was 20 months. 2-year estimated LRR occurred in 31.6% of Black and 18.6% of White patients although this was not statistically significant (p=0.387), and 2-year estimated DR and BCM were similar by race. Estimated 2-year outcomes are outlined. Models adjusted for race, age, stage, grade, treatment arm, and locoregional therapy did not identify race as an independent predictor of LRR, DR, or BCM. Higher pathologic stage was the only consistent independent predictor of recurrent disease or BCM (stage III with HR 6.14 for LRR; HR 5.16 for DR; HR 6.84 for BCM; all p<0.001). Conclusions: In this population of high-risk patients with residual TNBC after NAC with similar tumor biology treated on a clinical trial, there was a trend towards increased LRR in Black patients and similar DR and BCM between Black and White patients at 2 years of follow-up. This suggests that differences in BCM in other breast cancer populations may be at least partially driven by differences in tumor biology. Clinical trial information: NCT02445391. Research Sponsor: None.

Kaplan-meier estimates of 2-year LRR, DR, and BCM by race.

<table>
<thead>
<tr>
<th>Estimated 2-year Outcome</th>
<th>Black</th>
<th>White</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated LRR</td>
<td>14.3%</td>
<td>4.3%</td>
<td>0.719</td>
</tr>
<tr>
<td>Any LRR</td>
<td>31.6%</td>
<td>18.6%</td>
<td>0.387</td>
</tr>
<tr>
<td>Any DR</td>
<td>42.2%</td>
<td>42.9%</td>
<td>0.873</td>
</tr>
<tr>
<td>BCM</td>
<td>23.8%</td>
<td>30.1%</td>
<td>0.274</td>
</tr>
</tbody>
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Association of minimizing the false negative rate of axillary staging surgery in patients with cN1 breast cancer after neoadjuvant chemotherapy with surgical overtreatment.

Alison Laws, Saskia Leonard, Julie Vincuilla, Tonia Parker, Olga Kantor, Elizabeth A. Mittendorf, Anna Weiss, Tari A. King; Dana-Farber Brigham Cancer Center, Boston, MA; University of Rochester, Rochester, NY

Background: Efforts to minimize the false negative rate (FNR) of axillary staging in cN1 breast cancer patients (pts) treated with neoadjuvant chemotherapy (NAC) have received much attention since the publication of ACOSOG Z1071. We first adopted sentinel node biopsy (SNB) with a requirement of retrieving ≥3 nodes, and later transitioned to targeted axillary dissection (TAD) with a requirement of retrieving the biopsy-proven clipped node (CN) and ≥3 nodes overall. Group consensus was to perform axillary lymph node dissection (ALND) if these technical requirements were not met. This study evaluates likelihood of surgical overtreatment with ALND due to technical failures of SNB or TAD in cN1 pts who converted to ypN0 status, and reports oncologic outcomes with each approach. Methods: Among 598 cN1 breast cancer pts treated with NAC from 2017-2022 in our prospective institutional database, we included 191 (31.9%) with attempted SNB or TAD and ypN0 status. We used descriptive statistics and chi-squared tests to compare technical complications of SNB vs. TAD resulting in requirement for ALND per group consensus despite ypN0 status. Kaplan Meier methods were used to determine oncologic outcomes in those treated with SNB or TAD alone. Results: Planned axillary surgery was SNB in 77 (40.3%) pts and TAD in 114 (59.7%). The CN was not visualized for seed localization in 14 pts (12.2% of planned TAD) and the seed was not found to be within the CN intra-operatively in 20 pts (20.0% of those with seed placed). Technical failures resulting in requirement of ALND per group consensus criteria occurred in 14 (18.2%) pts with planned SNB and 17 (14.9%) with planned TAD. Among planned TAD pts, the rate of not retrieving the CN did not change over time (p=0.52). Median follow-up in those treated with SNB alone (n=79) was 3.5 years with 1 (1.3%) axillary recurrence as well as 2 local and 2 distant recurrences and 1 non-breast cancer death. 3-yr recurrence-free survival was 90.4% (95%CI: 79.5-95.7%). Median follow-up in those with TAD alone (n=92) was 1.8 years with no recurrences or deaths. Conclusions: This study contributes to a growing body of literature supporting the oncologic safety of omitting ALND in cN1 ypN0 pts treated with NAC, irrespective of the axillary staging approach. Technical limitations in identifying ≥3 nodes or localizing and retrieving CNs resulted in overtreatment with ALND in a significant proportion (≥15%) of ypN0 pts, without significant differences between SNB vs. TAD approaches. These data support consideration of re-evaluating NCCN guidelines recommending retrieval of ≥3 nodes and localization of the CN to minimize risk of overtreatment. Research Sponsor: None.

<table>
<thead>
<tr>
<th></th>
<th>Planned SNB (n=77)</th>
<th>Planned TAD (n=114)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed mapping</td>
<td>5 (6.5%)</td>
<td>3 (2.6%)</td>
<td>0.19</td>
</tr>
<tr>
<td>&lt;3 nodes</td>
<td>9 (11.7%)</td>
<td>6 (5.3%)</td>
<td>0.11</td>
</tr>
<tr>
<td>CN not confirmed to be retrieved</td>
<td>8 (7.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>14 (18.2%)</td>
<td>17 (14.9%)</td>
<td>0.55</td>
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</tbody>
</table>
A phase II randomized clinical trial to assess toxicity and quality of life of patients with breast cancer with hypofractionated versus conventional fractionation radiotherapy with regional nodal irradiation.

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**Background:** The primary aim was comparing acute toxicity between conventional fractionated radiation therapy (CF-RT) and hypofractionated radiation therapy (HF-RT) for patients undergoing breast-conserving surgery or mastectomy with breast or chest wall and regional nodal irradiation (RNI). The secondary endpoints were acute and subacute toxicity, cosmesis, quality of life, and lymphedema features. **Methods:** Unblinded randomized trial with total of 86 patients treated with CF-RT (n = 33; 50 Gy/25 fractions ± sequential boost [10 Gy/5 fractions]) versus HF-RT (n = 53; 40 Gy/15 fractions ± concomitant boost [8 Gy/15 fractions]). Toxic effects and cosmesis evaluation used the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) and the Harvard/NSABP/RTOG scale. Patients-reported QoL was determined using European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) and the breast cancer-specific supplementary questionnaire (QLQ-BR23). Lymphedema determination compared volume differences between the affected and contralateral arms using the Casley-Smith volume formula. **Results:** Grade 2 and grade 3 skin rash dermatitis were lower with HF-RT than with CF-RT (28% vs. 52%, 0% vs. 6%; p = 0.022, respectively). HF-RT vs. CF-RT had lower rate of grade 2 hyperpigmentation (23% vs. 55%; p = 0.005). No differences in overall rates of any physician-assessed grade 2 or higher and grade 3 or higher acute toxicity between HF-RT vs. CF-RT were registered. There was no statistical difference between the CF-RT and the HF-RT regarding cosmesis, lymphedema rate (13% vs. 12% HF-RT vs. CF-RT; p = 1.000, respectively), and functional and symptom scales during irradiation and after six months of treatment. **Conclusions:** HF-RT showed lower rates of acute toxicity, with no changes in quality-of-life outcomes. Clinical trial information: NCT04015531. Research Sponsor: None.
Invasive disease free survival and brain metastasis rates in patients treated with neoadjuvant chemotherapy with trastuzumab and pertuzumab.

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Background: Patients (pts) with human epidermal growth factor receptor 2 (HER2) positive (+) early breast cancer (EBC) receiving neoadjuvant systemic therapy (NAST) have poorer outcomes if they have residual disease (RD) after surgery. HER2 negative (-) RD has been reported in 1/3 of pts after NAST. The KATHERINE trial suggests that pts with HER2- RD (8%) have better invasive disease-free survival (IDFS) with adjuvant (adj) trastuzumab emtansine (T-DM1) versus trastuzumab (H) alone. However, only 18% of the pts enrolled in the trial received NAST with trastuzumab and pertuzumab (HP). We aimed to analyze IDFS and brain metastasis (BM) rates in pts with HER2+ EBC in a modern population homogenously treated with NAST. We also report the incidence of pts with HER2- RD and their outcomes. Methods: Clinicopathologic data for pts with HER2+ EBC who received NAST between 1 Jan 2019 and 31 Jan 2022 were reviewed. External assessment of HER2 status before NAST was allowed. HER2 status of the surgical specimens with RD were assessed internally at our center. IDFS was defined as the time from surgery until first occurrence of invasive cancer recurrence, distant recurrence, or death from any cause. Results: The total cohort was 594 pts. 456 (77%) and 138 (23%) received antracycline-taxane and taxane based chemotherapy, respectively during NAST. 587 (99%) received HP and 7 (1%) received H alone. NAST was completed by 566 (95%) of pts. pCR (ypT0/isN0) was achieved in 325 (55%) and RD was seen in 269 (45%) pts. In 269 pts with RD, 46 (17%) did not have HER2 retesting and were excluded from the final analysis. In the remaining 223 pts, 143 (64%) were HER2+ and 80 (36%) were HER2-. In the 143 pts with HER2+ RD, adj TDM1, HP, H alone and no HER2 directed therapy were received by 120 (84%), 16 (11%), 1 (1%) and 6 (4%) of pts, respectively. In the 80 pts with HER2- RD, adj TDM1, HP, H alone and no HER2 directed therapy were received by 44 (55%), 27 (34%), 3 (4%) and 6 (7%) of pts, respectively. With a median follow up of 24 months, 7 pts developed BM at initial recurrence, 3/325 (0.9%) with pCR and 4/143 (2.8%) with HER2+ RD. None of the pts who developed BM had HER2- RD. IDFS events occurred in 22/594 (3%) pts. RD pts had a higher likelihood of having an IDFS event, 14/269 (5%) in RD and 8/325 (2%) in pCR (p = 0.04). In the evaluable 223 pts with RD there was no difference in IDFS between 10/143 (7%) pts with HER2+ RD or 4/80 (5%) with HER2- RD (p = 0.10). Conclusions: At a single center, in pts who predominantly received HP with chemotherapy as NAST, pts with RD had higher IDFS events than those with pCR. In those with RD, 36% lost HER2+ status; IDFS events appeared similar in those with HER2+ RD versus those with HER2- RD. The HER2 loss rate is higher than reported in KATHERINE possibly due to majority of pts receiving dual HP as NAST. The BM events seen in those with RD and pCR highlights the need for more effective therapy in NAST and adj setting to minimize BM risk. Research Sponsor: None.
Effect of tumor microenvironment on chemotherapy response of patients with triple-negative breast cancer receiving neoadjuvant chemotherapy.

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Background: Triple-negative breast cancer (TNBC) is a breast cancer subtype that has poor prognosis and exhibits a unique tumor microenvironment, including the corresponding immunological environment. Analysis of the tumor microbiome has indicated a relationship between the tumor microenvironment and treatment response. Therefore, we attempted to reveal the role of the tumor microbiome in patients with TNBC that were receiving neoadjuvant chemotherapy. Methods: We collected TNBC patient RNA-seq samples from the Gene Expression Omnibus (GEO; n of pathological complete response [pCR] = 38, n of residual disease [RD] = 50) and extracted microbiome count data using Kraken2 and Bracken. Differential and relative abundance were estimated with linear discriminant analysis effect size (LEfSe). We calculated the immune cell fraction with CIBERSORTx and conducted survival analysis using the Cancer Genome Atlas patient data (n = 115). Correlations between the microbiome and immune cell compositions were analyzed and a prediction model was constructed to estimate drug response using random forest (RF) and support vector machine (SVM). Results: Among the drug response group, the beta diversity varied considerably; consequently, 20 genera and 24 species were observed to express a significant differential and relative abundance using LEfSe analysis. The drug response prediction model accuracy exhibited 76.47 and 88.24 percent in RF and SVM, respectively; specifically, Pandoraea pulmonicola and Brucella melitensis were found to be important features in determining drug response. In correlation analysis, Geosporobacter ferrireducens, Streptococcus sanguinis, and resting natural killer cells were the most correlated factors in the pCR group, whereas Nitrosospira briensis, Plantactinospora sp. BC1, and regulatory T cells (Tregs) were key features in the RD group. Further, M2 macrophages and Brucella showed significant differences in survival between the pCR and RD groups (p < 0.05). Conclusions: Our study demonstrated that the microbiome analysis of tumor tissue can predict chemotherapy response of patients with TNBC receiving neoadjuvant chemotherapy. Further, the immunological tumor microenvironment may be impacted by the tumor microbiome, thereby affecting the corresponding survival and treatment response. Research Sponsor: Medical Research Center program (2018R1A5A203879) from National Research Foundation of Korea, and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute; Ministry of Health & Welfare, Republic of Korea (HI22C1377); Research institute for Convergence of biomedical science and technology (30-2020-000), Pusan National University Yangsan Hospital Institutional Funding.
Neoadjuvant giredestrant + palbociclib (P) vs. anastrozole (A) + P in postmenopausal women with estrogen receptor-positive, HER2-negative, untreated early breast cancer (ER+, HER2− eBC): Patient (pt)-reported outcomes (PROs) in the randomized, open-label, international phase II coopERA BC study.

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Background: Endocrine therapies (ETs) are the therapeutic mainstay for ER+ BC but persistent adverse events (AEs; eg joint pain, especially with aromatase inhibitors) negatively impact quality of life, and resistance impacts efficacy. Giredestrant, a highly potent, nonsteroidal, oral selective ER antagonist and degrader (PO SERD), may help address these issues. coopERA BC (NCT04436744) evaluated giredestrant in eBC and met its primary endpoint, demonstrating a greater reduction of Ki67 with giredestrant vs. A after 2 weeks. Giredestrant was well tolerated as a single agent and with P. We report exploratory PRO analyses.

Methods: Pts with cT1c-cT4a-c (≥ 1.5 cm within cT1c) ER+, HER2− untreated eBC and baseline Ki67 score ≥ 5% were randomized 1:1 to 30 mg PO daily (QD) giredestrant or 1 mg PO QD A on days (D)1–14 of a window-of-opportunity phase. A 16-week neoadjuvant phase added 125 mg PO QD P on D1–21 of four 28-D cycles. Presence/frequency/severity/interruption of relevant symptomatic AEs were assessed at Cycles 1–4 via NCI PRO-CTCAE library items; overall burden due to AEs, via FACT-G item GP5. Results: PRO completion rates were ≥ 80% at all time points. PRO-CTCAE postbaseline frequency scores were comparable between arms and mostly 0/1 (never/rare; reported for: Diarrhea > 80% of pts; hot flash > 60%; joint pain > 65%; nausea > 90%; vomiting > 90%). No rash was reported by > 90% of pts; fatigue at 0/1 severity (none/mild) by > 75% and at 0/1 interference (none at all/a little bit) by 80%. Hot flash frequency scores of 2–4 (occasionally/frequently/almost constantly) were reported by 30% of pts in the giredestrant + P arm and 37% in the A + P arm; joint pain frequency scores of 2–4, by 25% and 35%. Worst postbaseline scores of 3–4 are shown in the table. FACT-G GP5 showed greater proportions of “improved/no change” responses in the giredestrant + P than the A + P arm at Cycles 2–4 (Cycle 2 75%; Cycle 3 71%; Cycle 4 68% vs. 62%; 66%; 53%), and smaller proportions of “worsened” responses (25%; 29%; 32% vs. 38%; 34%; 47%). Conclusions: This is the first analysis to our knowledge of PROs with a PO SERD in eBC; it showed that most pts reported minimal symptomatic AEs at frequency and severity levels that were generally numerically lower in the giredestrant + P than the A + P arm (particularly joint pain). Furthermore, there were numeric trends towards greater stability and improvement and less worsening of treatment burden in the giredestrant + P arm. Studies to further assess giredestrant’s clinical benefit are ongoing in the adjuvant setting. Clinical trial information: NCT04436744. Research Sponsor: F. Hoffmann-La Roche Ltd.

<table>
<thead>
<tr>
<th>n/N pts (%)</th>
<th>Giredestrant + P</th>
<th>A + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0/108 (0)</td>
<td>3/103 (3)</td>
</tr>
<tr>
<td>Hot flash</td>
<td>18/106 (17)</td>
<td>12/101 (12)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>8/108 (7)</td>
<td>17/103 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1/107 (1)</td>
<td>0/103</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0/107</td>
<td>0/103</td>
</tr>
<tr>
<td>Fatigue severity</td>
<td>2/107 (2)</td>
<td>7/101 (7)</td>
</tr>
</tbody>
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Use of machine learning to predict pathological complete response using multi-modal data from I-SPY2 clinical trials.

Fahad Shabbir Ahmed; Alghorismus, LLC, Detroit, MI

**Background:** The objective of the current analysis of the I-SPY 2 data from multiple breast cancer clinical trials for stages II and III cancers was to look at the possibility of developing a machine learning algorithm to predict pathological complete response using multimodal data. **Methods:** Imaging, clinical and biomarkers data form the I-SPY 2 trial was used in this analysis. Four different experiments were designed for to assess different data pre-processing and machine learning methods mainly deep neural networks (DNN) and random forest (RF) classifiers. Experiment 1 and 3 use DNNs while Experiment 2 and 4 used RFs; more over the first two experiments used data that was continuous in nature from the point of view of pre-performed imaging analysis while in later two experiments we had binarized all the variables using a median cutoff for high vs low values. The variables used were treatment received, HER2/neu receptor status, hormone receptor status, age, ethnicity, gynecological history, MRI feature data. All models were evaluated using robust testing methods that included sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), accuracies (training and test sets), area-under the receiver-operator curve and F1-Score. **Results:** From a total of 985 patients with clinical data we used 384 that had multi-feature MRI data. Time series data for the initial scan (T0) and a scan 3 weeks later (T1). The final comparative analysis showed the best model among the 4 experiment the best performing algorithms for this analysis was random forests using median cutoffs with a best F1-score (0.43), specificity (86.4%), PPV (47.8%), accuracies (train sets, 100%; test sets, 75%), and AUROCs (0.78, 0.56-0.73). **Conclusions:** The use of machine learning to predict pathological complete response using multimodal data shows good potential as a digital biomarker. However, these results need further validation before a clinical tool is available for the clinicians. 

**Research Sponsor:** None.

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Train set accuracy</th>
<th>Test Set accuracy</th>
<th>AUROC (95% CI)</th>
<th>F1-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Continuous data (DNN)</td>
<td>28.57</td>
<td>71.59</td>
<td>24.24</td>
<td>75.90</td>
<td>93.66</td>
<td>61.21</td>
<td>0.55 (0.44-0.62)</td>
<td>0.26</td>
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<tr>
<td>2. Continuous data (RF)</td>
<td>32.14</td>
<td>88.64</td>
<td>47.34</td>
<td>80.41</td>
<td>100.0</td>
<td>75</td>
<td>0.78 (0.56-0.73)</td>
<td>0.38</td>
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<tr>
<td>3. Hi/Low median cutoff data (DNN)</td>
<td>100</td>
<td>0.00</td>
<td>24.13</td>
<td>-</td>
<td>31.72</td>
<td>24.14</td>
<td>0.60 (0.13-0.28)</td>
<td>0.39</td>
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<tr>
<td>4. Hi/Low median cutoff data (RF)</td>
<td>39.29</td>
<td>86.36</td>
<td>47.82</td>
<td>81.72</td>
<td>100.0</td>
<td>75</td>
<td>0.78 (0.56-0.73)</td>
<td>0.43</td>
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</tbody>
</table>
Background: Previously, we showed that addition of lobaplatin (L) to taxane combined with anthracycline could improve the pathologic complete response (pCR) rate and lengthen survival significantly if employed as neoadjuvant therapy in patients with triple-negative breast cancer (TNBC). We evaluated the efficacy and safety of neoadjuvant chemotherapy of taxane (T) combined with lobaplatin (L) or anthracycline (E) for patients with TNBC. Methods: Ninety-five patients with TNBC (stage I–III) who had not undergone any type of treatment were divided randomly into two groups: TL (docetaxel at 75 mg/m² and lobaplatin at 30 mg/m², D1, one cycle = 21 days, a total of six cycles) or TE (docetaxel at 75 mg/m² and epirubicin at 80 mg/m², D1, one cycle = 21 days, a total of 6 weeks or epirubicin at 80 mg/m² and cyclophosphamide at 600 mg/m², sequential docetaxel at 75 mg/m², D1, one cycle = 21 days, a total of eight cycles). Efficacy was evaluated every two cycles. The final surgical procedure was completed after fulfillment of neoadjuvant chemotherapy. The primary endpoint was the total pathologic complete response (tpCR) rate. The secondary endpoints were the objective response rate (ORR), safety, event-free survival (EFS), and overall survival (OS). The exploratory endpoint was biomarker analysis. Results: From June 2019 to November 2022, 97 patients were screened. Finally, 95 patients were enrolled. The median age of the study cohort was 49 years. Nine patients (9.5%) had stage-I disease, 61 patients (64.2%) had stage II, and 25 patients (26.3%) had stage III. Sixty-five patients (68.4%) had Ki67 ≥40% and 30 patients (31.6%) had Ki67 < 40%. Seventy patients (73.7%) were cytokeratin (CK)5/6+ and 25 patients (26.3%) were CK5/6−. Of 95 patients, 47 were in the TL group and 48 in the TE group. The tpCR rate in the TL group was 46.8% (22/47), which was significantly higher than that in the TE group (22.9% (11/48); odds ratio (OR) = 2.960, 95% confidence interval (CI) = 1.223–7.164, \(P = 0.016\)). The ORR in the TL group was 95.7% (45/47), which was significantly higher than that in the TE group (75.0% (36/48); OR = 27.500, 95% CI = 1.576–35.683, \(P = 0.011\)). The prevalence of grade III/IV neutropenia in the TE group was 41.0% (9/22), which was significantly higher than that in the TL group (7.7% (2/26); OR = 8.308, 95% CI = 1.557–44.320, \(P = 0.013\)). There was no significant difference in the prevalence of other adverse reactions between the two groups. Conclusions: In the neoadjuvant treatment of TNBC, the TL regimen had a higher tpCR rate and ORR than those of the TE regimen, and was safer. Clinical trial information: ChiCTR1900023776. Research Sponsor: None.
Use of PLR and NLR to evaluate the efficacy and prognosis of neoadjuvant chemotherapy with lobaplatin in triple-negative breast cancer.

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Background: Previously, we showed that addition of lobaplatin (L) to taxane (T) combined with anthracycline (E) could improve the pathological complete response (pCR) rate of neoadjuvant therapy for triple-negative breast cancer (TNBC) and lengthen long-term survival significantly, but the therapeutic markers of this regimen are not known. We investigated if the platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) could be used to predict the efficacy of the TEL regimen.

Methods: Eighty-three patients with TNBC (stage I–III) who received TEL (docetaxel (T) at 75 mg/m², epirubicin (E) at 80 mg/m², and lobaplatin (L) at 30 mg/m²) from January 2014 to August 2019 were recruited. They received four cycles before surgery and two cycles after surgery. Patients were divided into four groups according to the mean values of the PLR (145.71) and NLR (2.74): high PLR (PLR+), low PLR (PLR−), high NLR (NLR+), and low NLR (NLR−). Differences in the total pathologic complete response (tpCR) rate, event-free survival (EFS), and overall survival (OS) were analyzed in different groups of patients using the TEL protocol.

Results: The tpCR rate in the PLR− group was 49.0% (25/51), which was significantly higher than that in the PLR+ group (25.0% (8/32); odds ratio (OR) = 2.885, 95% confidence interval (CI) = 1.093–7.612, P = 0.032). The tpCR rate in the NLR− group was 49.1% (26/53), which was significantly higher than that in the NLR+ group (23.3% (7/30); OR = 3.164, 95% CI = 1.161–8.626, P = 0.024). The tpCR rate of the PLR−NLR− group was 53.7% (22/41), which was significantly higher than that of the PLR+/NLR+ group (26.1% (11/42), with a high proportion of any index (OR = 3.263, 95% CI = 1.298–8.204, P = 0.012). The median duration of follow-up was 69 months. EFS and OS in the NLR− group were significantly longer than those in the NLR+ group (hazard ratio (HR) = 5.946, 95% CI = 1.526–23.169, P = 0.010 for EFS; HR = 7.803, 95% CI = 1.565–38.907, P = 0.012 for OS). Five-year EFS was 95.1% for the PLR−NLR− group, 91.0% for the PLR+/NLR− group, 76.0 for the PLR+NLR+ group, and 59.1% for the PLR−NLR+ group. Compared with the PLR+/NLR+ group, patients in the PLR-NLR- group had the longest EFS (P = 0.002). Conclusions: PLR and NLR could be used to predict the efficacy of neoadjuvant therapy with taxane, anthracycline, and lobaplatin regimen in TNBC, and the low-proportion group had a higher tpCR rate and a better long-term prognosis. Clinical trial information: ChiCTR-TRC-14005019. Research Sponsor: None.
Association between pCR, TILs, and Ki-67 at baseline and after 2 weeks in patients with triple-negative breast cancer (TNBC) treated with atezolizumab and chemotherapy +/- a preceding atezolizumab monotherapy window: A translational analysis of the neoMono trial.

Ramona Erber, Hans-Christian Kolberg, Johannes Schumacher, Michael Braun, Peter A. Fasching, Eva-Maria Grischke, Christian Schem, Michael Patrick Lux, Mustafa Deryal, Oliver Hoffmann, Bernhard Heinrich, Georg Kunz, Kristina Luebbe, Petra Krabisch, Oliver Hoffmann, Bernhard Heinrich, Georg Kunz, Kristina Luebbe, Petra Krabisch, Eva-Maria Grischke, Christian Schem, Michael Patrick Lux, Mustafa Deryal, Oliver Hoffmann, Bernhard Heinrich, Georg Kunz, Kristina Luebbe, Petra Krabisch, Oliver Hoffmann, Bernhard Heinrich, Georg Kunz, Kristina Luebbe, Petra Krabisch; Institute of Pathology, Universitätsträger Universitätsklinikum Erlangen-Nürnberg, Comprehensive Cancer Center Erlangen-EMN (CCC ER-EMN), Erlangen, Germany; Department of Gynecology and Obstetrics, Marienhospital Bottrop, Bottrop, Germany; Palleos Healthcare GmbH, Wiesbaden, Germany; Red Cross Hospital Munich, Germany; München, Germany; Department of Obstetrics and Gynecology, University Hospital Erlangen, Erlangen, Germany; University Women’s Clinic Tubingen, Eberhard Karls University, Tubingen, Germany; Mammazentrum Hamburg – Brustklinik am Krankenhaus Hamburg, Hamburg, Germany; Department of Gynecology and Obstetrics, St. Louise Frauen- und Kinderklinik, St. Vincenz Krankenhaus, Paderborn, Germany; Caritas-Kliniken Saarbrücken, Saarbrücken, Germany; Universitätsklinikum Essen, Essen, Germany; Hematological/Oncological Praxis, Augsburg, Germany; St. Johannes Hospital Dortmund, Dortmund, Germany; Frauenklinik Henriettensorf, Hannover, Germany; Klinikum Chemnitz, Chemnitz, Germany; Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany; palleos healthcare, Wiesbaden, Germany; Universitätsklinikum Essen, Essen, Germany; University Hospital Essen, Berlin, NC, Germany

Background: neoMono randomized patients (pts) with triple negative breast cancer (TNBC) to receive (Arm A) or not to receive (Arm B) 2-week Atezolizumab monotherapy prior to neoadjuvant 24-week Atezolizumab + chemotherapy. In prespecified interim analysis, no difference regarding pathological complete response (pCR) was observed among all pts. However, in regard to pCR rates, pts with PD-L1 positive TNBC seem to benefit from addition of the monotherapy window. Here we analyze the association between central TILs and Ki-67 at baseline (BL) / after 2 weeks (2w) and pCR.

Methods: Ki-67 expression (% positive tumor cells) was analyzed using immunohistochemistry. Analysis of stromal TILs was performed according to the International TILs Working Group. Differences from BL at the 2w time point were denoted as Ki-67-diff and TIL-diff, respectively. Associations between pCR and BL/2w measurements were analyzed using logistic regression. Akaike information criterion (AIC) was used to evaluate goodness-of-fit between models. Since the a priori chosen biomarker thresholds (< = 30% [Ki-67] and < = 60% [TILs]) resulted in very low subgroup sizes, k-means clustering analysis was performed and association of the cluster labels with pCR was then investigated.

Results: The analysis included 50 (Arm A) and 51 (Arm B) pts. The threshold of Ki-67 (< = 30%) was reached in 98% (BL) and 92% (2w), that of TILs (< = 60%) in 11% (BL) and 18% (2w), respectively. PD-L1 (BL) was < = 1 in 26%. In separate logistic regression models (including BL and change), both BL-Ki-67 and BL-TILs were significantly though moderately associated with pCR. A combined model using both biomarkers yielded the best AIC. BL-Ki-67 and BL-TILs, as well as TIL-diff were highly significantly though again moderately associated with pCR. Cluster analysis I using BL-Ki-67, Ki-67-diff, and PD-L1 yielded cluster 1 (medium BL-Ki-67 and subsequent increase) with a pCR rate of 50% compared to 77% in cluster 2 (high BL-Ki-67 and decreasing Ki-67). Similarly, cluster analysis II using BL-TILs, TILs-diff and PD-L1 yielded cluster 3 (low BL-TILs/non-essential TILs change) with a low pCR rate of 55% compared to 84.4% and 85.7% for clusters 4 (low BL-TILs/substantial increase) and 5 (high BL-TILs/non-essential change), respectively. In a combined regression model of all clusters above, clusters 2 and 4 had the highest pCR probability. Conclusions: Our results demonstrate that while BL-Ki-67 and BL-TILs are highly informative of pCR probability, Ki-67-diff and even more so TIL-diff added further significant information. Analysis of the full neoMono dataset will allow us to investigate this association further and to potentially develop a predictive algorithm regarding pCR based on baseline and dynamic biomarkers. Research Sponsor: Roche Pharma AG.
Neoadjuvant therapy of HER2 directed conventional dendritic cell (DC1) intratumoral (IT) therapy plus weekly paclitaxel, trastuzumab, and pertuzumab in patients with HER-2 positive breast cancer: NATASHA trial.

Hyo S. Han, Ricardo L Costa, Avan J. Armaghani, Susan Hoover, John Kiluk, Marie Catherine Lee, Hatem Hussein Soliman, Hung T. Khong, Loretta S. Loftus, Qianxing Mo, Jennifer A Childress, Edith Abraham, Kaitlin Hendrix, Amy Aldrich, Marina Sehovic, Zena Jameel, Shannon Falcon, Robert J Weinfurtner, Aixa Elena Soyano Muller, Brian J. Czerniecki; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center, Tampa, FL; H. Lee Moffitt Cancer Center, Tampa, FL

Background: Early stage HER2 positive breast cancer (BC) patients (pts) are commonly treated with neoadjuvant HER2-targeted therapy. Optimizing neoadjuvant therapy by improving efficacy while reducing toxicity is a critical unmet need. IT DC1 therapy combined with an IgG1 antibody mediating ADCC drives strong anti-HER-2 CD4 Th1 responses and complete tumor regression in preclinical models. We initiated a phase I/II neoadjuvant study to explore the efficacy and immune stimulation effects of an initial 6 weeks of immunotherapy phase (IP) using IT DC1 vaccine plus trastuzumab (H) and pertuzumab (P) (as source of IgG1) followed by 12 weeks of paclitaxel (T) and HP.

Methods: Early stage HER2+ BC pts with tumor ≥ 1 cm were eligible. Treatment included IT DC1 weekly x 6 followed by paclitaxel 80 mg/m² IV weekly x 12. Trastuzumab IV every (q) 3 weeks (8 mg/kg loading dose, then 6 mg/m²) and pertuzumab IV q 3 weeks (840 mg loading dose, then 420 mg) x 6 cycles starting from day 1. Two dose levels (DL) of IT DC1 (DL1 = 50 million and DL2 = 100 million cells) were evaluated including 6 pts in each DL. Once the optimal DL is determined based on toxicities, additional 22 patients will be enrolled in expansion phase 2 trial. The primary end point of the phase 1 is the safety, immune responses (measured by ELISPOT). MRI breast was performed at the baseline, post-immunotherapy and post-chemotherapy. Here we are reporting the safety and immune correlates in phase 1 study.

Results: Twelve pts were enrolled between 10/2021 and 10/2022. Median age was 57 (range 34-74). Nine pts had hormone receptor positive disease with clinical stage I/II/III (5/5/2) and 4 pts had node positive disease. All pts completed IP and 10 patients completed THP chemotherapy as of 2/1/2023. Radiologic response per MRI breast on pre and post-IP showed 6 partial response, 3 complete response and 3 stable disease. Nine pts underwent surgery and 6 out of 9 pts had pCR (RCB 0). The most frequently observed toxicities were chills (50%), diarrhea (42%), nausea (42%), fatigue (42%), and headache (42%). ELISPOT demonstrated a significant decrease of HER2-specific T cell response following 6 weeks of DC1 IT injections in DL2 compared to DL1.

Conclusions: The addition of IT DC1/HP to neoadjuvant chemotherapy was well tolerated with manageable toxicities. The 100 million DC1 led to a significant decrease in peripherally circulating anti-HER2 T cell response at week 6 following IP and improved radiologic tumor responses which correlates with a higher likelihood of pCR. Data from another IT DC1 trial suggests decreased circulating HER2 responsive T cells are due to increased trafficking of reactive T cells out of circulation into the tumor possibly leading to an enhanced anti-tumor effect. Updated results including correlative biomarkers will be presented at the meeting.

Clinical trial information: NCT05325632. Research Sponsor: Moffitt Cancer Center Breast Research Funding.
Artificial intelligence (AI) –based machine learning models (ML) for predicting pathological complete response (pCR) in patients with hormone receptor (HoR) –positive/HER2-negative early breast cancer (EBC) undergoing neoadjuvant chemotherapy (NCT): A retrospective cohort study.

Luca Mastrantoni, Giovanna Garufi, Noemi Maliziola, Elena Di Monte, Giorgia Arcuri, Valentina Frescura, Angelachiara Rotondi, Giulia Giordano, Luisa Carbognin, Alessandra Fabi, Ida Paris, Fabio Marazzi, Franco Antonio, Gianluca Franceschini, Armando Orlandi, Antonella Palazzo, Giovanni Scambia, Giampaolo Tortora, Emilio Bria; Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli–IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy; Fondazione Policlinico Universitario "A. Gemelli" - IRCCS - UOC Oncologia Medica, Roma, Italy; Università Cattolica del Sacro Cuore, Roma, Italy; Policlinico Gemelli, Roma, Italy; Fondazione Policlinico Gemelli, Rome, Italy; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Precision medicine in senology Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy; Fondazione Policlinico Gemelli, Rome, Italy; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy; Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy, Italy

Background: The rates of pCR after NCT in HoR positive/HER2 negative EBC are low. Thus, clinicians need validated, unbiased, and reliable tools to better predict pCR at individual patients’ level. In this regard, AI can generate ML algorithms with these features, using clinical and pathological characteristics. Methods: Medical records were retrospectively retrieved for patients with EBC receiving NCT followed by surgery. Missing data were imputed using chained random forests. pCR was defined as absence of residual invasive cancer on pathologic evaluation of the breast specimen and lymph nodes (ypT0/isN0). Differences between pCR and non-pCR patients were assessed using t test or chi-squared test. Eight ML models (c5.0, k-nearest neighbour, random forest [RF], neural network, support vector machine [linear/radial], boosted trees and boosted logistic regression) were trained and tuned. A stratified ten-fold cross-validation was used to prevent overfitting. Models performance was evaluated using the area under the receiver operating characteristics curve (AUC). Features importance was assessed. Disease-free survival (DFS) was evaluated using the Kaplan-Maier method and hazard ratios (HRs) using Cox regression. Results: 572 patients were included: 332 (58%) were pre-menopausal and median age was 49.0 (IQR 43-57); 330 (58%) were T2 and 273 (48%) were N1; 437 (76%) had a ductal adenocarcinoma and 308 (54%) were grade 3. Median estrogen and progesterone receptor (ER/ PgR) expression was 90 (IQR 80-90) and 57.5 (IQR 5-90); median Ki67 was 35 (IQR 25-55) and 230 (40%) patients were HER2 zero. 565 (99%) patients received a combination of anthracyclines and taxanes; 434 (76%) received sequential and 137 (24%) concomitant CT. pCR was achieved in 87 patients (15%, 95% CI 12-18). Ten variables were included in the model: menopausal status, age, histology, grade, clinical T and N stage, ER/PgR status, Ki67 and HER2 status (zero/low). Among the evaluated models, the RF algorithm had the best performance: the AUC was 0.77 (95% CI 0.71-0.83) and sensitivity and specificity were 0.86 (95% CI 0.82-0.88) and 0.56 (95% CI 0.46-0.66). Variables with the highest importance were Ki67, ER/PgR status, age and nodal status. 511 patients were evaluable for survival: patients with pCR had a significant longer DFS compared to those who did not achieve pCR (HR 0.30; 95% CI 0.14-0.65, p = 0.002). Patients whose pCR was predicted by the model had longer DFS compared to those who pCR was not predicted (HR 0.56, 95% CI 0.21-0.87, p = 0.01).

Conclusions: The RF-ML algorithm combining clinical and pathological characteristics has the potential to predict pCR in HoR positive/HER2 negative patients undergoing NCT, thus supporting clinicians to individualize treatment for EBC. Research Sponsor: None.
Association between genomic alterations and response of triple-negative breast cancers (TNBC) to talimogene laherparepvec (TVEC) in combination with neoadjuvant chemotherapy (NACT).

Hatem Hussein Soliman, Hyo S. Han, Blaise Mooney, Ricardo L Costa, Marie Catherine Lee, Bethany Niell, Alec Chau, Shannon Falcon, Aixa Elena Soyano Muller, Avan J. Armaghani, Nazanin Khakpour, Robert J Weinfurtner, Susan Hoover, John Kiluk, Christine Laronga, Marilin Rosa, Hung T. Khong, Brian J. Czerniecki; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Moffitt Cancer Center and Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center, Tampa, FL; Moffitt Cancer Center, Tampa, FL

**Background:** TVEC is an engineered oncolytic virus (OVs) 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. RNAseq was performed on 37 pretreatment samples from enrolled patients to identify potential predictive genomic alterations.

**Methods:** Transcriptomic RNA sequencing analysis was performed on macrodissected tumor tissue through the Moffitt Molecular Genomics core using Illumina Truseq RNA exome kits. Read adapters were detected using BBMerge (v37.88) and removed with cutadapt (v1.8.1). For gene expression analysis, processed raw reads were aligned to human genome HG19 using STAR (v2.5.3a). Gene expression was evaluated as read count at gene level with HTSeq (v0.6.1) and Gencode gene model v19. Gene expression data were normalized and differential expression between experimental groups were evaluated using DEseq2 (v 1.38.2). Ensembl was used for SNP data search.

**Results:** Tumor mutation burden was not significantly different between pCR and non-pCR samples (median 227 vs 222 mut/MB, p = .11). Top 5 upregulated non-immunoglobulin genes associated with pCR in baseline samples were MYBL1, DNAH8, NR2E1, FGFR2, and SLC12A1 (FDR < 1%). A single nucleotide polymorphism (SNP) of the EIF2A gene (c.C290G, p.T97S) was the top variant associated with response present in 21/37 samples (non-pCR = 17/21 vs. pCR = 4/21, FDR = < 1%). This exon 4 coding region SNP is present in 17% of Black, 35% of White, and 46% of Asian individuals but its biologic or clinical significance is unknown. Lower EIF2A pathway activation was associated with inferior response to therapy. Additional data will be presented at the meeting.

**Conclusions:** Genomic alterations including a EIF2A SNP were correlated with response to OV plus NAC in TNBC. EIF2A is an important mediator of cellular responses to OV and may play a role in susceptibility to oncolysis. Additional investigation and validation of these variations in experimental models of OV susceptibility may provide predictive biomarkers for TNBC patients treated with OV plus NAC therapy. Clinical trial information: NCT02779855. Research Sponsor: Amgen.
Longitudinal MRI-based fusion novel model to predict pathological complete response in breast cancer treated with neoadjuvant chemotherapy: A multicenter, retrospective study.

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Background: Accurate identification of pCR to neoadjuvant chemotherapy (NAC) is important for determining appropriate surgery strategy and guiding the resection extent in breast cancer. However, a non-invasive tool to predict pCR accurately is lacking. Our study aims to develop ensemble learning models using longitudinal multiparametric MRI to predict pCR for each molecular subtype of breast cancer.

Methods: In this study, all patients underwent pre-NAC and post-NAC MRI examinations, and we collected multiparametric MRI sequences. Post-operation pathologic results were used to determine the pathologic complete response (pCR). We extracted 14676 radiomics and 4096 deep learning features and calculated a set of additional delta-value features. Then in the primary cohort (n = 409), inter-class correlation coefficient test, U-test, Boruta and the least absolute shrinkage and selection operator (LASSO) regression were used to select the most optimal feature set for each subtype of breast cancer. Finally, 20, 15 and 13 features were selected to construct the models based on 5 specific algorithms with cross-validation method for predicting pCR in HR+/HER2-, HER2+ and TNBC subtypes. The ensemble learning strategy was used to integrate the single-modality models outputs and improve the prediction performance. The diagnostic performances of models were evaluated in the three external cohorts with larger sample size of patients (n = 343, 170 and 340, respectively).

Results: A total of 1262 patients with breast cancer from four centers were enrolled in this study, and pCR rates were 10.6% (52/491), 54.3% (323/595) and 37.5% (66/176) in HR+/HER2-, HER2+ and TNBC subtype. After model development, the Multi-Layer Perception (MLP) neural network yields the best diagnostic performances in all subtypes and feature sets. In the three subtypes, the stacking model integrating pre-, post- and delta- models yielded the highest AUCs of 0.959, 0.974 and 0.958 in the primary cohort, and AUCs of 0.882-0.908, 0.896-0.929 and 0.837-0.901 in the three external validation cohorts, respectively. In all subtypes, the stacking model had accuracies of 85.0%-88.9%, sensitivities of 80.0%-86.3%, and specificities of 87.4%-91.5% in the external validation cohorts.

Conclusions: Our study established a novel tool to predict the responses of breast cancer to NAC and achieve excellent performance. The models could help to determine post-NAC surgery strategy for patients with breast cancer. Research Sponsor: National Science Foundation of China (82171898).
Association of HER2/CEP17 ratio with pCR after HER2-directed neoadjuvant treatments in the phase III NeoALTTO trial.

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Background: HER2-directed therapies are approved for the treatment of patients with HER2-positive invasive breast cancer as defined by HER2 protein overexpression, or HER2 gene amplification based on HER2/chromosome enumeration probe (CEP17) ratio ≥ 2.2. Above this accepted HER2 status determination, however, it is still unknown whether the efficacy of HER2-directed therapy in early breast cancer increases with increasing HER2/CEP17 ratios. Therefore, the purpose of the presented work is to evaluate whether quantitative assessment of the HER2/CEP17 ratio predicts pathological complete response (pCR) and event-free survival (EFS) of patients treated with neo-adjuvant HER2-based regimen in the prospective phase III NeoALTTO trial.

Methods: 455 women with HER2-positive early breast cancer, who had received neo-adjuvant trastuzumab and/or lapatinib for 6 weeks and then together with 12 cycles of weekly paclitaxel were included in this analysis. The HER2/CEP17 ratio in the primary tumor samples was correlated with pCR and survival outcome. Results: The Median HER2/CEP17 ratio in NeoALTTO was 5.1 (range: 1.1 – 100.0), and ratios were not associated with age, hormone receptor status, or any of the other clinicopathological variables analyzed. The log HER2/CEP17 ratio significantly predicted for pCR in both uni-variate (OR: 1.83; 95% CI: 1.11 - 3.01, p = 0.0176) and multivariate analysis (OR: 1.79; 95% CI: 1.07 - 2.99, p = 0.0257). Higher HER2/CEP17 ratios were, however, not associated with improved EFS (adjusted HR = 0.79; p = 0.3537). A pCR prediction model which included HER2/CEP17 ratio, treatment arm, and hormone receptor status improved the predictive strength of treatment arm alone from a ROC AUC value of 0.60 to 0.69.

Conclusions: In patients treated with HER2-based neoadjuvant therapy, quantitative analysis of the readily available pre-treatment HER2/CEP17 ratio by FISH is predictive of pCR but not EFS. Research Sponsor: The NeoALTTO trial received financial support from GlaxoSmithKline (until January 2015) and Novartis Pharma AG (as of January 2015).
Circulating tumor DNA (ctDNA) monitoring in patients with breast cancer receiving neoadjuvant palbociclib and endocrine therapy: A secondary analysis of the NeoRHEA phase 2 study.

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Background: Personalized circulating tumor DNA (ctDNA) assays are being evaluated in early breast cancer (BC). We investigated the value of ctDNA monitoring in the NeoRHEA study. Methods: NeoRhea (NCT03065621) is a single arm phase 2 study in which patients with estrogen receptor (ER)+/HER2-early breast cancer were treated with neoadjuvant palbociclib + endocrine therapy (ET) for 4 months. Plasma samples were collected at four timepoints: pre-treatment (BL), after the first treatment cycle (C1D28), before surgery (Surgery) and one month post Surgery (End of Study). ctDNA detection was evaluated using the personalized RaDaR assay. Whole-exome sequencing (WES) was performed on BL tumor biopsies followed by a personalized assay development using tumor, plasma and normal DNA in order to track up to 48-patient specific somatic variants in plasma cell-free DNA (cfDNA) using next generation sequencing. Associations between ctDNA detection and BL clinical-pathological characteristics, cell cycle arrest (CCCA) defined as Ki67 ≤2.7% at surgery, residual cancer burden (RCB) rate and breast cancer free survival (BCFS) were investigated. Results: Of 100 patients enrolled, 78 patients and 302 plasma samples were successfully profiled by the RaDaR assay. The number of variants targeted by the assay ranged between 7-48 (median = 25). The median estimated variant allele fraction for ctDNA positive samples was 0.02% (range 0.0009%-0.91%). A total of 42/76 patients were ctDNA positive at BL, 4/76 at C1D28, 4/75 at Surgery and 0/75 at End of Study. Out of 78 patients, 68% were postmenopausal, 78 % had cT2 and 69% cN0 tumors, 20% had multifocal/multicentric tumors, 18% had histological grade 3 tumors, 76% had CCCA (Ki67 not available in 20 patients) and 34% RCB 3 at surgery. ctDNA detection at BL was higher in histological grade 3 tumors (p = 0.03), lower in multifocal/multicentric tumors (p = 0.01), higher in RCB III tumors, (p = 0.01) but was not associated with CCCA. With a median follow-up of 3.8 years (range 1-5 years), 4 patients developed distant and one patient locoregional recurrences. ctDNA detection after one month of treatment (logrank p = 0.02), but not at baseline (p = 0.59) nor at surgery (p = 0.67) was associated with worse BCFS. Conclusions: Detection of ctDNA in early-stage breast cancer is challenging. Our data suggests association of ctDNA detection with some pathological and clinical variables. Independent validation is needed. Clinical trial information: NCT03065621. Research Sponsor: Pfizer; INIVATA; Les Amis de l’Institut J. Bordet; F.N.R.S.
Neoadjuvant tislelizumab plus nab-paclitaxel and carboplatin followed by adjuvant tislelizumab in patients with early triple-negative breast cancer.

**Background:** Triple-negative breast cancer (TNBC) is the subtype with the least favorable outcomes. However, TNBC is associated with higher immune cell abundance than other subtypes, making it a good candidate for immunotherapy. Neoadjuvant chemotherapy is the preferred treatment approach for early TNBC. Emerging evidence shows that additional immune checkpoint inhibitors (ICI) in neoadjuvant therapy significantly increases pathological complete response (pCR) and event-free survival in early TNBC. Treatment regimens of paclitaxel and carboplatin (TP) is class I recommendation for TNBC neoadjuvant therapy, the application of ICI with TP regimens is worth exploring.

**Methods:** In this multicenter, open-label, phase II study, patients with untreated, histologically confirmed TNBC in stage II-III (per AJCC 8th edition) were enrolled. Patients received six cycles of neoadjuvant therapy with tislelizumab at 200 mg once every 3 weeks plus nab-paclitaxel (125 mg/m² on days 1 and 8) and carboplatin (at a dose based on an area under the concentration 2 on days 1 and 8) every 3 weeks. Patients who either completed or discontinued the neoadjuvant treatment would undergo definitive surgery. After surgery, the patients received adjuvant tislelizumab every 3 weeks for up to 12 cycles. The primary endpoint was the rate of pCR (ypT0/Tis ypN0). The secondary endpoints included 1-, 2-, 3-year event free survival rates and overall survival rates. Based on the Simon's Two-Stage design, if 13 of 32 patients achieved pCR, the enrollment would proceed to full accrual of 62 patients as planned. If 29 of 62 patients achieved pCR, we would deem the study to have met the primary endpoint.

**Results:** From Mar 2021 to Jan 2022, 32 patients were enrolled; 18 of them achieved pCR, and therefore the study proceeded to complete the enrollment of 62 patients. At the data cut-off of Oct 13, 2022, 62 patients were enrolled, among which 50 patients received neoadjuvant treatment and underwent definitive surgery. The median age was 50 years. 36 (72.0%) patients had stage II breast cancer at diagnosis. 31 of the 50 patients achieved pCR (ypT0/Tis ypN0), and the pCR rate was 62.0% (95% CI, 47.2-75.4). Patients with immune cell PD-L1 expression ≥10% had numerically higher pCR rate (81.8% vs 53.6%) than those with PD-L1 expression ≥1%. All 50 (100%) patients reported any grade of neoadjuvant treatment-related adverse events (TRAEs). Grade ≥3 TRAEs occurred in 27 (54%) patients. The rate of immune-related adverse events (irAEs) was 34% (17/50), with the common occurring (10%) irAE of hypothyroidism (n = 8, 16%), 2 (4.9%) patients experienced grade ≥3 irAEs. Severe adverse events were reported in 5 (10%) patients. **Conclusions:** The study has met its primary endpoint. Tislelizumab plus nab-paclitaxel and carboplatin achieved a higher pCR and was generally well tolerated in the neoadjuvant treatment of early TNBC. Clinical trial information: ChiCTR2100041675. Research Sponsor: This study was supported by BeiGene (Beijing) Co., Ltd.
Neoadjuvant single-dose trilaciclib prior to combination chemotherapy in patients with early triple-negative breast cancer: Safety, efficacy, and immune correlate data from a phase 2 study.

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Background: Trilaciclib, an intravenous CDK4/6 inhibitor, induces transient G1 cell cycle arrest. In preclinical studies, trilaciclib demonstrated immune-modulating effects by enhancing T-cell activation, favorably altering the tumor microenvironment (TME), and improving long-term immune surveillance. Preliminary data from this phase 2, single-arm, open-label study of neoadjuvant trilaciclib in triple-negative breast cancer (TNBC; NCT05112536) showed that single-dose trilaciclib increased CD8+ T-cell/Treg ratios within the TME. Here, we combine immune analysis with clinical outcomes to identify correlates of treatment response. Methods: Patients (pts) with early-stage TNBC received single-dose trilaciclib followed by trilaciclib + dose-dense anthracycline/cyclophosphamide and taxane (AC/T). Per investigator discretion, pts received pembrolizumab (pembro) 400 mg Q6W from cycle 1 and/or carboplatin (carbo) AUC 1.5 QW from cycle 5. Tumor biopsies and blood samples were collected prior to treatment, 7 days post single-dose trilaciclib, and during surgery, with an additional blood sample at cycle 2. PDL1 status was assessed per Ventana SP142 assay (positive immune cell score $ \geq 1\%$). The primary objective is to evaluate the immune-based mechanism of action of single-dose trilaciclib. Results: As of January 3, 2023, 18/24 pts had completed treatment and/or had definitive surgery; 1 pt with neuroendocrine features discontinued due to disease progression. Median age was 57 years. At diagnosis, 79% of pts had stage II tumors (88% with ductal carcinoma; 38% with PDL1+ tumors). 18 pts received pembro + carbo, 3 pts pembro only, and 3 pts carbo only. Common treatment-related adverse events (TRAEs) were fatigue (79%), nausea, (67%), alopecia (67%), and neutropenia events (63%); 42% of pts had grade 3/4 neutropenia events. 4 serious TRAEs occurred in 2 (8%) pts: pembro-related colitis and hypertransaminasemia, trilaciclib/paclitaxel-related urosepsis, and AC-related febrile neutropenia. Response data were available for 15 pts; pathologic complete response (pCR) was observed in 7 (47%) pts, with pCR rates of 86% vs 13% for pts with PDL1+ vs PDL1–tumors, respectively. Immune analysis of the TME post trilaciclib monotherapy demonstrated several pCR-related features, such as increased stromal tumor-infiltrating lymphocytes and granzyme B+ cells. Correlative blood analysis revealed increased circulating baseline CD8+ T cells in pts achieving pCR. Conclusions: Safety and tolerability data are encouraging for trilaciclib in combination with AC/T ± pembrolizumab ± carboplatin in the neoadjuvant setting for early-stage TNBC. Preliminary efficacy data align with standard neoadjuvant chemotherapy regimens. Final pCR data from all pts and immune correlates from tumor and blood samples will be presented. Clinical trial information: NCT05112536. Research Sponsor: G1 Therapeutics, Inc.
NeoIRX trial: Immunologic induction with peri-lymphatic cytokines to enhance pembrolizumab (pembro) response in stage II/III triple-negative breast cancer (TNBC).

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Background: The addition of pembro to neoadjuvant chemotherapy (NACT) improves pathological complete response (pCR) rate and recurrence-free survival in stage II/III TNBC, albeit with substantial chemotherapy-attributed toxicity. We hypothesize that locoregional cytokine therapy could be combined with pembro to optimize immune response and clinical outcome. In a phase 1b early-stage breast cancer trial, we previously demonstrated that peri-lymphatic cytokine injection (IRX-2 regimen, comprised of physiologic doses of IL-2, IFNg, and other cytokines derived from activated donor lymphocytes, given with low-dose cyclophosphamide) is well tolerated and associated with increased intratumoral lymphocytes, T-cell activation, and PD-L1 expression. Here, we report preliminary outcomes of neoIRX, a phase II trial evaluating induction IRX-2 + pembro preceding NACT + pembro. Methods: Subjects with stage II/III TNBC were randomized to receive induction pembrolizumab (all subjects: 200mg IV) +/- peri-areolar IRX-2 (IRX-2 arm: 1 ml SQ x2 daily for 10 days + cyclophosphamide 300 mg/m2 IV x 1) preceding initiation of NACT + pembro. The primary endpoint was pCR rate following NACT + pembro (n = 15 subjects/arm planned); secondary endpoints were safety and tolerability. We explored post-induction/pre-NACT radiographic (ultrasound) and histologic outcomes (TILs, tumor regression) as a biomarker strategy to predict pCR.

Results: The trial terminated after n = 12 subjects due to withdrawal of drug support for IRX-2. The IRX-2 arm achieved 83% pCR (n = 5/6, CI 36-100%) compared to 33% pCR with pembro alone (n = 2/6, CI 4-78%). The regimen was well-tolerated with minimal IRX-2-attributed toxicities (67% grade I skin bruise). Toxicities during NACT + pembro were similar to Keynote-522. 67% (n = 4/6) of IRX-2 subjects experienced week 3 radiographic regression, with evidence of brisk lymphocyte infiltration on week 3 biopsy, and with 100% pOR rate (n = 4/4) following NACT + pembro. n = 2/6 subjects receiving pembro+IRX-2 experienced pCR on week 3 biopsy, versus n = 0/3 evaluable in control arm. Conclusions: Induction IRX-2 + pembro is well tolerated and is associated with encouraging outcomes, supporting further study of peri-lymphatic induction cytokine therapy in stage II/III TNBC. Post-induction radiographic and histologic outcomes may identify patients with immune-responsive tumors, for whom NACT de-escalation may be a promising therapeutic approach to mitigate toxicity. Clinical trial information: NCT04373031. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.; Brooklyn Immunotherapeutics.
Moderate physical exercise and immune system modulation in patients with breast cancer treated with neoadjuvant chemotherapy.

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Background: The link between physical activity (PA) and immune system is known. However, are not clearly understood which mechanisms are activated by PA. We investigated the effect of moderate PA (MPA), on a panel of circulating cytokines during neoadjuvant chemotherapy (CT) in patients (pts) with breast cancer. Methods: Pts received sequential epirubicin and cyclophosphamide for 4 cycles followed by weekly paclitaxel + trastuzumab. MPA consisted of Nordic or fit walking, 3 workouts/week, 1 hour each, in the 9 weeks before Surgery (S). Blood samples were collected in pts underwent MPA (TR) and in a group of pts who declined MPA (UN) at baseline (T0), at day 1 of week 6 of paclitaxel (starting MPA) (T1) and before S (T2). At each time point the level of 22 cytokines (IL1b, IL2, IL4, IL5, IL6, IL7, IL8, IL10, IL12, IL13, IL15, IL17a, IL18, IL21, CCL2, CCL4, CXCL10, CCL22, IFNγ, TGFβ, TNFα, VEGF) was measured using Simple Plex Ella. Sample size was calculated using effect size method considering a Cohen’s d of 0.65 as observed for a candidate cytokine (IL-6) between two groups. Considering a desired statistical power of 0.8 and a probability level of 0.05 a minimum of 78 patients were required. The difference among the median value of cytokines was analysed using non parametric Mann Whitney U test. Comparisons between time points in the same group were analysed with Wilcoxon signed-rank test. Results: Accrual is completed. 61 pts were TR and 20 UN. Main patients’ characteristics are listed. At T0 IL4, IL17, IL18 and VEGF level was significantly higher in UN respect to TR pts. At T1 IL4, IL17 and IL18 level remained significantly higher in UN pts. At T2, UN pts showed significantly higher level of IL4, IL6, IL7, IL8, IL17, IL18 VEGF and TGFβ. IL21 was significantly higher in TR pts. Longitudinal analysis between T0 and T1 in TR and UN pts showed significantly lower level of CCL22 and significantly higher level of IL7, IL13 and CXCL10 in TR pts and significantly higher level of IL8 in UN pts. Longitudinal analysis between T1 and T2 showed significantly higher level of IL21, CXCL10, CCL22, TNFα and significantly lower level of IFNγ, IL6, IL8, CCL2, TGFβ in TR pts and significantly lower level of CXCL10 in UN pts. Conclusions: TR and UN pts differed modestly at baseline including acceptance of MPA. The longitudinal analysis TO-T1 showed that CT induced more evident changes in TR than in UN pts. Longitudinal analysis T1-T2 demonstrated major changes in Th1 and Th2 cytokines only in TR pts. Overall, CT induced weak changes in UN and greater changes in TR pts strengthened by the addition of MPA. These observations suggest a more efficient immune system in TR pts and a possible additional benefit derived from MPA. Research Sponsor: GONO Foundation; ARCO Foundation.
Prospective evaluation of pathologic response with neoadjuvant chemo-immunotherapy in metaplastic breast cancer.

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Background: Metaplastic breast cancer (MpBC) is a rare aggressive histologic type of breast cancer that is often resistant to standard chemotherapy with pathologic complete response (pCR) rates ranging between 2-23%. PDL1 expression has been reported in up to 95% of primary MpBCs suggesting that response rates may be improved with addition of immune checkpoint blockade (ICB). Here we evaluate pCR rates (ypT0/is ypN0) in stage I-III MpBCs receiving neoadjuvant chemo-immunotherapy (NAT).

Methods: The Memorial Sloan Kettering Cancer Center Rare Breast Cancer Program (CARE-4-RARE) is a new clinical and translational program dedicated to the study of rare breast cancers. Since the start of the program, 15 patients (pts) with early-stage MpBC have completed treatment with the neoadjuvant KEYNOTE-522 regimen. Wilcoxon rank-sum and Fisher’s exact tests were used to compare characteristics according to pCR status. All statistical tests used a significance level of 5%. Results: Median age at diagnosis was 50 (range, 43-60). All pts were female, 13% self-identified as Asians, 33% as Black and 53% as White. All tumors were poorly differentiated and of triple-negative phenotype, median tumor size was 3.2cm, 80% had stage II disease and 20% were clinically node positive. Metaplastic subtypes included 5 matrix-producing (33%), 3 spindle (20%), 4 squamous (27%), 3 mixed (20%). Of the 15 pts, 4 (27%) achieved a pCR, which suggest the possibility of a higher than expected pCR rate in MpBC with the addition of ICB to chemotherapy. We did not observe a significant difference in clinicopathological features between pCR vs. non-pCR groups. We observed numerical differences in pCR between MpBC subtypes though the p-value was not significant due to limited sample size. Of these 4 pts, 2 had matrix-producing and 2 had mixed subtypes. Two pts with pCR only received Cb+P+Pem. Three pts (20%) experienced PD (squamous n = 2, spindle n = 1) necessitating discontinuation of NAT and expediting surgery.

Conclusions: This is the first prospective study to evaluate neoadjuvant ICB in MpBC. These data suggest the possibility of a higher than expected pCR rate in MpBC with the addition of ICB to chemotherapy (27%). This work suggests that neoadjuvant ICB should be considered in MpBC with close monitoring. Notably, 50% of reported pCR in this cohort were in pts who only received Cb+P+Pem. In spite of improved pCR rates, 20% of pts progressed during NAT highlighting the need for better treatment strategies in this treatment-refractory subset of MpBC and close monitoring to allow resection before progression to inoperability. The dichotomy in responses to ICB (super-responsive vs. super-refractory) may suggest the presence of unique biomarkers for immune response in MpBC. By the 2023 ASCO Annual Meeting a total of 26 pts will have completed NAT; we will report updated outcomes along with correlative immune biomarkers (sTIL, PDL1, TMB). Research Sponsor: None.
A prospective, phase II, neoadjuvant clinical study based on chemotherapy sensitivity in hormone receptor–positive, HER2-negative breast cancer: FINEST study.

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Background: Neoadjuvant therapy for hormone receptor positive/HER2-negative breast cancer presents challenges in patient selection and treatment modalities. Chemotherapy and endocrine therapy are neoadjuvant options for this type of breast cancer. Neoadjuvant endocrine therapy (NET) has a similar response rate to chemotherapy. However, patient selection is a key factor. We designed this study to further optimize the selection of target population and treatment strategy. Methods: For breast cancer patients eligible for inclusion, patients were allocated to 2 cycles of chemotherapy using nab-paclitaxel with carboplatin. For patients with better efficacy ($\geq 40\%$ regression after 2 cycles), the original regimen was continued to complete 6 cycles (group A). For patients who had poor efficacy ( 40\% regression after 2 cycles), patients were randomly assigned (1:3:1) to group B, C, D. Group B continued to use the same chemotherapy. Group C were received dalpiciclib, letrozole and adebrelimab plus goserrelin if patient was premenopausal. Group D were directly received surgery. Primary endpoints were pathologic complete response (pCR) rate and objective response rate (ORR). As the trial progresses, according to Bayesian model, the posterior distribution of pCR rates of group C would be updated. To explore the genomic feature, a genetic panel which includes 484 genes that are targets of approved and experimental therapies and frequently mutated genes in breast cancer was used. Results: From Nov 16, 2020 to Jun 10, 2022, 121 patients were enrolled. 76 patients with better efficacy were continued to complete 6 cycles (group A). And 45 patients were randomly assigned to groups C (27 patients), B (9 patients) and D (9 patients). The primary objective was not met. The total pCR rate was 4.1\% (5/121) with all pCR patients are in group A. No significant differences were observed in pCR between group B, C and D. ORR was 81.8\% in total cohort with 100\% in group A, 20\% in group B, 81.5\% in group C and 0\% in group D, respectively. Decreases in Ki-67 were similar across arms. According to the Bayesian model, there is no probability of success of phase 3 study. Therefore, the study was closed. Our analysis illustrated the most prevalent mutations were PIK3CA (41\%), followed by TP53 (28\%) and GATA3 (17\%). We found that AKAP3, ASXL1, INSR, RET or TBX3 mutations were related to the limited treatment benefit of chemotherapy. Mutations in MAP3K1 were likely to be associated with the worse outcome in Group C. Conclusions: Neoadjuvant chemotherapy and neoadjuvant endocrine therapy are not mutually exclusive. The overall treatment strategy did not improve the efficacy, but there is still a possibility that some people can get an improvement from the strategy adjustment. Precision analysis may yield the characteristics of patients who would benefit from this shift in treatment strategy. Clinical trial information: NCT04215003. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. Ltd. China.
Association of biophysics-based biomarker with tumor volumetric response in breast cancer treated with immunotherapy.

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Background: The treatment landscape of triple negative breast cancer (TNBC) has rapidly changed in recent years, with immuno-oncology (IO) therapies, such as immune checkpoint inhibitors, leading to improvement in patient outcomes. However, the number of patients who benefit is less than 15%, and the therapy itself can prompt severe immune-related adverse events. Breast cancer tumor volume measurements derived from magnetic resonance imaging (MRI) have proven to be a strong predictor of outcome (survival) in patients who either achieve pathological complete response (pCR) or have residual cancer burden (RCB) (ACRIN6657/CALGB150007 I-SPY1). Using an integrative computational approach, we developed both the TumorIO biomarker and the TumorIO Score to predict response to IO therapy in breast cancer patients. Here, we assess the volumetric response in IO-treated patients and its relationship with the TumorIO Score.

Methods: We assessed the relationship between breast tumor volumetric response to IO therapy and the TumorIO Score, a previously developed metric that relates probability of IO responsiveness to spatially-resolved tumor biology. We grouped patients into TumorIO Score high vs. low populations, and compared final volumes assessed by MRI and percent response to therapy between groups.

Results: We analyzed the volumetric response of IO-treated patients from the I-SPY2 trial and from an independent cohort (total n = 67). Over 96% of the IO-treated patients in the I-SPY2 trial (n = 55) had a greater than 90% volumetric response, while in the independent cohort (n = 12) only 50% of patients had greater than 90% volumetric response. Across both cohorts, 95.8% of patients with a high TumorIO Score achieved > 90% reduction in tumor volume. Additionally, we identified three patients in our cohort that appeared not to respond to IO therapy, who were later classified as progressor, pseudo-progressor, and non-responder patients. The TumorIO biomarker was able to differentiate these three patients, as it associates a unique distinctive biological phenomenon with either response or lack of response.

Conclusions: The TumorIO Score provides a novel technology to address several challenges in neoadjuvant IO therapy, namely: predicting which patients are likely to have pCR in response to IO therapy, as well as identifying patients likely to have a substantial volumetric response to IO. Additionally, this method may facilitate subcategorizing patients likely to show radiological pseudo-progression prior to IO administration, although a larger cohort is needed to validate these findings. Research Sponsor: SimBioSys, Inc.
Whole-genome sequencing based assessment of HER2 focal amplification for precision oncology of breast cancers.

Ryul Kim, Joonoh Lim, Hansol Park, Seongyeol Park, Baek-Lok Oh, Sangmoon Lee, Ji-Yeon Kim, Seok Jin Nam, Seok Won Kim, Jeong Eon Lee, Jonghan Yu, Ji In Ryu, Jeong Seok Lee, Minsuk Kwon, Jeongmin Lee, Yeon Hee Park, Young Seok Ju; Genome Insight Inc., San Diego, CA; Samsung Medical Center, Seoul, South Korea; Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Samsung Medical Center, Gangnam-Gu, South Korea; Research Institute for Future Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Ajou University, Suwon-Si, South Korea; The Catholic University of Korea Seoul St. Mary’s Hospital, Seoul, South Korea

Background: Focal oncogene amplification confers a growth advantage to tumor cells and drives cancer evolution. Herein, we aimed to explore focally amplified HER2 in breast carcinomas. Methods: We performed whole genome sequencing (WGS) and whole-transcriptome sequencing (WTS) in 787 breast cancer samples. HER2 focal amplification was defined as having a segment length less than 3Mbp and ≥4 higher copy number than the surrounding region. Results: Most of the patients were pre-menopausal women (n = 574, 72.9%) with a median age of 37 (range 21-76) years. We identified 57 (58.8%) and 27 (5.0%) samples with HER2 focal amplification in HER2-positive (n = 97) and even HER2-negative (n = 536) by immunohistochemistry (IHC) and in-situ hybridization (ISH) according to ASCO guideline for breast cancer, respectively. Regardless of HER2-positivity, HER2 focal amplification was significantly associated with higher HER2 RNA expression. Among 28 patients who received six cycles of docetaxel/carboplatin/trastuzumab/pertuzumab neoadjuvant therapy followed by curative surgery, 21 patients had HER2 focal amplification and 14 (66.7%) achieved pathologic complete remission (pCR). Intriguingly, all patients without HER2 focal amplification (n = 7) failed to achieve pCR. HER2 focal amplification showed enrichment of TP53 mutations (OR 0.245, q < 0.001), but was mutually exclusive with GATA3 mutations (OR 2.82, q = 0.055). The mutational spectrums suggested that the activity in APOBEC family of cytidine deaminases were responsible for the somatic single-nucleotide variants of breast cancer with HER2 focal amplification. Compared to samples without HER2 focal amplification, samples with HER2 focal amplification were less likely to have defective homologous recombination DNA repair pathway. HER focal amplifications were closely associated with various types of structural variations. Translocation partners of HER2 were widespread across the entire genome with notable exceptions on chromosome 2, and most of them were close to super-enhancers implying enhancer hijacking as one of mechanisms of HER2 overexpression. Breast cancers with or without HER2 focal amplification showed distinct RNA expression patterns. Notably, activity of genes involved in doxorubicin-resistance and AKT1 signaling were significantly associated with HER2 focal amplification. Conclusions: Our analysis demonstrates that WGS enables better classification of the HER2 amplification status in breast cancer than IHC with ISH, suggesting WGS as a sensitive tool for screening breast cancers for anti-HER2-targeted therapies. Research Sponsor: None.
Social determinants of health and utilization of neoadjuvant chemotherapy in patients with triple negative breast cancer (TNBC) in the community oncology setting.


Background: TNBC has a higher incidence in African American women compared to European American, often presents at a younger age or more advanced stage, and is associated with worse outcomes. The use of multi-agent neoadjuvant chemotherapy (NC) improves event-free survival and overall survival in patients with early-stage TNBC and is considered standard of care. Race and other social determinants of health (SDOH) have been shown to affect outcomes in patients with TNBC. Differences in use of NC associated with SDOH may be a contributing factor to inferior outcomes. The aim of this study is to determine if SDOH measures affect utilization of NC in patients with early-stage TNBC.

Methods: This retrospective observational cross-sectional study examined patient profiles, treatment patterns and SDOH indicators among patients newly diagnosed with early-stage breast cancer in The US Oncology Network. Using iKnowMed EHR data, patients diagnosed with TNBC between 03/31/2017 and 09/30/2021 with stages II-IIIB disease or tumor size $\geq 2cm$ (T2 or higher) were included. The initial TNBC diagnosis date was used as the index date for each patient and records were assessed from 6 months pre- to 6 months post-diagnosis for NC initiation, baseline characteristics, and social determinants, including Area Deprivation Index (ADI), a validated measure of socioeconomic status.

Results: 3321 patients with TNBC were identified, with a mean age of 58 years; 59% were White, 15% Black, 3% Asian, and 23% other/unknown; and 2139 (64%) received NC. Patients who received NC relative to those who did not were younger (mean 55.9 vs 61.8; p=0.001), had higher BMIs (70% with BMI $> 25$ vs $\leq 25$, p=0.045), and had commercial or Medicaid insurance (67.5% with commercial insurance or Medicaid vs. 52.5% with Medicare; p=0.001). Regional differences were observed, with proportionally fewer patients receiving neoadjuvant chemotherapy in the south US census regions and more in the west. There was no difference in NC use in Black vs White patients (66% vs 64%). No significant differences in receipt of NC were found for race, ethnicity, or ADI.

Conclusions: In the community oncology setting, we did not observe inequities in the use of NC based on social determinants analyzed in this study, such as race, ethnicity, and ADI. Poorer outcomes observed in Black patients with TNBC may not be a result of underutilization of NC. Research Sponsor: None.
Use of PROMIS to capture patient reported outcomes over time for patients on I-SPY2.

Saya Jacob, Hongmei Yu, Denise M. Wolf, Aheli Chattopadhyay, Susie Brain, Carol Simmons, Kathryn Jean Ruddy, Irene Kang, Anne Hudson Blaes, Amrita B Somani, Dawn L. Hershman, Laura Esserman, Michelle E. Melisko; University of California San Francisco, San Francisco, CA; Quantum Leap Healthcare Collaborative, San Francisco, CA; UCSF Breast Science Advocacy Core, Palo Alto, CA; UCSF Breast Science Advocacy Core, San Francisco, CA; Mayo Clinic, Rochester, MN; City of Hope, Orange County, Irvine, CA; University of Minnesota, Minneapolis, MN; University of California, San Francisco, San Francisco, CA; Columbia University, New York, NY

Background: Patient reported outcomes (PROs) capture direct feedback from patients in clinical trials. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) is an open source and validated PRO platform. Data on PROMIS score trajectories over time for breast cancer patients undergoing neoadjuvant chemotherapy (NAC) are limited. Methods: We administered paper surveys to patients enrolled on the I-SPY2 trial, a multicenter, randomized phase 2 trial comparing novel agents to standard NAC in high-risk breast cancer. PRO domains included PROMIS Physical Function, Anxiety, Depression, Applied Cognition and Fatigue. Surveys were administered at baseline (post-consent), C1D1, inter-regimen (~12 wks into NAC), pre-surgery and at 1, 6, 12, and 24 months post-surgery. Responses were scored using the HealthMeasures Scoring Service to generate a standardized T score, with a score of 50 representing the general US population mean. Higher Anxiety, Depression and Fatigue scores represent worse symptoms; higher Physical Function and Applied Cognition scores represent better symptoms. We calculated average scores by time-point and compared changes from baseline to various grouped time points using a paired t-test. Results: From 1/2012 to 7/2020, 1631 patients enrolled in I-SPY 2 with 959 completing the baseline survey. 62% had at least two “on-treatment” surveys, and 52% had at least one follow-up time-point. Average baseline PROMIS scores for Physical Function, Anxiety, Depression, Applied Cognition and Fatigue were 46.7, 55.1, 47.2, 53.3 and 46.0 respectively. Between baseline and the latest on-treatment time point we observed improvement in Anxiety (-5.2) and worsening in Physical Function, Applied Cognition and Fatigue (-5.4, -6.9 and +8.2 respectively). Between baseline and the latest post-surgery time point, we saw improved Anxiety (-5.9) and worsened Physical Function, Applied Cognition and Fatigue (-5.9, -3.6 and +4.3). Depression changed minimally. Conclusions: Using PROMIS, patients on I-SPY2 experienced worse Physical Function, Applied Cognition and Fatigue but improved Anxiety during and after treatment compared to baseline. While changes in Applied Cognition and Fatigue recovered partially after treatment, Physical Function scores did not, suggesting potential for longer term impact on quality of life. Clinical trial information: NCT01042379. Research Sponsor: U.S. National Institutes of Health; Quantum Leap Healthcare Collaborative.

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↑=improved; ↓=worsened.
Oral paclitaxel and dostarlimab with or without trastuzumab in early-stage, high-risk breast cancer: Results from the neoadjuvant ISPY 2 TRIAL.

Rebecca Arielle Shatsky, Alexandra Thomas, Christina Yau, Amy Jo Chien, Carla Isadora Falkson, Erica Michelle Stringer-Reasor, Coral Oghenerukevwe Omene, Meghna S. Trivedi, Judy Caroline Boughey, Amy Sanford, Mili Arora, Tara B. Sanft, Rita Nanda, Claudine Isaacs, Thelma Brown, Nola Hylton, Angela DeMichele, Douglas Yee, Laura Esserman, I-SPY Investigators; University of California San Diego Medical Center, La Jolla, CA; Wake Forest University School of Medicine, Winston-Salem, NC; University of California, San Francisco, San Francisco, CA; University of Rochester Medical Center Department of Medical Oncology, Rochester, NY; University of Alabama at Birmingham, Birmingham, AL; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Columbia University, New York, NY; Mayo Clinic, Rochester, MN; Sanford Health, Sioux Falls, SD; UC Davis Comprehensive Cancer Center, Sacramento, CA; Yale University, New Haven, CT; University of Chicago, Chicago, IL; Lombardi Cancer Center, Georgetown University, Washington, DC; Susan G. Komen, Birmingham, AL; University of California San Francisco, San Francisco, CA; University of Pennsylvania, Philadelphia, PA; Masonic Cancer Center, Minneapolis, MN

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, 2023, issue of the Journal of Clinical Oncology.
The proliferation biomarker SPAG5 expression in HER2 low and HER2 overexpression early breast cancer (BC) predicting tumour response to neoadjuvant chemotherapy (NACT) with and without trastuzumab.

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Background: HER2 low is defined by HER2 immunohistochemistry (IHC) score 1+ or 2+ with negative florescent in situ hybridization (FISH-). In metastatic BC the HER2 directing antibody drug conjugates (ACDs) had shown significant efficacy; however, its curative role in early BC has not defined yet. Here we aimed to study the clinical and molecular features of HER Low in 3850 cases of early BC and its response to NACT; Anthracycline/Taxane with/without Trastuzumab to optimize its clinical utility.

Methods: Paired sections from pre and post NACT samples of 1250 early BCs (NACT cohort) were profiled for HER2 and SPAG5 using IHC and FISH. A novel triple coloured SPAG5 HER2 Ch17 probe was used as well HER2 Ch17 probe. ASCO guidelines were followed. Pre therapy samples of 400 BC were profiled for 450 customised genes using the Nano String nCounter platform. Moreover, 2600 cases of early BC who received adjuvant non-HER2 targeted therapies (ADJ cohort) were studied. The primary end point was pathological complete response (pCR). The Secondary endpoints were relapse free survival and bookmarks changes. Results: HER2 low was expressed in 31% (800/2600) of ADJ and 39% (490/1250) of NACT cohorts whereas HER2 overexpression (+) (HER2 IHC+3 or IHC+2/FISH+) was detected in 21% (540/2600) and 32% (401/1250) of ADJ and NACT cohorts; respectively. Compared to those with HER2 IHC 0 expression, HER2 low was associated with more aggressive features: ER-, PR-, Ki67+, SPAG5+, high grade, and p53 mutation and enriched in ERBB2 and its related genes EGFR, ERBB4, GRB7, SPAG5 and FGRF4; p < 0.0001. After NACT, HER2 low had the lowest pCR rate (16%; 57/348) compared to HER2 IHC+3 (54%; 120/223), HER2 IHC+2/FISH+ (23%; 14/60) and HER2 IHC 0 (25% (66/264); p < 0.0001. Compared to either HER2+ or HER2 IHC 0 cases; HER2 low had higher risk of 5 relapse [(HR (95% CI) = 2.04 (3.05-1.36); p = 0.001) and (HR (95% CI) = 1.45 (1.001-2.09); p = 0.05); respectively] after NACT. SPAG5 overexpression (+) determined the response for NACT. None of HER2 IHC +2 with negative SPAG5 (-) expression (0/170) either with FISH+ (0/112) or FISH- (0/58) achieved pCR whereas 47% (31/66) of those of HER IHC+2 with SPAG5+ achieved pCR after NACT (p < 0.0001). Similarly 73% (78/107) of HER2 IHC+3 with SPAG5+ achieved pCR after NACT+ Trastuzumab compared to 11% (10/95) of those with SPAG5-; p < 0.0001. Changes of HER2 expression after NACT was common (50%); 31% (106/348) of the resituate HER2 low tumours were HER2 IHC0 and 7% were HER2+. Meanwhile 28% (17/60) of HER2 IHC+2/FISH+, 7% (15/223) of HER2 IHC+3 and 14% of HER2 IHC 0 changed into HER2 low.

Conclusions: HER2 low is common in early BC and is associated with resistance to the anthracycline/Taxane NACT. Significant change of HER2 expression in the residual tumour is common after NACT. SPAG5 expression could help to optimize the use of NACT and ACDs in early BC. Research Sponsor: UK NIHR Invention for Innovation and Nottingham University Hospital Charity.

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LESS: Single-arm study to de-escalate adjuvant endocrine therapy duration in post-menopausal women with HR+ HER2- early-stage breast cancer at very low risk of metastasis.

Elise Deluche, Stefan Michiels, Daniele Fric, Christophe Perrin, Caroline Bailleux, Thomas Bachelot, Pascal Ko Kivok Yun, Gaetan De Rauglaudre, Marie-Ange Mouret-Reynier, Romauld Le Scodan, Ines Vaz-Luis, Magali Lacroix-Triki, Clara Guyonneau, Fabrice Andre; Centre Hospitalier Universitaire, Limoges, France; Office of Biostatistics and Epidemiology, Gustave Roussy, Villejuif, France; Groupe Hospitalier Mutualiste de Grenoble, Grenoble, France; Centre Eugène Marquis, Rennes, France; Centre Antoine Lacassagne, Nice, France; Medical Oncology, Centre Léon Bérard, Lyon, France; Centre Hospitalier International, Mont De Marsan, France; Institut du cancer Sainte-Catherine, Avignon, France; Centre Jean Perrin, Clermont-Ferrand, France; St. Gregoire Private Hospital Centre, Saint-Gregoire, France; Breast Cancer Survivorship Group, INSERM Unit 981, Gustave Roussy, Villejuif, France; Gustave Roussy, Villejuif, France; Gustave Roussy, Villejuif, France; R&D UNICANCER, French Breast Cancer Intergroup, Paris, France; Institut Gustave Roussy, Villejuif, France

Background: Adjuvant Endocrine Therapy (ET) is the cornerstone treatment of localized hormone-receptor positive (HR+) breast cancer, with demonstrated benefits on overall survival (30-40% relative decrease in mortality) but also on the risk of local and contralateral relapse (43-50% relative decrease). While the relative benefit of 5 years of ET is identical for small tumors as compared to larger ones, the absolute benefit is much lower, and the risk-benefit ratio becomes questionable given the frequent and impactful side effects of ET which are associated with non-adherence. If recent trials tested longer durations as compared to 5 years for high-risk cancers, older trials have tested shorter durations. Five years appeared at that time as the gold standard because of optimal benefit-risk ratios of tamoxifen among rather high-risk patients. However, shorter treatments of 2-3 years were already associated with substantial benefits and may be enough for very low risk patients. The purpose of this study is to demonstrate that adjuvant ET limited to 2 years of aromatase inhibitor (AI) in postmenopausal women at very low risk of recurrence as determined with a MammaPrint and BluePrint Ultra Low Risk Luminal test result can ensure very high survival without metastatic relapse and allows a reduction of side effects and a better quality of life. Methods: LESS (NCT05297617) is a prospective, national, multicenter, single-arm, interventional, non-threshold crossing phase II study evaluating a therapeutic de-escalation that limits adjuvant ET to 2 years of AI. Approximately 696 post-menopausal patients with an invasive unilateral, HR+, HER2-negative, without indication of adjuvant chemoT and genomically-assessed MammaPrint/BluePrint Ultra Low risk Luminal A breast cancer tumors, will be enrolled. LESS will include two sub cohorts: the majority of patients with Grade 2, pT1c-2, pN0/N1mic tumors, and up to 80 patients ≥65 years with Grade 1, pT1, pN0 and Ki67<10% tumors. The primary endpoint is distant metastasis free survival (DMFS) defined as the time from date of registration to date of first event of distant recurrence, death, or second primary non-breast invasive cancer. Secondary endpoints include the assessment of quality of life parameters and psychological aspects related to this de-escalation. The null hypothesis (H0) that, in the study population after 2 years of adjuvant AI, DMFS at 5 years is lower or equal to 94.5% will be tested against the alternative - that it is above 94.5%. For an expected DMFS of 96.7% under the alternative hypothesis, a total of 37 DMFS events are required in order to provide approximately 85% power at a one-sided significance level of 0.05 to reject H0 using a logrank test. The 1st patient was included in October 2022, initiating the 2-year inclusion period and 10 years FU per patient. Clinical trial information: NCT05297617. Research Sponsor: Agendia.
Background: Despite best management with standard ETs, ≤ 20% of pts with ER+, HER2– eBC develop resistance (due to ESR1 mutations that can drive estrogen-independent transcription and proliferation) and have high recurrence rates. New treatments are needed to reduce recurrence risk and improve survival, tolerability, quality of life, and adherence. Giredestrant, a highly potent, nonsteroidal oral selective ER antagonist and degrader, achieves robust ER occupancy and is active against ER-sensitive or ESR1-mutated tumors. It is more potent in vitro and achieves higher ER occupancy in vivo than fulvestrant. Early-phase studies showed that 30 mg daily as a single agent has promising clinical and pharmacodynamic activity and is well tolerated for ER+, HER2– BC.

Methods: lidERA BC (NCT04961996) is a Phase III, global, randomized, open-label, multicenter study evaluating adjuvant giredestrant vs. PCET in ER+, HER2– eBC. Pts are randomized 1:1 to oral 30 mg daily giredestrant or PCET (tamoxifen, anastrozole, letrozole, or exemestane; per prescribing information). Stratification factors: Risk (medium vs. high, based on anatomic [tumor size, nodal status] and biologic features [grade, Ki67, gene signatures if available]); geographic region (US/Canada/Western Europe vs. Asia-Pacific vs. rest of the world); prior chemotherapy (no vs. yes); menopausal status (pre-/peri- vs. postmenopausal). Pts will be treated for ≥ 5 years. Continuing PCET > 5 years is per investigator discretion and local standard of care. Eligibility: Female/male; medium-/high-risk stage I–III ER+, HER2– eBC; prior curative surgery; completion of (neo)adjuvant chemotherapy (if given) and/or surgery < 12 months before enrollment; no prior ET (< 12 weeks of [neo]adjuvant ET allowed). For men and pre-/perimenopausal women, an LHRH agonist will be given per local prescribing information (mandatory for the giredestrant arm). Primary endpoint: Invasive disease-free survival (IDFS, excluding second non-primary BC). Secondary endpoints: Overall survival; IDFS (STEEP definition, including second non-primary BC); disease-free survival; distant recurrence-free survival; locoregional recurrence-free interval; safety; pharmacokinetics; pt-reported outcomes. This study also aims to improve health equity in research and expand clinical trial access. It will use/develop digital healthcare solutions, enabling better understanding of pts’ needs and adherence to ET. The primary endpoint analysis will use a stratified log-rank test at an overall 0.05 significance level (two-sided). Interim and futility analyses are planned; an independent data monitoring committee will be in place. 2950/4100 pts have been recruited globally. Clinical trial information: NCT04961996. Research Sponsor: F. Hoffmann-La Roche Ltd.
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 neoadjuvant 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. In a prospective, randomized, single-blinded, placebo-controlled, multicenter Phase IIb study, no recurrences were observed in the HER2+ population after 5 years of follow-up, if the patient was treated with GLSI-100, survived, and was followed for more than 6 months \( (p = 0.0338) \). Immunotherapy elicited a potent response measured by skin tests and immunological assays. 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 for a total of 11 injections over 3 years. The participant duration of the trial will be 3 years treatment plus 1 additional year follow-up for a total of 4 years following the first year of treatment with trastuzumab-based therapy. Patients will be stratified based on residual disease status at surgery, hormone receptor status and region. 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 100 non-HLA-A*02 subjects will be enrolled in an open-label arm. The patient population is defined by these key eligibility criteria: HER2/neu positive and HLA-A*02; residual disease or High risk pCR (Stage III at presentation) post neo-adjuvant therapy; exclude stage IV; completed at least 90% of planned trastuzumab-based therapy. Trial objectives were to determine if GP2 therapy increases IBCFS, to assess the safety profile of GP2 and to monitor immunologic responses to treatment and assess relationship to efficacy and safety. The study has been initiated at a number of sites in the US. The study is also expected to be opened in Spain, Germany, and France. Clinical trial information: NCT05232916. Research Sponsor: Greenwich LifeSciences.
Prospective single-arm study of endocrine therapies with ovarian function suppression in premenopausal patients with node-positive early breast cancer with low genomic risk (INTERSTELLAR trial, KBCSG-25).

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Background: It is unclear whether the clinical benefit of cytotoxic adjuvant chemotherapy (CT) could be replaced by ovarian-function suppression (OFS) in premenopausal, estrogen receptor (ER)+HER2-breast cancer patients who have high clinical risk score and low genomic risk assessed by multigene assays. The TAILORx trial included a subgroup of premenopausal women with high clinical risk scores and midrange RS scores and found that CT, in addition to endocrine treatment (ET), offered clear benefits in terms of invasive disease-free survival (iDFS) and distant-recurrence-free survival (DRFS) compared to ET alone. However, a majority of the patients did not receive OFS, and the use of OFS as an alternative to chemotherapy in this population is still an area of ongoing research and debate. In addition, in premenopausal women of the RxPonder trial, which enrolled node-positive disease, it is noted that the addition of OFS to ET for at least 12 months improved iDFS numerically in the ET-alone arm, although this improvement did not reach statistical significance. We hypothesized that a favorable DRFS could be achieved by OFS plus ET without CT in premenopausal, pN1, ER+HER2- breast cancer with low genomic risk identified by an NGS-based multigene assay, the OncoFREE.  

Methods: The INTERSTELLAR trial is a prospective, multicenter, single-arm, non-inferiority clinical study. Premenopausal women aged ≤50 years with pT1-2 ER+HER2- breast cancer and 1-3 lymph node metastasis will be enrolled. They will be tested with OncoFREE, an NGS-based breast cancer prognosis multigene assay developed and available in South Korea, where a higher portion of the patients is premenopausal. Patients with low genomic risk (Decision Index ≤20) are administered OFS plus tamoxifen or an aromatase inhibitor for five years. We hypothesize that the 5-year DRFS of the single arm treated with OFS plus ET would be not inferior to 96.1%, which is observed in the chemo-ET arm from the premenopausal subgroup of the RxPonder trial. The one-sided test with a non-inferiority margin of 3% and statistical power of 80% at a significance level of 0.05 resulted in a sample size of 380 patients with low genomic risk. Considering a 70% designation to low genomic risk by OncoFREE and a 10% drop-out rate, 604 patients will be enrolled from 15 tertiary care hospitals in South Korea. The primary endpoint will be tested in the 380 patients with low genomic risk. The patients with high genomic risk will receive CT followed by ET and will be followed for survival analysis as a secondary endpoint. The trial has not enrolled its first patient yet at the time of submission. Clinical trial information: NCT05333328. Research Sponsor: None.
ASCENT-05/optimICE-RD (AFT-65): Phase 3, randomized, open-label study of adjuvant sacituzumab govitecan (SG) + pembrolizumab (pembro) vs pembro ± capecitabine (cape) in patients (pts) with triple-negative breast cancer (TNBC) and residual disease after neoadjuvant therapy (NAT) and surgery.

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Background: TNBC has an aggressive disease course with poor prognosis for pts with residual disease (RD) after NAT. In Ph 3 KEYNOTE-522, pts treated with polychemotherapy + the immune checkpoint inhibitor (ICI) pembro for ~1 year only had a 3-year event-free survival of 85% (Schmid P, et al. NEJM. 2022). SG is a Trop-2–directed antibody-drug conjugate approved for pretreated metastatic TNBC (mTNBC). In Ph 3 ASCENT, SG significantly improved both progression-free survival and overall survival (OS) compared with standard chemotherapy (CT) in pts with mTNBC who received ≥2 lines of therapy, with a manageable safety profile (Bardia A, et al. NEJM. 2021). Preclinical data suggest that SG also potentiates the activity of ICIs. The ASCENT-05 study will assess the value of adding SG to a pembro-based adjuvant therapy in pts with RD after NAT. Methods: ASCENT-05/optimICE-RD (AFT-65, NCT05633654) is an open-label, global, multicenter, randomized, phase 3 study that evaluates efficacy and safety of SG + pembro versus pembro ± cape (per treating physician discretion) in pts with TNBC and RD in the post-NAT setting. Key eligibility criteria include pts ≥18 years with a history of cT1, ≤cT4, ≤cN2a TNBC with RD in the breast or lymph node(s) after NAT and surgery. TNBC diagnosis per local assessment is based on estrogen receptor and progesterone receptor, ≤10%, and HER2-negative per ASCO/CAP. Other inclusion criteria are receipt of ≥6 cycles of neoadjuvant anthracycline- and/or taxane-based CT ± PD-(L)1 inhibitor ± radiotherapy postoperatively as clinically indicated, and adequate organ function with ECOG performance status 0-1. Key exclusion criteria include metastatic disease, prior ipsilateral/contralateral invasive breast cancer, prior treatment directed to another stimulatory/coinhibitory T-cell receptor, HER2-directed agents or TOPO-1 inhibitors, evidence of recurrent or distant metastatic disease after preoperative therapy and surgery, germline BRCA mutations, myocardial infarctions ≤6 months of enrollment or history of serious ventricular arrhythmia or LVEF < 50%, and active serious infections requiring treatment. Pts will be randomized 1:1 to receive SG (10 mg/kg IV on d1 and d8, every 21 d for 8 cycles) + pembro (200 mg IV on d1 every 21 d for 8 cycles). Cape (1000 mg/m² twice daily, orally on d1-14, every 21 d for 8 cycles) may be added to pembro in the control arm. The primary endpoint is invasive disease-free survival. Key secondary endpoints include OS, distant disease-free survival, incidence of treatment-emergent adverse events and clinical laboratory abnormalities, and time to worsening of quality of life based on FACT-B TOI scores. ASCENT-05 will enroll ~1500 pts and is currently open for recruitment. Clinical trial information: NCT05633654. Research Sponsor: Gilead Sciences, Inc.
A phase II single-arm, open-label trial of T-DM1 (ado-trastuzumab emtansine) and neratinib for HER2-positive breast cancer with molecular residual disease (KAN-HER2 MRD).

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Background: HER2-positive breast cancer is a biologically and clinically aggressive subtype that has historically been associated with poor outcomes, but for which there are now multiple effective targeted therapies. Patients who have residual disease following standard neoadjuvant therapy have an elevated risk of metastatic recurrence. In addition, the detection of circulating tumor DNA (ctDNA) in the adjuvant period is strongly associated with relapse and can further stratify patients with residual disease. The ctDNA-based detection of molecular residual disease (MRD) is an emerging strategy to identify patients for treatment intensification, and may enable the development of novel curative treatment strategies for “recurrence interception”. Preclinical and clinical evidence support the investigation of neratinib, an irreversible inhibitor of the HER2 tyrosine kinase, in combination with standard T-DM1 in the adjuvant setting for patients with HER2-positive breast cancer and evidence of MRD. Methods: KAN-HER2 MRD is a multicentre, investigator-initiated, open label, single arm phase II trial to evaluate the addition of neratinib to standard T-DM1 in patients with detected MRD. Participants with HER2-positive breast cancer and residual disease following neoadjuvant therapy are pre-screened (Part A) for MRD using a tumor-informed assay (NeoGenomics RaDaR). Those with ctDNA detected following 2-6 cycles of adjuvant T-DM1 will proceed to the interventional phase (Part B) where neratinib is added to standard T-DM1 at the previously-determined recommended phase 2 combination dose of 160 mg/day, in continuous cycles. The primary endpoint is the rate of ctDNA clearance at 12 weeks after treatment initiation (ctDNAwk12); the study is designed with a 2-stage approach and has sufficient power to detect a clearance rate of 40%. Secondary endpoints include MRD rates and their clinical correlates, invasive disease free survival (iDFS), and safety. Bio-specimens including diagnostic biopsies, residual disease, and peripheral blood are being collected from all participants for additional correlative studies. Enrolment in Part A was initiated at the first trial site (Princess Margaret Cancer Centre) in December 2022. KAN-HER2 represents the first reported MRD-directed interception trial for HER2-positive breast cancer. Clinical trial information: NCT05388149. Research Sponsor: Ontario Institute for Cancer Research (OICR) Clinical Acceleration Team Award; Princess Margaret Cancer Foundation; Knight therapeutics, NeoGenomics.
FLEX, a real-world evidence full transcriptome study of 30,000 patients with early-stage breast cancer.

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Background: Clinical trials have been an invaluable tool in providing improvements in the discovery, treatment, and quality of life for various diseases and disorders including breast cancer, which impacts millions of people each year. Historically, patient trial populations have not been racially diverse due to several factors such as bias, healthcare distrust, access, and eligibility criteria. However, current efforts are focused on improving diversity and inclusion to promote efficacy and health equity across all races/ethnicities. The ongoing, multi-center FLEX trial (NCT03053193), which pairs clinical data and full transcriptome expression data, seeks to enroll 30,000 patients to accelerate real world research. Due to the size of the database, it is also expected to capture patients typically underrepresented in clinical trials. Methods: FLEX is the first of its kind, prospective, observational trial that enrolls patients who are 18 years old with histologically proven stage I-III breast cancer with up to 3 positive lymph nodes. Patient eligibility for study enrollment include standard of care MammaPrint testing with or without BluePrint and consent to clinically annotated full transcriptome data collection. The study infrastructure facilitates the generation of hypotheses for targeted sub-studies. The FLEX network fosters collaboration with 114 sites, including one site in Greece and Israel, encouraging participating investigators to initiate sub-studies that can address research questions that are important for breast cancer management. All proposed sub-studies are vetted and approved by Research and Scientific Review Committees. Since launching in April 2017, 12,569 patients have been enrolled including those who have been historically underrepresented in trials (African American n= 1025; Latin n= 341; Asian n=156). Forty-two investigator initiated sub-studies have been approved and are in progress, with 40 abstracts accepted in national and international congresses. Five ongoing sub-studies within FLEX address differences in underlying biology and treatment response/management among African American, Latina, and Asian American patients with early-stage breast cancer. These studies provide a broader understanding of how differential gene expression patterns unique to racial/ethnic groups can impact treatment outcomes. With the large FLEX database, enrollment and sub-studies are extended to other racial/ethnic groups that are underrepresented in clinical trials, but not limited to specific groups. Overall, the FLEX study strives to use full transcriptome data to improve precision medicine in early-stage breast cancer. Clinical trial information: NCT03053193. Research Sponsor: Agendia Inc.
MRD assay to evaluate recurrence and response via a tumor-informed assessment: MARIA-Breast observational trial.

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Background: The recognition that cancers release nucleic acids into the peripheral circulation of the patient has enabled a new paradigm for disease detection and surveillance. Detectable ctDNA in patients with solid tumors has been associated with disease prognosis pre-treatment, assessing response to therapy in the form of minimal residual disease (MRD), and monitoring for recurrence after curative intent treatment. Utilizing patient-specific genomic mutation profiling of an individual’s cancer from a tissue sample, in conjunction with the patient’s germline DNA, to create a personalized sequencing panel to then systematically analyze for a subset of these genetic mutations from ctDNA in blood is a strategy that has high sensitivity in detection of MRD. Studies have shown that pretreatment levels of ctDNA using this approach are a potential early indicator of disease recurrence after surgery, that ctDNA clearance may be an early predictor of favorable outcomes and have been shown to correlate with pathologic complete response (Forde et al. N Engl J Med. 2022, PMID:35403841), and that this approach has high sensitivity in its ability to detect recurrence for patients in advance of the current standard of care (Abbosh et al. Cancer Res (2020) 80 (16_Supplement): CT023). Methods: This is a multi-site, prospective, observational trial in the United States of 200 patients with early stage breast cancer undergoing curative intent treatment, who have FFPE tissue available from resection sufficient for a patient-specific bespoke MRD assay who are willing to provide serial whole blood specimens for ctDNA analysis. Participants are asked to provide study specimens prior to initial treatment intervention, after curative intent surgical resection, during adjuvant therapy (as applicable) and pre-recurrence follow-up. ctDNA will be analyzed with an NGS-based, tumor-informed MRD assay that identifies somatic mutations from DNA obtained from the patient’s tumor tissue, subtracts germline variants via NGS-based analysis of the patient’s germline DNA, and detects a selected set of between 18-50 tumor-specific ctDNA in their blood. All primary tumor specimens will undergo full exome sequencing using the Personalized Cancer Monitoring (PCM) assay. Impact of results of this CLIA-approved MRD assay on clinical decision making will be captured. The primary objective is to assess the ability of MRD to predict post-treatment recurrence. Further objectives are to correlate MRD status with pathologic complete response, determine the lead time to detection of recurrence compared to standard of care, and the association of MRD status with overall survival. Active enrollment started in March, 2022. Clinical trial information: NCT05219734. Research Sponsor: Invitae.
NRG-BR007: A phase III trial evaluating de-escalation of breast radiation (DEBRA) following breast-conserving surgery (BCS) of stage 1, HR+, HER2-, RS ≤ 18 breast cancer.

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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, freeing them from excess toxicity. Genomic assays are also recognized as prognostic for in-breast recurrence (IBR) after 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 in-breast recurrence and breast preservation in women intending endocrine therapy (ET) for stage 1 invasive breast cancer (ER &/or PR positive, HER2-negative with an Oncotype DX Recurrence Score [RS] of ≤ 18). Stratification is by age (<60; ≥ 60), tumor size (≤ 1 cm; >1-2 cm), and RS (< 11, 11-18). Pts are randomized post-BCS to Arm 1 with breast RT using standard methods (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 &/or PR positive (ASCO/CAP), HER2-negative (ASCO/CAP), and Oncotype DX RS of ≤ 18 (diagnostic core biopsy or resected specimen). Primary endpoint is in-breast recurrence (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% vs 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% per yr. Some of the 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. Current accrual (02-08-2023) is 370 screened and 323 randomized (~87% of predicted accrual). Clinical trial information: NCT04852887. Research Sponsor: U.S. National Institutes of Health.
Selective avoidance of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with HER-2 positive/triple negative breast cancer: Prospective, multi-center, single-arm study (ASLAN).

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Background: According to advanced neoadjuvant chemotherapy (NACT), which dual HER2 blockage in HER2+ BC and adding carboplatin or immunotherapy in triple-negative breast cancer (TNBC) increased pathologic complete response (ypCR) rates up to 68% and 80%. Because ypCR patients showed better survival, the indications for NACT have expanded to early BC and the expected ypCR rate has increased. Therefore, it may be reasonable to consider omitting surgery in cases with excellent responses to NACT. Several recent retrospective studies and pilot prospective studies have reported axillary pathologic complete response (ApCR) is highly correlated with breast pathologic complete response (BpCR) in HER2+ or TNBC after NACT. The current report describes the design of omission of sentinel lymph node biopsy (SLNB) after NACT in HER2+ or TNBC patients with excellent response. Similarly, EUBREAST-01 (NCT04101851) study is ongoing omission of sentinel lymph node biopsy (SLNB) after NACT in HER2+/TNBC with radiologic complete remission and a BpCR. Methods: The ASLAN trial is a prospective, multicenter, single-arm, clinical study. Five tertiary care hospitals in South Korea are participating. Inclusion criteria: women aged 20-69; cT1-3N0-1M0; HER2+ or TNBC (defined by ER-negative (<10% positive cells in IHC) and PgR-negative (<10% positive cells in IHC)); expected complete remission at physical examination and radiological expected Tumor size ≤ 2cm or non-mass enhancement ≤ 4cm at breast MRI after standard NACT; planned breast conserving surgery (BCS) with whole-breast irradiation; ECOG performance status 0-1. Exclusion criteria: SLNB before NACT; previous axillary surgery; bilateral BC. Patients who are eligible proceed BCS. After BCS, patients who showed BpCR are enrolled with omission of SLNB. Patients with no BpCR proceed with routine axillary surgery. The assumption for acceptable 5-year RFS ≥ 84% is based on previous study findings. The calculated total case number for per-protocol analysis is N=178. Primary endpoint: 5-year recurrence free survival. Secondary endpoint: local recurrence free survival, breast cancer specific survival, overall survival, ipsilateral axillary recurrence interval, distant metastasis free survival, contralateral breast free survival, re-operation rate according to breast biopsy after NACT, adverse event, and quality of life. The first patient was enrolled on September 2021. Among 147 patients who screened, 106 patients have been enrolled in January 2022. We plan to complete the target accrual by December 2025. Clinical trial information: NCT04993625. Research Sponsor: NRF 2021R1A2C94010.
SMALL: Open surgery versus minimally invasive vacuum-assisted excision for small screen-detected breast cancer—A UK phase III randomised multi-centre trial.

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Background: Mammographic screening programmes reduce breast cancer mortality but detect many small tumours with favourable biology which may not progress. These are treated with surgery and adjuvant therapies, but associated morbidities mean there is a need to reduce overtreatment. Minimally invasive treatments such as vacuum-assisted excision (VAE) have been described but there is no prospective randomised evidence to support their routine use. SMALL (ISRCTN 12240119) is designed to establish the feasibility of using VAE to treat small tumours detected within the UK NHS Breast Screening Programme (BSP).

Methods: Phase III multicentre randomised trial comparing surgery with VAE for screen-detected good prognosis cancers. Eligibility criteria are age ≥47 years, unifocal grade 1 tumours (maximum diameter 15mm), strongly ER/PR+ve and HER2-ve, with negative axillary staging. Patients are randomised 2:1 to VAE or surgery, with no axillary surgery in the VAE arm. Excision is assessed radiologically, and if incomplete, patients undergo surgery. Adjuvant radiotherapy and endocrine therapy are mandated in the VAE arm. Co-primary end-points are 1) Non-inferiority comparison of the requirement for a second procedure. 2) Single arm analysis of local recurrence (LR) at 5 years after VAE. Recruitment of 800 patients will permit demonstration of 10% non-inferiority of VAE for requirement of a second procedure, ensuring sufficient patients for single arm analysis of LR rates, where expected LR free survival is 99% at 5 years, with an undesirable survival probability after VAE of 97%. Secondary outcome measures include time to ipsilateral recurrence, overall survival, complications, quality of life and health economic analysis. A QuinteT Recruitment Intervention (QRI) is integrated throughout SMALL to optimise recruitment and informed consent. Recruitment challenges are identified by analysing recruiter/patient interviews, audio-recordings of trial discussions, and by review of screening, eligibility and recruitment data and study documentation. Solutions are developed collaboratively, including recruiter feedback and recruitment tips documents. Results: At 10th February 2023, 231 patients had been recruited from 32 centres, (~45% of eligible patients), with per site recruitment of 0.4-0.5 patients/month. Based on preliminary QRI findings, a recruitment tips document has been circulated (on discussing SMALL, providing balanced information on treatment options and explaining randomisation), with individual recruiter feedback underway and wider feedback planned shortly. Conclusion: SMALL has excellent recruitment to date, confirming feasibility and acceptability, and is expected to have a global impact on treatment of screen-detected breast cancer. Clinical trial information: ISRCTN12240119. Research Sponsor: National Institute for Health Research Health Technology Assessment Programme (UK).

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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%. 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 the majority of studies, the patient’s perspective with regard to discomfort and pain level has not been evaluated. The aim of MELODY is to evaluate different imaging-guided localization methods with regard to oncological safety, patient-reported outcomes, and surgeon and radiologist satisfaction.

Methods: The EUBREAST and the iBRA-NET have initiated the MELODY study to assess breast localization techniques and devices from several perspectives (NCT05559411, http://melody.eubreast.com). MELODY is a prospective intergroup cohort study which enrolls female and male pts. requiring breast-conserving surgery and 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, comparison of patient-reported outcomes, rates of “lost markers” and diagnostician/radiologist’s and surgeon’s satisfaction as well as the health economic evaluation of the different techniques. Target accrual: 7,416 patients. Enrollment started in January 2023. The study will be conducted in 20 countries and is supported by the Oncoplastic Breast Consortium (OPBC), AWOgyn, AGO-B and SENATURK. Clinical trial information: NCT05559411. Research Sponsor: Endomag, Merit Medical, Sirius Pintuion and Hologic.
Omission of breast surgery for predicted pCR patients with MRI and vacuum-assisted biopsy in breast cancer after neoadjuvant chemotherapy: A multicenter, single-arm, non-inferiority trial (OPTIMIST trial).

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Background: Advances in chemotherapeutic and targeted agents have increased pathologic complete response (pCR) rates after neoadjuvant systemic therapy (NST). The role of surgery is essential to remove cancer when residual tumor is present, but it may be limited to pathologic confirmation in those with a pCR. As an alternative, pCR can be accurately evaluated with vacuum-assisted biopsy (VAB) in patients suggested to have a pCR on imaging. We aim to show a non-inferiority of omitting breast surgery in patients evaluated to have a pCR on image-guided VAB. Methods: The OPTIMIST trial is a prospective, multicenter, single-arm, non-inferiority clinical study. Sixteen tertiary care hospitals in South Korea are participating. Women diagnosed with invasive ductal carcinoma, a clip marker placed in the tumor, and who had completed NST with exceptional response are screened for eligibility. Inclusion criteria: women aged 19-75; cT1-2N0-2M0; triple-negative, HER2+, or low estrogen receptor (<10%); post-NST MRI size ≤1cm and lesion-to-background signal enhancement ratio ≤1.6. Exclusion criteria: malignant calcification >2cm; multifocal, bilateral, or inflammatory breast cancer; other malignancy within five years; BRCA1/2 mutation carrier. Under ultrasound or stereotactic guidance, VAB is performed targeting the clip marker to obtain a minimum of 6 cores using 7-10 G needles. When pCR is confirmed, breast surgery is omitted. cN0 patients with post-NST MRI tumor size ≤0.5cm and no suspicious lymph nodes, axillary lymph node surgery could also be omitted. Patients with residual tumor or atypical cells proceed with routine surgery. All patients are required to receive whole breast irradiation with tumor bed boost. According to previous studies, the 5-year disease-free survival (DFS) for patients with a pCR after NST was assumed to be 88%. The one-sided test with a non-inferiority margin of 4% and statistical power of 80% at a significance level of 0.05 resulted in a sample size of 384 patients to forego breast surgery. An expected 20% residual tumor on VAB and a 10% dropout resulted in a total of 533 subjects. Primary endpoint: 5-year DFS. Secondary endpoint: 5-year ipsilateral breast tumor recurrence-free survival, 5-year overall survival, 5-year invasive DFS, residual axillary lymph node rate, quality of life scores, symptoms (VAS), and medical cost. An interim analysis is planned at 50% enrollment with a median follow-up period of 1 year. The data safety monitoring board will determine the continuation of the study considering the 1-year DFS. The first patient was enrolled on September 22, 2022, and 12 patients have been enrolled as of February 14, 2023. We plan to complete the target accrual by December 2025. Clinical trial information: NCT05505357. Research Sponsor: National Cancer Center of Korea.
Tailored axillary surgery (TAS) in patients with clinically node-positive breast cancer in the upfront surgery setting: A prospective, single-arm, multicenter trial.

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Background: Axillary lymph node dissection (ALND), which can induce lymphedema, has been omitted in clinically node-negative (cN0) patients with positive sentinel lymph nodes (SLNs) if they meet the eligibility criteria of ACOSOG Z0011. Furthermore, the omission of ALND has been attempted through targeted axillary dissection (TAD) in patients whose cN+ status converts to ycN0 after neoadjuvant chemotherapy. However, ALND remains the standard of care in patients with cN+ who undergo upfront surgery. The aims of this trial are to establish a surgical method of tailored axillary surgery (TAS), which combines TAD and SLN biopsy among patients with cN+ who undergo upfront surgery, and to determine the appropriate criteria for a Phase III TAS trial.

Methods: We have planned a single-arm Phase II trial to confirm the feasibility and assess patient eligibility for TAS. A total of 300 patients will be enrolled from 33 study sites in Japan. The eligibility criteria are as follows: 1) histologically-proven invasive breast cancer, 2) upfront surgery is planned, 3) pathologically-diagnosed metastatic lymph node (cytology or core needle biopsy), 4) 1-3 LN metastases in level I by imaging, 5) cT1-3, and 6) females aged $\geq 18$ and $\leq 74$ years on the enrollment date. TAS involves removing marking lymph nodes by TAD (clip, wire, or tattoo) and SLNB, and ALND up to Level II are performed after TAS. These LNs are defined as non-TAS LNs. The primary endpoint is the non-TAS LNs positive rate. Clinicopathological factors (the number of suspected metastases by imaging, the number of metastases in LNs resected by TAS, tumor size, and invasive ductal/lobular carcinoma) are analyzed to predict the non-TAS LN metastasis rate (e.g., $< 10\%$). By using these clinicopathological factors, we determine the eligibility of TAS to omit ALND safely. The secondary endpoints are TAS LNs identification rate, labeled LNs identification rate, marked lymph node resection rate, arm edema incidence rate, and QOL (FACT-B, QuickDASH). After this feasibility study, we will conduct a phase III trial that omits ALND using TAS to investigate the regional recurrence rate. Research Sponsor: Okayama University.
Phase 1 dose-escalation, dose-expansion trial of intratumoral HER2- and HER3-primed dendritic cells injections for the treatment of early-stage TNBC and HR low positive breast cancer: DecipHER trial.

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Background: Patients with breast cancers (BCs) harboring low expression of hormone receptors (HRs) and human epidermal growth factor receptor-2 (HER2) have poor outcomes. Results from the KEYNOTE-522 trial showed that activation of the immune system using a PD1/PD-L1-targeted approach improves outcomes of patients with these high-risk tumors. Antigen-presenting cells (eg, dendritic cells [DCs]) are pivotal for robust cytotoxic responses due to broader activation of the adaptive immune system (ie, CD4+ and CD8+ Th1) against tumor-associated antigens (ie, HER2 or HER3) expressed by high-risk BCs. Methods: DecipHER is a dose-escalation, dose-expansion phase 1 trial designed to assess the safety and the preliminary efficacy of autologous, HER2- and HER3-primed DCs in combination with KEYNOTE 522 regimen in 30 patients. Patients with clinical stage cT1cN1/2 or cT2-4cN0-2, HR 20, HER2-negative BCs are eligible. Patients with inflammatory BC cancer and uncontrolled immune mediated diseases are excluded. After collection through aphaeresis, autologous DCs will be primed ex vivo against 6 HER2 and 8 HER3 immunogenic peptides. Participants will receive alternating ultrasound-guided intratumoral HER2 and HER3 DC injections administered twice a week for 8 doses in total starting 2 weeks prior to neoadjuvant therapy with KEYNOTE 522 regimen. The dose-escalation phase of the study has 3 planned cohorts (10-20, 30-50, 80-100 million DCs) and follows a 3+3 design (maximum n=18). The 12 additional patients enrolled will be treated at the maximum tolerated dose (MTD) in the dose-expansion cohort. The MTD will be defined as the highest dose level at which < 2 of 6 patients experience dose-limiting toxicities (grade ≥ 3 non-hematologic, ≥ 3 hematologic toxicity thought be at least possibly related to DCs; any grade 4 nausea, vomiting, or diarrhea [or grade 3 if duration > 3 days]) during the 5 weeks following treatment initiation with DCs. Secondary endpoints include the absolute risk of adverse events, clinical and pathological responses, and recurrence free survival. Tumor tissue, blood and stool samples will be collected for correlative analyses. The study is open at H. Lee Moffitt Cancer Center. Clinical trial information: NCT05504707. Research Sponsor: Shula’s Foundation.
Background: Preclinical research has shown that fasting and/or a fasting mimicking diet (FMD) in addition to chemotherapy can enhance cancer treatment effectiveness and reduce side-effects. The previous DIRECT1 phase 2 study (de Groot S, Nat. Commun. 2020) indicated that FMD could increase effectiveness of neoadjuvant chemotherapy in patients with HER2-negative breast cancer. 

Methods: 

DIRECT2 is a multicenter, randomized, open label phase 3 study that investigates whether FMD compared to a regular diet during neoadjuvant chemotherapy can improve the pathological and/or radiological response rate in patients with hormone receptor positive (HR+), HER2-negative, stage II/III breast cancer. Secondary endpoints include quality of life, cognition, toxicity ≥ grade 3 and the immunomodulating effect of FMD. The FMD consists of a low-caloric diet of 600kcal/day starting 3 days prior to, and on the day of chemotherapy administration every 4 weeks, for a total of 5 FMD cycles during neoadjuvant chemotherapy (4 times dose dense Adriamycin plus cyclophosphamide followed by 12 times weekly paclitaxel). Patients will be supported and monitored by a centralized dietician during each FMD cycle. An additional MRI will be conducted after 4ddAC to evaluate efficacy mid-way through chemotherapy. Furthermore, an optional tumor biopsy will be done to determine the immunomodulatory effects of the FMD which will be determined using cutting-edge RNA sequencing and multi-spectral imaging techniques. Pathological response will be graded on the surgical specimen according to Miller & Payne 4/5, indicating a 90-100% tumor cell loss. Radiological response will be determined by MRI (RECIST1.1). In total 240 patients are needed to detect an increase from 20% to 37.5% in pathological response rate in the FMD arm allowing for 15% dropout, using a two-sided Z test with pooled variance and 5% significance level with a power of 80%. Randomization will be performed in Castor EDC with variable block sizes and stratified by clinical stage (stadium II versus III) and BMI (< 25kg/m^2 versus ≥ 25kg/m^2). Inclusion criteria are HR+, HER2- breast cancer stage II-III, BMI > 18.5 kg/m^2, WHO status 0-2, without a history of malignancy in the past 5 years, invasive or ipsilateral non-invasive breast cancer. Patients will be excluded in case of pregnancy, lactation or metabolic disease that affects gluconeogenesis and adaptability to FMD. The trial is supported by grants from the Dutch Cancer Society and WCRF. The study is open since February 2023 for inclusion for 4 years and plans to recruit 240 patients in total in 20 participating hospitals in the Netherlands. Clinical trial information: NCT05503108. Research Sponsor: Dutch Cancer Society; World Cancer Research Fund (WCRF).
Metformin with neoadjuvant chemotherapy in localized triple negative and HER2 neu-positive breast cancer: A prospective phase 2 open label randomised controlled trial (McBETH).

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Background: Repurposing of drugs in cancer is an attractive strategy and metformin has long been an agent with promising yet unproven activity in breast cancer. Despite some recent studies showing inadequate efficacy in adjuvant setting, there is a lack of well powered studies in neo-adjuvant setting in localised breast cancer. Few past studies suggest that metformin may have anticancer effects in the subsets of Her2 neu positive as well as Triple negative breast cancer (TNBC). We initiated this study to investigate if metformin in combination with standard neo-adjuvant chemotherapy is effective in improving pathological complete response rates in these subsets among localised breast cancers.

Methods: This is an investigator initiated randomised, open label, parallel-group superiority trial. All non diabetic localised chemo-naïve breast cancer patients aged ≥18 years planned for neo-adjuvant chemotherapy will be randomly allocated (stratified by HER 2 positive and TNBC) to receive standard neo-adjuvant chemotherapy with or without metformin (850mg twice daily) till the day of surgery. The patients will be followed up until the surgery. The primary objective of this study is to compare the pathological complete response rates(ypT0ypN0) in each arm. The secondary objectives are to compare pathological complete response rates in predefined subsets of HER2 positive and triple negative breast cancer, clinical response rates in each arm, patient reported outcomes in each arm (ESAS-r Scale), breast conservation surgery rates in each arm, incidence and severity of adverse events in both arms.

Trial statistical design: Planned accrual is total 242 patients including 10% drop out rate. It is a superiority design with an absolute improvement of 11% in pathological complete response from a baseline of 33% in the standard arm. Conduct to date: study activation: May 2022. Enrolment: 116 subjects. Clinical trial information: REF/2022/05/054208. Research Sponsor: None.
ORACLE-RIPA study: A phase II, randomized, open-label, parallel-group study comparing the immune modulation effect of neoadjuvant ribociclib, palbociclib, and abemaciclib in early ER+/HER2- breast cancer.

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Background: CDK4/6 inhibitors (CDK4/6i), ribociclib, palbociclib, and abemaciclib, provide similar progression-free survival (PFS) benefits when combined with endocrine therapy in ER+/HER2-metastatic breast cancer (MBC) patients. However, not all CDK4/6i have demonstrated overall-survival (OS) benefits in their respective phase III trials. Both, ribociclib and abemaciclib, have shown significant OS benefits in ER+/HER2- MBC patients, but palbociclib has not. Because of similar benefits of the 3 CDK4/6i on PFS, the OS benefit is likely not a result of differences in their synergistic efficacy of a CDK4/6i with endocrine therapy. CDK4 inhibition on cancer cells can also result in upregulation of MHC-I and MHC-II expression on cell surface and Rb-dependent interferon-gamma secretion. CDK6 inhibition might inhibit T cell and NK cell proliferation causing a negative effect on the tumor microenvironment. CDK6 inhibition can also reduce regulatory T cell numbers and increase cytokine production to enhance cytotoxic T cell function. Thus, we hypothesize that the differential impact of the 3 CDK4/6i on OS might be resulting from different immunomodulation effects. To investigate the functional alterations of the CDK4/6i on the BC microenvironment, the neoadjuvant treatment setting is best to compare the immune modulation effects of CDK4/6i from pre-treatment and post-treatment tumor tissues. Methods: This phase II multicenter, randomized, open-label, parallel-group study evaluates the immunomodulation effects of the 3 different CDK4/6i (ribociclib, palbociclib, or abemaciclib) combined with letrozole in neoadjuvant early ER+/HER2- breast cancer patients. A total of 20 patients will be enrolled into each treatment arm. The major inclusion criteria are female patients aged ≥ 20 years old, having a histologically and/or cytologically confirmed diagnosis of ER+ (> 10%) and/or PR+, HER2 negative (IHC 0+/1+, or IHC 2+ plus FISH negative) breast cancer, stage II/III, and adequate organ function. The treatment will last 12 weeks of letrozole plus a CDK4/6i. Premenopausal patients will receive GnRH agonist. Breast tumor biopsy, blood and stool samples will be collected prospectively at the time prior to treatment initiation, at 2 weeks after treatment, and at surgery. A description summary will be utilized to compare the results between the 3 CDK4/6i. The trial results will address questions about differences or similarities of the 3 CDK4/6i within the same study. The study is currently enrolling at 3 medical centers in Taiwan. Clinical trial information: Pending formal number assignment. Research Sponsor: Novartis; National Taiwan University Hospital.
A randomized phase 2 non-inferiority trial of (Z)-endoxifen and exemestane + goserelin as neoadjuvant treatment for premenopausal women with ER+/HER2- breast cancer (EVANGELINE).

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Background: Ovarian function suppression (OFS) when combined with tamoxifen or an aromatase inhibitor is the standard of care for premenopausal estrogen receptor positive (ER+) human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC) based on SOFT (Francis 2022) and TEXT (Pagani 2022) clinical trials and confirmed in a metaanalysis (EBCTCG 2022). However, estrogen deprivation in premenopausal women is associated with significant morbidity and up to 40% of premenopausal women with ER+/HER2- BC are intolerant of OFS. For these women, tamoxifen monotherapy is the only FDA approved option. Therefore, there is substantial room to improve endocrine therapy for premenopausal women with ER+/HER2- BC. (Z)-endoxifen is one of the most active anti-estrogen tamoxifen metabolites, with preclinical data demonstrating superiority to tamoxifen and letrozole in aromatase expressing xenograft models and evidence for antitumor activity in early phase clinical trials in patients with prior progression on endocrine therapy including tamoxifen. In addition to its ability to potently block ERα, (Z)-endoxifen at clinically achievable concentrations inhibits protein kinase C beta 1 (PKCβ1), resulting in downstream AKT inhibition and apoptosis. It is hypothesized that (Z)-endoxifen, when delivered as monotherapy at doses that dually target both ERα and PKCβ1, will potently inhibit BC proliferation while obviating the need for OFS in premenopausal women. If successful, this innovative approach could spare women with endocrine sensitive BC from the side effects of OFS. Methods: To further study (Z)-endoxifen in premenopausal women, a multicenter study in the United States, with possible expansion to other countries was designed (EVANGELINE; NCT05607004). This is a Phase 2, open-label, randomized, neoadjuvant study in premenopausal women with Stage IIA or IIB ER+/HER2- BC. Subjects are randomized 1:1 to either exemestane plus goserelin or (Z)-endoxifen. The primary objective is to determine whether the endocrine sensitive disease (ESD) rate (defined as Ki-67 ≤ 10% after 4 weeks of neoadjuvant therapy) with (Z)-endoxifen is non-inferior to exemestane plus goserelin. Subjects will be enrolled with the intent of surgical treatment in the involved breast(s) after completing 6 months of neoadjuvant treatment. Safety, tolerability, response rates and surgical outcomes will be assessed. Disease progression will be monitored throughout study participation. Paired tumor biopsies and blood sampling will allow for a robust biomarker evaluation. Prior to initiating the Treatment Cohort (162 subjects), up to 12 subjects will be enrolled in a pharmacokinetic (PK) Run-in Cohort to identify the optimal dose for the Treatment Cohort. Enrolment in the PK Run-in cohort began in February 2023. Clinical trial information: NCT05607004. Research Sponsor: Atossa Therapeutics, Inc.; U.S. National Institutes of Health.
Neoadjuvant HER2-targeted therapy ± immunotherapy with pembrolizumab (neoHIP): An open label randomized phase II trial.

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Background: Immune checkpoint inhibition (ICI) is synergistic with HER2-directed therapy in pre-clinical models. Clinically, pembrolizumab (K)-mediated ICI plus HER2-directed therapy with trastuzumab (H) was safe and demonstrated modest activity in H-resistant HER2-positive (HER2+) metastatic breast cancer. Because ICI may confer more robust activity when administered earlier in the course of disease, H and K administered in the curative-intent, treatment-naive setting may allow for de-escalation of cytotoxics; confer life-long, tumor-specific immunity; and ultimately, improve cure rates. Moreover, the synergy of H and K with paclitaxel (T) may overcome the need for dual HER2-blockade with H plus pertuzumab (P). In this randomized, multicenter, phase II, open-label trial the efficacy and safety of neoadjuvant THP vs THP-K vs TH-K are explored. Methods: Patients (pts) ≥18y with previously untreated, stage II-III, HER2+ breast cancer are being randomized and stratified by clinical nodal status (positive vs. negative) and hormone receptor status (positive vs. negative). In arm A, pts received T at 80mg/m2 weekly for 12 weeks, H at 8mg/Kg (loading dose) and then 6mg/Kg every 3 weeks x 3 doses, P at 840mg (loading dose) and then 420mg/Kg every 3 weeks x 3 doses (THP). In arm B, pts received THP plus K at 200mg every 3 weeks x 4 doses (THP-K). In arm C, pts received TH-K. After enrollment of 22 pts to arm C, a prespecified interim efficacy analysis was conducted, and enrollment to this arm was subsequently terminated. Enrollment to the other arms continues with 32/58 pts enrolled to arm A and 33/58 pts enrolled to arm B as of 2/14/2023. Definitive surgery is 3-6 weeks after the last dose. After surgery, pts are treated per the treating physician’s discretion per local clinical standard. The primary end point is pathologic complete response (pCR) rate in the breast and axilla (ypT0/Tis ypN0). Secondary end points include pCR rate by ypT0ypN0 and ypT0/Tis, residual cancer burden index, event free survival, breast conserving surgery rate, safety and overall survival. Exploratory correlative studies will characterize potential immune biomarkers predictive of efficacy and/or toxicity. Clinical trial information: NCT03747120. Research Sponsor: Merck; BCRF.
A single-arm phase 2 study of peri-operative immune checkpoint inhibition and cryoablation in women with hormone receptor-negative, HER2-negative, early-stage/resectable breast cancer.

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Background: Local tumor destruction with cryoablation (cryo) induces inflammation and releases antigens that can activate tumor-specific immune responses. Pre-clinically, cryo with immune checkpoint inhibition (ICI) augmented tumor-specific immune responses and prevented recurrence. Clinically, we established that peri-operative (peri-op) cryo with ICI [ipilimumab (ipi) +/- nivolumab (nivo)] was safe in patients (pts) with operable, early stage breast cancer (ESBC) and generated robust intra-tumoral and systemic immune responses. In this phase 2 study, we evaluate the disease specific impact of peri-op ICI in women with residual triple negative breast cancer (TNBC) after neoadjuvant chemotherapy (NAC), a subset at high risk of early relapse. Methods: Eligible women are ≥18y, with ER <10%, PR <10%, HER2 negative (per ASCO/CAP definition), ≥ 1.0 cm, residual operable disease after taxane-based NAC. As of 2/14/21, 16/80 pts have been enrolled and treated with ipi/nivo/cryo followed by breast surgery and adjuvant nivo. Pts undergo percutaneous, image-guided cryo with concurrent research core biopsy 7-10 days prior to surgery and received ipi (1mg/kg IV) with nivo (240mg IV) 1 to 5 days prior to cryo. After surgery, pts received 3 additional doses of nivo at 240mg IV Q2 weeks. To reflect the US FDA approval of curative-intent pembrolizumab (pembro) in 2021, the protocol was recently amended to allow standard-of-care pembro as an alternative ICI option. Adjuvant capecitabine or olaparib is recommended for all patients per local standard-of-care. Patients will be stratified by NAC platinum administration, NAC anthracycline administration, and clinical nodal status (positive versus negative). The primary endpoint is 3-year Event Free Survival (EFS). Secondary endpoints include Invasive Disease-Free Survival (IDFS), Distant Disease-Free Survival (DDFS), overall survival (OS) and safety. Exploratory correlative studies will be performed on tumor and serum to characterize the immunologic impact of the intervention and to explore predictors of efficacy and toxicity. Clinical trial information: NCT03546686. Research Sponsor: Komen; ASCO; Bristol-Myers Squibb, BTG International Ltd.
A phase II study of concurrent WOKVAC vaccination with neoadjuvant chemotherapy and HER2-targeted monoclonal antibody therapy.

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Background: HER2+ breast cancer (BCa) is an aggressive breast cancer subtype. The treatment of Stage I-III HER2+ BCa with neoadjuvant chemotherapy and HER2 monoclonal antibodies (trastuzumab and pertuzumab) induces a pathologic complete response in 43-67% of patients. Residual HER2+ disease (i.e. residual cancer burden) after neoadjuvant therapy is associated with a significantly higher risk of recurrence. Evidence supports that HER2 immunity is progressively lost in HER2 oncogenesis and that restoration of HER2 specific CD4+ Th1 immunity is associated with a lower risk of recurrence. Trastuzumab can partially restore HER2 specific immunity, but only in a minority of patients. We have demonstrated that HER2 specific vaccination can augment HER2 specific immunity. While taxane chemotherapy can deplete immunosuppressive cells (MDSCs) 13 – 17 days after treatment creating an optimal time for vaccination. The WOKVAC vaccine is a plasmid vaccine encoding Th1 selective epitopes from HER2 and two other high-risk cancer antigens IGFBP-2 and IGF-1R. The Phase I trial of this vaccine reported that it is safe and all doses induced antigen specific Type I immune responses. We hypothesize that addition of WOKVAC to neoadjuvant chemo/HER2 targeted therapy will induce a significant increase in the number of patients with Th1 CD4+ and CD8+ T cells after neoadjuvant vaccine/chemo/HER2 therapy. Methods: Trial Design: Phase II single arm trial of WOKVAC vaccination with concurrent neoadjuvant taxane based chemotherapy, trastuzumab, and pertuzumab in patients with Stage I-III HER2+ (HR+/-) breast cancer. Enrolled patients will receive WOKVAC vaccine 150mcg on day 13 of cycles 1-3. WOKVAC vaccination may be given with either TCHP or THP. A maximum of 16 patients will be enrolled in this study. Objectives: The primary objective is to evaluate whether concurrent WOKVAC vaccine with chemotherapy and HER2 antibody therapy can significantly increase T-bet+ CD4+ and CD8+ TIL. Secondary objectives are to determine: (1) whether concurrent WOKVAC with neoadjuvant chemo/HER2 therapy is safe, (2) if the magnitude of vaccine induced antigen specific Th1 immunity after neoadjuvant therapy is associated with pathologic response. Statistical Methods: (1) In order to detect a 30% increase in the number of patients with Tbet+ CD4+ and CD8+ TIL in the enrolled patients with 80% power and a one-side alpha of 0.05, our enrollment goal for this study will be 16 patients. (2) Safety will be assessed per CTCAE v5.0, Benchmarks for safety needed to advance this trial concept to a Phase III study will be a grade 3 toxicity rate of ≤13% and a grade 4 toxicity rate of ≤7%. (3) The induction of Th1 immunity will be compared against the presence or absence of a complete pathologic response to determine if there is a significant correlation using Pearson r correlation analysis. Targeted Accrual: The study will accrue up to 16 patients. Clinical trial information: NCT04329065. Research Sponsor: Department of Defense.
Nine-weeks versus one-year trastuzumab for early-stage HER2+ breast cancer: 10-year update of the Short-HER phase III randomized trial.

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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, 2023, issue of the Journal of Clinical Oncology.