

First results from the OPTIMA phase III randomized non-inferiority trial of test-directed chemotherapy in patients with high clinical risk ER-positive HER2-negative early breast cancer.

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Background: Tumor gene expression tests are widely used to assist adjuvant chemotherapy decisions for women with early breast cancer (EBC). OPTIMA (Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis) is an international RCT comparing chemotherapy decisions made with the Prosigna (PAM50) gene expression test with standard treatment in mostly node-positive patients. **Methods:** Women and men aged >40 recommended to receive chemotherapy for ER+ HER2- EBC with 0-9 involved axillary nodes and T size >30mm if node negative were eligible. Randomization was between standard chemotherapy followed by endocrine therapy (CET) or to a Prosigna test directed chemotherapy decision. Patients with Prosigna ROR score > 60 tumors were assigned CET whilst those with low ROR score (≤ 60) tumors received endocrine therapy (ET) alone. ET for premenopausal women included ovarian function suppression (OFS) in the absence of chemotherapy-induced ovarian insufficiency. ROR scores were not disclosed, and patients receiving CET were blinded to their randomization. OPTIMA was designed to demonstrate non-inferiority (NI) of 5-year invasive breast cancer free survival (IBCFS) in the test-directed arm with a 3% margin in the per protocol (PP) population using a 5% 1-sided alpha. Control arm testing allowed treatment comparison within the low ROR score population at a 3.5% NI margin. **Results:** From 16th Jan 2017 to 12th Dec 2025 4429 patients were randomized, 2215 to the control arm and 2214 to the test-directed arm of whom 2061 (93%) and 2097 (95%) were included in the respective PP group. Patient characteristics in the PP population were well-balanced; 62% were postmenopausal, 37% premenopausal and 0.8% male. 73% had pN1/pN1sn, 8% had pN0/pN1mi and 19% had pN2 tumors. 68% had low ROR score tumors. With a median follow-up of 3.9 years (interquartile range 2.0-5.9), 280 IBCFS events occurred (141 on control arm; 139 on test directed arm) of which 66% were distant recurrences. The 5-year IBCFS rate in the control arm was 91.5% [95% CI 89.7- 92.9%] and 90.4% [95% CI 88.6- 92.0%] in the test-directed arm, Hazard Ratio (HR) 0.99 [90% CI 0.81- 1.20], NI p = 0.013, thereby meeting the pre-defined NI margin. The corresponding 5-year IBCFS rates for the low ROR score population were 94.9% [95% CI 92.9- 96.4%] and 93.7% [95% CI 91.8- 95.2%] for the two arms respectively, HR 1.06 [90% CI 0.78- 1.46] NI p = 0.0051 again demonstrating non-inferiority. There was no significant outcome heterogeneity between subgroups including for menopausal and nodal status. **Conclusions:** The OPTIMA trial demonstrates that women and men with ER+ HER2- EBC and ROR score ≤ 60 tumors can safely avoid chemotherapy. It provides evidence for the utility of test-directed chemotherapy in premenopausal women treated with OFS and patients with high levels of nodal involvement. Clinical trial information: ISRCTN42400492. Research Sponsor: UK National Institute for Health Research Health Technology Assessment Programme; 10/34/501; Norwegian Cancer Society; KLINBEFORSK (Norway); Pink Ribbon (Norwegian Breast Cancer Association); Breast Cancer Trials (Australia); Veracyte.

Prognostic and predictive impact of baseline gene expression (exp) in the NATALEE trial of adjuvant (adj) ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in HR+/HER2— early breast cancer (EBC).

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Background: In the NATALEE clinical trial, RIB + NSAI significantly improved invasive disease-free survival (iDFS) vs NSAI alone in patients (pts) with stage II/III HR+/HER2— EBC. We report on the prognostic and predictive value of baseline gene exp in NATALEE. **Methods:** Pts were randomized 1:1 to RIB + NSAI or NSAI alone. Men and premenopausal women received goserelin. Eligible pts had anatomical stage IIA (if No with additional risk factors [G3, or G2 with Ki67 $\geq$ 20% or high genomic risk] or N1 [1–3 axillary lymph nodes]), IIB, or III disease per AJCC (8th ed). Gene exp in surgical samples was profiled by NanoString BC360 panel. PAM50-based intrinsic subtype $\times$ treatment (tx) interaction was estimated by likelihood ratio test. Prognostic and predictive effects of PAM50 subtypes and genomic risk/proliferation signature scores created from gene exp data were assessed with Cox proportional hazards models. Differences in genomic risk and proliferation scores were analyzed by Wilcoxon test. Associations between gene exp and RIB benefit were estimated with Cox models. **Results:** In all, 3022 baseline surgical samples were analyzed. iDFS benefit with RIB + NSAI was consistent in the biomarker (hazard ratio [HR], 0.72) and intent-to-treat populations (HR, 0.71). PAM50 subtype distribution was comparable across tx arms and differed between No and N1–N3 in pts with luminal A (LumA; 50% vs 68%), luminal B (LumB; 41% vs 26%), and basal-like (BSL; 6.4% vs 2.5%) disease, with similar percentages for HER2-enriched (HER2E; 2.5% vs 3.0%). PAM50 subtypes were strongly prognostic (HRs vs LumA: LumB, 1.39; HER2E, 2.62; BSL, 3.92). RIB had benefit across all PAM50 subtypes (HRs: LumA, 0.77; LumB, 0.71; HER2E, 0.50; BSL, 0.42), with no significant subtype $\times$ tx interaction ($P = .34$). Higher genomic risk signature or proliferation signature scores showed a trend for increased RIB benefit, again with no significant interaction. Pts with No vs N1–N3 had significantly higher genomic risk scores and proliferation scores. Exploratory analysis of the predictive effect of gene exp on RIB benefit identified several genes for which higher (eg, *CEACAM6*, *NOD2*, and *GPX3*) or lower exp (eg, *GATA3*, *SLC39A6*, and *MAPT*) was associated with increased RIB benefit. **Conclusions:** In this analysis of NATALEE, which examined the largest dataset of surgical tumor samples from any adj CDK4/6i trial in HR+/HER2— EBC, RIB had benefit across all PAM50 subtypes, with a trend for increased benefit in pts with higher genomic risk signature or proliferation signature scores. Baseline exp levels of several genes were associated with differential RIB benefit in EBC, showing potential predictive and prognostic value. The findings reinforce the therapeutic benefit of RIB in combination with ET across HR+/HER2— EBC populations. Clinical trial information: NCT03701334. Research Sponsor: Novartis Pharmaceuticals Corporation.

Efficacy and safety of giredestrant (GIRE) in patients (pts) with estrogen receptor–positive, HER2-negative early breast cancer (ER+, HER2– eBC) in the phase III lidERA BC clinical trial: Results by menopausal status.

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Background: The lidERA BC trial (NCT04961996) demonstrated a statistically significant, clinically meaningful improvement in invasive disease-free survival (IDFS) with GIRE (a next-generation oral SERD and full ER antagonist) vs standard-of-care endocrine therapy (SOC ET) in ER+, HER2–, Stage I–III eBC (Bardia SABCS 2025). We report efficacy and safety in pre-menopausal (PRE-M) vs post-menopausal (POST-M) pts. **Methods:** Pts with ER+, HER2– eBC who had BC surgery and (neo)adjuvant chemotherapy (if indicated) were randomized 1:1 to once-daily 30 mg GIRE or SOC ET (anastrozole/letrozole/exemestane [aromatase inhibitors; AIs] or tamoxifen [TAM]) for 5 years (y) of treatment (tx). PRE-M pts on GIRE and on AIs received an LHRH. **Results:** In the efficacy-evaluable population (n = 4170), 40.7% of pts were PRE-M and 59.3% POST-M. 58.0% of pts on TAM received LHRH. PRE-M pts generally had a slightly higher baseline risk of recurrence vs POST-M pts (high risk, 70.5% vs 66.4%; medium risk, 28.4% vs 32.5%; higher use of [neo]adjuvant chemotherapy, 91.2% vs 78.9%). GIRE showed IDFS benefit and higher 3-y rates in both PRE-M and POST-M subgroups; a similar trend was observed for distant recurrence-free interval (DRFI) (Table). Adverse events (AE) were comparable in both subgroups and across txs (Table). Fewer pts discontinued GIRE due to AEs compared with pts receiving an AI, regardless of menopausal status. Discontinuation due to musculoskeletal pain occurred in 1.6% vs 4.5% of pts receiving GIRE vs AI, respectively. More pts switched to alternative ET in the SOC ET arm vs GIRE (10.1% vs 5.7%), mainly due to AEs for both arms. **Conclusions:** Adjuvant GIRE improved IDFS and DRFI vs SOC ET; benefit was consistent irrespective of menopausal status. PRE-M pts experienced a 42% reduction in the risk of developing metastatic disease and POST-M pts a 24% reduction. Safety was comparable between menopausal groups and there were few discontinuations, regardless of menopausal status, although PRE-M and POST-M pts receiving GIRE had fewer tx discontinuations than those receiving an AI or TAM in the PRE-M and POST-M settings. Clinical trial information: NCT04961996. Research Sponsor: F. Hoffmann-La Roche Ltd.

	GIRE PRE-M n = 849	SOC ET PRE-M n = 838		GIRE POST-M n = 1220	SOC ET POST-M n = 1236			
IDFS hazard ratio (HR)	0.65			0.74				
3-yr rate, %	94.0	91.5		91.3	88.3			
DRFI HR	0.58			0.76				
3-yr rate, %	95.5	92.6		93.6	91.6			
	PRE-M n = 1672			POST-M n = 2440				
Pts, %	GIRE n = 840	SOC ET n = 832	SOC ET (AI) n = 563	SOC ET (TAM) n = 269	GIRE n = 1209	SOC ET n = 1231	SOC ET (AI) n = 1183	SOC ET (TAM) n = 48
All Grade/Grade 3–4 AE	95.5/18.2	95.3/17.3	96.3/16.9	93.3/18.2	94.5/20.7	93.7/18.4	94.1/18.6	85.4/14.6
AE leading to tx discontinuation	4.9	7.8	7.5	8.6	5.7	8.5	8.2	16.7
Musculoskeletal pain*	58.1	53.5	59.7	40.5	50.8	53.6	54.6	29.2

HRs are unstratified vs SOC ET.

*Includes other related terms.

Omission of completion axillary dissection in patients with breast cancer and sentinel lymph node macrometastases: Overall survival and patient-reported arm morbidity from the randomized SENOMAC trial.

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Surgical de-escalation of implant-based breast reconstruction (IBBR) after mastectomy for breast cancer treatment or prevention: The international randomized phase III PREPEC trial (OPBC-02).

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Background: The optimal positioning of implants following skin- (SSM) or nipple-sparing mastectomy (NSM) for breast cancer treatment or prevention is unclear. Pre-pectoral IBBR obviates the need to dissect the major pectoral muscle but provides less soft tissue coverage of the implant. The PREPEC trial hypothesized pre-pectoral IBBR would result in improved long-term quality of life (QoL) compared to sub-pectoral IBBR. **Methods:** OPBC-02/PREPEC (NCT04293146) was a pragmatic, international, randomized, phase III superiority trial. Women ≥ 18 years undergoing SSM or NSM for treatment or prevention of breast cancer were randomized (1:1) to pre-pectoral or sub-pectoral IBBR. Surgery otherwise followed standards of care. The primary endpoint was patient-reported physical well-being chest as assessed by BREAST-Q 24 mo after surgery (prespecified MID 4 points; SD 13). 372 pts provided 80% power (two-sided t-test $\alpha = 0.05$). Multiple imputation was implemented for missing scores across all timepoints (day 10; 1, 6, 12, 18, 24 mo). The IBBR assignment difference at 24 mo was estimated by linear mixed modeling, adjusted for baseline score, stratification factors, pre-selected covariates, and random center effect. Loss or replacement of expander or implant for any reason within 24 mo was the primary safety endpoint. **Results:** From July 2020 to February 2023, 383 pts were randomized at 26 OPBC centers in 10 countries. The full analysis set comprised 380 pts (191 randomized to pre-pectoral, 189 to sub-pectoral IBBR). Surgery was unilateral in 72.9% of pts and NSM in 58.4%. The setting was therapeutic in 77.9% of pts, therapeutic and preventive in 15.5%, and preventive in 6.6%. BREAST-Q completion was 83–95% across 6 post-baseline timepoints. Pre-pectoral IBBR significantly improved physical well-being at 24 mo compared to sub-pectoral IBBR (least-square means 79.2 [95%CI 75.5–82.8] vs 74.3 [70.7–78.0], respectively). The mean difference of 4.8 (95%CI 1.0–8.7; $p = 0.01$) surpassed the predefined threshold for a clinically meaningful difference. The effect was robust in sensitivity analyses, and consistent in subgroup analyses. Loss or replacement of expander or implant for any reason within 24 mo occurred in 68 pts, 21.1% vs 14.5% after pre-pectoral and sub-pectoral IBBR, respectively. The covariate-adjusted model estimated 5.7% (95%CI –2.4% – 13.8%) more implant loss with pre-pectoral IBBR. At least one complication occurred in 54.1% vs 55.9% of pts, respectively. Early complications were more frequent after pre-pectoral IBBR (crude estimated increase range 3–5%); late complications were more frequent after sub-pectoral IBBR. **Conclusions:** Pre-pectoral IBBR significantly and relevantly improved long-term QoL at the cost of a higher risk of loss or replacement of expander or implant compared to sub-pectoral IBBR. Clinical trial information: NCT04293146. Research Sponsor: Swiss National Science Foundation; Krebsliga beider Basel; Swiss Cancer Research foundation.

Prediction of axillary response in 5,262 patients with node-positive breast cancer treated with neoadjuvant chemotherapy: Results from the prospective multicenter AXSANA/EUBREAST-03/AGO-B-053 study.

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Background: Axillary lymph node dissection (ALND) for node-positive breast cancer (BC) converting to clinical node-negativity after neoadjuvant chemotherapy (NACT) is increasingly being replaced by less invasive procedures, such as sentinel lymph node biopsy (SLNB) or targeted axillary dissection (TAD). Concerns remain regarding the use of de-escalated procedures in patients with high initial nodal burden. We aimed to determine factors associated with nodal response, with a focus on tumor biology and nodal burden, to enable less extensive surgery without compromising oncological outcomes. **Methods:** AXSANA is an ongoing study investigating oncological and patient-reported outcomes after different axillary procedures in cN+ BC treated with NACT. In the present analysis, the impact of nodal involvement and tumor biology on axillary response was analyzed. The entire dataset is continuously and systematically monitored for data quality assurance. **Results:** 7,071 patients from 288 sites in 26 countries were included between June 2020 and January 7th, 2026. Of these, 5,262 had completed surgery at the time of analysis. 2,341 patients (44.5%) had HR+ HER2- disease, followed by HR+ HER2+ (1,244; 23.6%), triple-negative (1,053; 20.1%) and HR- HER2+ (618; 11.7%). 91.3% of patients had an invasive ductal carcinoma of no special type (NST). 1,158 (22.1%) had ≥ 4 suspicious nodes at time of diagnosis. The highest nodal pCR rate (ypNo) was observed in patients with HR- HER2+ disease (86.1%), followed by HR+ HER2+ (70.7%), triple-negative (68.5%), and HR+ HER2- (30.5%; $p < 0.001$). Nodal pCR rate was higher in patients with NST tumors (55.6%), compared to those with invasive lobular (35.2%) and mixed histology (43.8%; $p < 0.001$). Patients with higher Ki67 ($p < 0.001$), higher grading ($p < 0.001$), multicentric tumors ($p = 0.001$), and without lymphangitis carcinomatosa ($p = 0.046$) were more likely to achieve nodal pCR in the univariate analysis. In contrast, the number of suspicious nodes at the time of diagnosis was not associated with axillary response (ypNo: 54.4% in pts. with 1-3 suspicious nodes vs. 53.6% in ≥ 4 suspicious nodes; $p = 0.670$). In the multivariable analysis, receptor status, Ki67, and grading, but not the number of suspicious lymph nodes at the time of diagnosis, were significantly associated with axillary response to treatment. **Conclusions:** This large prospective analysis shows that tumor biology, rather than the extent of nodal involvement is associated with axillary response to NACT. This challenges current guidelines and the common approach of restricting surgical de-escalation to patients with a low axillary tumor burden at presentation, and suggests that the selection of candidates for a potential de-escalation should be based on tumor biology rather than the extent of axillary disease at diagnosis. Clinical trial information: NCT04373655. Research Sponsor: AGO-B; AWOgyn; Claudia von Schilling Foundation for Breast Cancer Research; Ehmann Foundation Savognin; EndoMag; Merit Medical; Mammotome; Sirius Medical.

Updated overall survival results from a randomized phase III trial of non-cross-resistant adjuvant chemotherapy plus endocrine therapy versus endocrine therapy alone in HR+/HER2−/lymph node-positive breast cancer with residual disease following neoadjuvant chemotherapy (NCT01019616).

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Background: Patients with HR+/HER2−, node-positive breast cancer and residual disease after neoadjuvant chemotherapy (NAC) represent a high-risk population yet substantial recurrence risk. Whether additional non-cross-resistant chemotherapy after surgery provides long-term survival benefit beyond endocrine therapy remains uncertain. Our previous analysis of this phase III trial (NCT01019616) with shorter follow-up (median, 72.4 months) did not show a statistically significant survival benefit. Here we report updated survival outcomes with extended follow-up. **Methods:** Women aged < 65 years with invasive HR+/HER2−, node-positive breast cancer who completed anthracycline-containing NAC and had residual disease (Miller-Payne grade 1–3 and/or residual nodal involvement) were randomized 1:1 to receive either 4 cycles of non-cross-resistant adjuvant chemotherapy plus endocrine therapy (CT+ET) or endocrine therapy alone (ET). The primary endpoint was distant disease-free survival (DDFS); overall survival (OS) was a secondary endpoint. Hazard ratios (HRs) were estimated using Cox proportional hazards models with multivariable adjustment. **Results:** A total of 379 patients were randomized (CT+ET, $n = 187$; ET, $n = 192$) with balanced baseline characteristics. At median follow-up of 135.0 months, 52 deaths occurred: 18 (9.6%) in CT+ET versus 34 (17.7%) in ET. OS was significantly improved with CT+ET (log-rank $P = 0.023$). Ten-year OS rates were 89.9% versus 82.9% (adjusted HR, 0.56; 95% CI, 0.32–0.99; $P = 0.048$). DDFS showed a favorable trend ($P = 0.059$) with 10-year rates of 85.5% versus 78.3% (adjusted HR, 0.67; 95% CI, 0.41–1.09). Greatest benefit was observed in patients with residual node-positive disease (OS HR, 0.47) and Miller-Payne grade 3 response (OS HR, 0.31). **Conclusions:** This randomized phase III trial demonstrates long-term overall survival benefit from the addition of non-cross-resistant chemotherapy to endocrine therapy for HR+/HER2−, node-positive patients with residual disease after NAC. Clinical trial information: NCT01019616. Research Sponsor: None.

Neoadjuvant pembrolizumab or placebo plus chemotherapy followed by adjuvant pembrolizumab or placebo for high-risk early-stage TNBC: Final analysis results from the phase 3 KEYNOTE-522 study.

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Background: KEYNOTE-522 (NCT03036488) showed statistically significant and clinically meaningful improvements in pCR, EFS, and OS with the addition of pembrolizumab (pembro) to chemotherapy (chemo) in participants (pts) with high-risk early-stage TNBC. Here, we present updated results from the final analysis. **Methods:** Eligible pts with previously untreated, non-metastatic, centrally confirmed TNBC (stage T1c N1-2 or T2-4 N0-2 per AJCC) were randomized 2:1 to neoadjuvant pembro 200 mg Q3W or placebo (pbo), both given with 4 cycles of paclitaxel + carboplatin, then 4 cycles of doxorubicin or epirubicin + cyclophosphamide. After definitive surgery, pts received adjuvant pembro or pbo for 9 cycles or until recurrence or unacceptable toxicity. Dual primary endpoints are pCR (ypTo/Tis ypNo) and EFS (time from randomization to disease progression that precluded definitive surgery, local/distant recurrence, second primary cancer, or death from any cause); OS is the key secondary endpoint. **Results:** 1174 pts were randomized to pembro (n = 784) or pbo (n = 390). At the data cutoff date (October 14, 2025), median follow-up (range) was 93.8 mo (84.7-102.8). The 7-yr EFS rate (95% CI) was 78.3% (75.3-81.1) in the pembro group vs 69.8% (65.0-74.2) in the pbo group; the HR was 0.68 (95% CI, 0.54-0.86). The 7-yr OS rate (95% CI) was 85.1% (82.5-87.5) in the pembro group vs 77.2% (72.7-81.1) in the pbo group; the HR was 0.64 (95% CI, 0.49-0.85). The benefit of pembro on EFS and OS was generally consistent across most prespecified subgroups, including those defined by PD-L1 expression, nodal status, and disease stage. Rates of grade ≥ 3 treatment-related AEs were 77.1% in the pembro group and 73.3% in the pbo group (death incidence, 0.5% vs 0.3%, respectively); rates of any grade immune-mediated AEs were 35.0% vs 13.1%, respectively. **Conclusions:** After a median follow-up of 7.8 years, neoadjuvant pembro + chemo followed by adjuvant pembro continues to show a clinically meaningful survival benefit compared with neoadjuvant chemo alone in pts with high-risk early-stage TNBC. Clinical trial information: NCT03036488. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Adjuvant capecitabine and trastuzumab for stage IA HER2-positive breast cancer (IRIS-A): A phase II clinical trial.

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Background: Weekly paclitaxel and trastuzumab represents a standard option for most stage I human epidermal growth factor receptor type 2 (HER2)-positive breast cancer (BC)s based on results of the single arm phase II APT trial. However, the protocol-induced toxicity was not absent, prompting interest in better tolerated approaches that retain high clinical efficacy. The series of “IRIS” study including cohort A(2020, capecitabine and trastuzumab), B(2020, endocrine therapy and trastuzumab), C (2021, short-period capecitabine and trastuzumab) and D (2021, vinorelbine and trastuzumab) were designed as single arm trials regarding de-escalation of adjuvant therapy without intravenous chemotherapy in early-stage HER2+ BCs. Herein we reported the results of IRIS-A, a single-group, phase II study to determine whether treatment with capecitabine and trastuzumab was well tolerated and yielded clinically acceptable outcome among stage IA HER2-positive breast cancer. **Methods:** Patients with stage IA (T1N0: hormonal receptor (HR) < 10%, T≤2cm or HR≥10%, 1cm < T≤2cm) confirmed HER2+ BC were received oral capecitabine (1000 mg/m² twice daily for two weeks), and trastuzumab(8 mg/kg load→6 mg/kg) every 3 weeks for 6 cycles, followed by 11 cycles of trastuzumab monotherapy (6 mg/kg once every 3 weeks). The primary end point was survival free from invasive disease (iDFS). **Results:** A total of 187 patients were enrolled in this study between May 20, 2020 and May 27, 2021 at Fudan University Shanghai Cancer Center in China. Among all these patients, 80.2% had tumors that measured 0.5 cm or less in the greatest dimension; a majority of tumors (87.2%) were hormone-receptor-negative. The median follow-up period was 62 months(ranges 56–68). The 5-year rate of survival free from invasive disease was 97.9% (95% confidence interval [CI], 94.4 to 99.2). Among the 4 relapses seen, 2 were due to contralateral primary invasive breast cancer (HER2-negative). Excluding these 2 patients and nonbreast cancers, 2 disease-specific events (1 with ipsilateral axilla and ipsilateral breast) were noted. There was no death in this trial. A total of 5 patients (2.7%) reported at least one episode of grade 3 adverse effect (AE) s, which did not influence the completion of treatment. The most common AE was hand-foot syndrome (46.5%), with 1.1% of patients experiencing a grade 3 event. **Conclusions:** Among patients with stage IA HER2+ BCs, treatment with adjuvant capecitabine plus trastuzumab was associated with an excellent 5-year iDFS of 97.9%. No adverse events that influence treatment continuity were observed. The regimen used in this trial would be an alternative in patients with small size HER2+ tumors with fewer toxic effects than the established regimens. A phase III study using the same protocol is being conducted currently. Clinical trial information: NCT04383275. Research Sponsor: None.

Neoadjuvant pyrotinib vs pertuzumab therapy for HER2-positive early breast cancer: The HELEN HER-013 randomized clinical trial.

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Background: Docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) is a standard neoadjuvant regimen for stage II–III human epidermal growth factor receptor 2 (HER2)–positive breast cancer; however, its use is associated with substantial treatment burden, particularly hematologic toxicity, highlighting the need for alternative strategies that maintain efficacy with different toxicity profiles. This study to determine whether a chemotherapy–de-escalated regimen of nanoparticle albumin–bound paclitaxel, trastuzumab, and the tyrosine kinase inhibitor pyrotinib (nab-PHPy) is noninferior to standard TCHP with respect to pathological complete response (pCR). **Methods:** The HELEN HER-013 trial was a multicenter, randomized, open-label, phase 3 noninferiority trial conducted at 15 centers in China. Women with previously untreated, operable stage II–III HER2–positive breast cancer were enrolled between May 2023 and May 2025. Participants were randomly assigned (1:1) to receive six 21-day cycles of either nab–paclitaxel, trastuzumab, and oral pyrotinib (nab-PHPy group) or TCHP group. The primary end point was pCR (ypT0/Tis ypN0), assessed in the modified intention-to-treat (mITT) population (patients who received ≥ 1 dose of study treatment). The prespecified noninferiority margin was -5.5% (ClinicalTrials.gov Identifier: NCT05918328). **Results:** Among 709 screened individuals, 610 were randomized, and 589 were included in the mITT population (295 in the nab-PHPy group and 294 in the TCHP group; all female). Median age was 51 years (interquartile range [IQR], 43–56) in the nab-PHPy group and 52 years (IQR, 45–57) in the TCHP group. The primary end point of pCR was achieved in 186 patients (63.1%; 95% CI, 57.4%–68.4%) in the nab-PHPy group and 174 patients (59.2%; 95% CI, 53.4%–64.8%) in the TCHP group. The between-group difference was 3.9% (95% CI, -4.2% to 11.9%), which met the prespecified criterion for noninferiority (noninferiority $P = .01$). Grade 3 or higher treatment-emergent adverse events occurred in 113 patients (38.3%) receiving nab-PHPy and 107 patients (36.4%) receiving TCHP. The most common grade 3 or higher adverse events were diarrhea (31.5% vs 17.0%), anemia (1.7% vs 10.2%), and nausea (0% vs 5.8%). No treatment-related deaths were reported. **Conclusions:** Among women with operable stage II–III HER2–positive breast cancer, neoadjuvant treatment with nab-PHPy was noninferior to TCHP with respect to pCR and was associated with a distinct toxicity profile, supporting its role as an alternative neoadjuvant strategy. Clinical trial information: NCT05918328. Research Sponsor: None.

Primary results of the BETTER-CARE trial: Implementation of a needs-adapted and individualized follow-up care after primary 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, 2026, issue of the *Journal of Clinical Oncology*.

The effects of Mediterranean diet, physical activity, and vitamin D on breast cancer recurrence and cardiometabolic health: A multicenter randomized trial.

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Background: Low quality diets and physical inactivity are two modifiable lifestyle factors that together with vitamin D deficiency have been associated with unfavorable breast cancer (BC) outcomes and cardiometabolic health. We therefore tested the effect of a lifestyle program on BC recurrence and cardiometabolic risk factors on a background of vitamin D sufficiency. **Methods:** Women aged 30–74 years were enrolled in a phase III trial (NCT02786875) within 12 months of their primary BC diagnosis (stages I–III) in 7 oncologic centres in Italy. Consenting participants were randomized to one of two lifestyle treatments lasting 33 months: 1) positive control (n = 249), standard advice on a Mediterranean diet (MedDiet) and avoidance of sedentary behavior; 2) intervention (n = 243), high intensity advice on low-glycemic index MedDiet and 30-minute additional daily brisk walking. Oral vitamin D₃ was administered throughout. Data were collected quarterly on health status, anthropometry, 7-day food records, daily steps, serum 25(OH)D concentrations and metabolic syndrome parameters. The primary outcome was BC recurrence (intention to treat analysis) at 33 months, with cardiometabolic risk factors as secondary outcomes. Hazard ratios (HR) and 95% confidence intervals (CI) for BC recurrence were computed using Cox proportional hazards models adjusted for recruitment center. One-year changes in treatment variables and cardiometabolic risk factors were tested by paired Student's t-test within each treatment arm and by analysis of covariance between treatment arms, adjusted for baseline values. **Results:** Approximately 58% of patients were aged ≥50 years, 94% were postmenopausal, 86% had stages I–IIB and 75% hormone-positive BC. A total of 37 recurrences were observed with no differences between arms (HR = 0.94, 95% CI: 0.49–1.79). Independently of randomization arm, women with hormone-positive BC who were more adherent to the intervention program (41%), showed 76% lower risk of BC recurrence (HR = 0.24, 95% CI: 0.06–0.95). Weight loss of 3 kg, representing a 4.2% drop of initial body weight, was significantly greater in the test arm compared to 1.7 kg or 2.4% in the control arm (p = 0.0034). This translated in reductions of body mass index from 27.5±5.7 to 26.3±5.4 kg/m² in the intervention arm and from 27.2±5.1 to 26.6±5.1 kg/m² in controls (p = 0.0032). The presence of metabolic syndrome dropped by 65% in the intervention arm and 34% in controls (p = 0.008). The probability of metabolic syndrome remission was 2.5-fold higher in the intervention arm. **Conclusions:** A safe and low-cost lifestyle program with low-glycemic index MedDiet, daily brisk walking and oral vitamin D supplementation resulted in weight loss, reduced metabolic syndrome prevalence and was significantly associated with lower recurrences in women with hormone-positive BC. Clinical trial information: NCT02786875. Research Sponsor: None.

Effect of elinzanetant on sleep disturbance and aspects of quality of life in women with breast cancer experiencing vasomotor symptoms: OASIS-4 subgroup analysis by type of endocrine therapy.

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Background: In the Phase III OASIS-4 trial, elinzanetant (EZN), a dual neurokinin (NK)-targeted therapy (NK-1 and NK-3 receptor antagonist), significantly improved vasomotor symptoms (VMS), sleep disturbance and menopause-related quality of life (QoL) in women taking endocrine therapy (ET) for breast cancer. This post hoc analysis evaluated the effect of EZN on sleep disturbance and menopause-related QoL by ET type. **Methods:** Women aged 18–70 years with ≥ 35 moderate-to-severe ET-associated VMS/week were randomized 2:1 to EZN 120 mg daily for 52 weeks or placebo (PBO) for 12 weeks then EZN 120 mg for 40 weeks. Mean change from baseline (BL) to week 12 in Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form (PROMIS SD SF) 8b total T-score (range 28.9–76.5; < 55 normal, $55 - < 60$ mild, $60 - < 70$ moderate, ≥ 70 severe) and Menopause-specific QoL questionnaire (MENQOL) total/domain scores (range 1–8; higher score indicates greater bother) were analyzed descriptively by ET type (tamoxifen [TAM], aromatase inhibitor [AI], ovarian function suppression [OFS], no OFS). **Results:** Mean BL PROMIS SD SF 8b total T-scores and MENQOL total scores were numerically similar across ET subgroups (Table), with some variability in MENQOL domain scores (ranges: vasomotor 6.6–6.9; psychosocial 3.3–4.2; physical 4.1–4.6; sexual 3.7–5.5). Greater numerical reductions with EZN vs PBO from BL to week 12 were observed across all subgroups for PROMIS SD SF 8b total T-score and MENQOL total score (Table), as well as MENQOL domain scores (ranges: vasomotor -2.6 to -2.9 vs -1.2 to -1.5; psychosocial -0.8 to -1.0 vs -0.4 to -0.6; physical -0.7 to -0.9 vs -0.3; sexual -0.5 to -0.9 vs -0.3 to 0.0). **Conclusions:** In this post hoc analysis, EZN consistently improved sleep disturbance and menopause-related QoL, including vasomotor, psychosocial, physical and sexual aspects, across all ET subgroups. Taken with previous data, findings suggest to support the efficacy of EZN in reducing VMS, sleep disturbance and improving menopause-related QoL independently of ET type. Research Sponsor: Bayer.

	TAM EZN (n=175)	PBO (n=90)	AI EZN (n=141)	PBO (n=68)	OFS EZN (n=88)	PBO (n=48)	No OFS EZN (n=228)	PBO (n=110)
PROMIS SD SF 8b total T-score, mean (95% CI)								
BL	61.0 (60.1, 61.9)	60.5 (59.0, 62.0)	60.1 (59.0, 61.2)	61.1 (59.5, 62.7)	60.4 (59.0, 61.7)	61.6 (59.5, 63.7)	60.7 (59.9, 61.5)	60.4 (59.1, 61.7)
Change from BL to Week 12	-11.0 (-12.3, -9.7)	-4.3 (-5.9, -2.6)	-10.0 (-11.4, -8.7)	-3.8 (-5.5, -2.0)	-10.4 (-12.1, -8.7)	-6.5 (-8.7, -4.2)	-10.6 (-11.8, -9.5)	-3.1 (-4.5, -1.7)
MENQOL total score, mean (95% CI)								
BL	4.7 (4.5, 4.9)	4.5 (4.2, 4.7)	5.0 (4.8, 5.2)	5.2 (4.9, 5.5)	4.9 (4.6, 5.1)	4.9 (4.5, 5.3)	4.8 (4.7, 5.0)	4.7 (4.5, 5.0)
Change from BL to Week 12	-1.4 (-1.6, -1.2)	-0.5 (-0.7, -0.3)	-1.2 (-1.4, -1.0)	-0.6 (-1.0, -0.3)	-1.2 (-1.5, -1.0)	-0.6 (-1.0, -0.3)	-1.3 (-1.5, -1.2)	-0.5 (-0.7, -0.3)

Does resection of cavity shave margins impact survival in breast cancer patients?

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Background: Randomized controlled trials have shown that resection of cavity shave margins (CSM) halves the margin positivity and re-excision rate in breast cancer (bc) patients (pts), but the impact on overall (OS) and disease-free survival (DFS) remains unclear. **Methods:** Between Oct 21, 2011 and Nov 25, 2013, the SHAVE trial enrolled 235 pts in a single center study. Between Jul 28, 2016 and Apr 13, 2018, SHAVE2 enrolled 396 pts across 9 other US sites. Both studies were similar in their study criteria and methods. Pts ≥ 18 years of age, with planned partial mastectomy (PM) for stage 0–3 bc were eligible. Surgeons performed their standard PM with excision of selective margins as needed based on gross evaluation and specimen radiograph. Pts were then randomized intraoperatively to either “shave” or “no shave” arms. In the former, surgeons were instructed to take additional CSM from ≥ 4 faces of the cavity; in the latter, to close. Pts were followed for a median of 60.4 months (mo). **Results:** Across both studies ($n = 631$), the median pt age was 64 (range; 29–94), and the median invasive tumor size was 1 cm (range; 0–8 cm). Forty pts had no further disease at the time of PM either due to all disease being removed in the core biopsy or due to neoadjuvant chemotherapy. Before randomization, margin positivity was similar between the “shave” and “no shave” arms (37.8% vs. 34.8%, $p = 0.457$). After randomization, the “shave” group had a significantly lower positive margin rate (14.0% vs. 34.8%, $p < 0.001$) and re-excision rate (9.2% vs. 24.1%, $p < 0.001$). In the “shave” arm, 13.3% of those with negative margins prior to randomization had cancer found in the CSM. Pts in the “shave” arm were less likely to have positive final margins (after re-excision where performed; 6.3% vs. 15.8%, $p < 0.001$). Both groups had similar rates of radiation therapy (XRT) (82.8% vs. 81.8%, $p = 0.831$). Local recurrence rates were nearly identical at a median follow-up of 60.4 mo (1.3% vs. 1.6%, $p = 1.000$). 5-year DFS (91.9% vs. 92.6%, $p = 0.820$) and OS were not significantly different between groups (93.5% vs. 93.5%, $p = 0.841$). On Cox proportional hazard modelling, including randomization arm, final margin (after re-excision), and use of XRT, only the use of XRT significantly improved DFS (5 yr DFS 86.3% vs. 94.4%, HR: 0.47; 95% CI: 0.256–0.865, $p = 0.015$). **Conclusions:** While CSM reduced margin positivity and re-excision rates, it does not have an impact on DFS or OS at a median of 60.4 mo of surveillance; only the use of XRT significantly improved DFS. Although resection of CSM removed additional disease in 13.3% of margin-negative pts and was associated with a lower final positive margin rate, this did not translate into lower local recurrence rates. These results suggest that XRT may effectively manage small-volume residual disease that remains after PM. Clinical trial information: NCT01452399; NCT02772731. Research Sponsor: Yale Cancer Center; David and Katie Burke Fund for Breast Cancer Research; Connecticut Breast Health Initiative; Troy Cancer Program; Cleveland Clinic Akron General Operations; Cleveland Clinic Akron General Foundation; Lineberger Comprehensive Cancer Center; Watson Clinic Center for Research Inc; LifeCycle.

Neoadjuvant rilvegostomig (R) + trastuzumab deruxtecan (T-DXd) in high-risk HER2-negative breast cancer: Results from the I-SPY 2.2 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, 2026, issue of the *Journal of Clinical Oncology*.

Role of neoadjuvant versus adjuvant chemotherapy, dose density, and treatment schedule in biologically high-risk HR+/HER2- breast cancer: A pooled analysis of the WSG ADAPT-HR+/HER2- and PlanB trials.

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Secondary safety analysis of trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in DESTINY-Breast05: Clinical and demographic risk factors of interstitial lung disease (ILD) and radiation pneumonitis (RP).

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Background: In DESTINY-Breast05 (NCT04622319), T-DXd showed superior efficacy vs T-DM1 in patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) early breast cancer (eBC) with residual invasive disease after neoadjuvant therapy (NAT) and high risk of recurrence—a population in which radiotherapy (RT) is broadly used. Safety was consistent with the established T-DXd profile; ILD remained an important risk, although most cases were low grade. Previous T-DXd pooled analyses suggested potential associations between ILD and clinical and demographic factors. We report additional safety outcomes stratified by these risk factors. **Methods:** Pts with residual invasive HER2+ eBC and at high risk of recurrence after NAT were randomized 1:1 to receive T-DXd 5.4 mg/kg (n = 818) or T-DM1 3.6 mg/kg (n = 817) once every 3 weeks for 14 cycles. All pts underwent low-dose non-contrast chest computed tomography (CT) at screening. Pts who received adjuvant RT (aRT; either concurrently with or sequentially before study therapy) underwent additional low-dose CT during and after treatment completion. CT scans showing ILD or RP underwent blinded central adjudication. **Results:** At data cutoff (July 2, 2025), 806 pts in the T-DXd arm and 801 pts in the T-DM1 arm received ≥1 dose of treatment; no pts were ongoing study treatment. In the T-DXd arm, 93.9% of pts received aRT vs 93.6% in the T-DM1 arm. Adjudicated drug-related (adj DR) ILD rates were generally consistent across global regions (Asia, Europe, North America [NA] + Australia, and Rest of World), though numerically lower in NA + Australia for T-DXd. In both arms, adj DR ILD rates were higher in pts from Japan (n = 147) vs outside Japan (n = 1460; T-DXd: 14.9% vs 8.9%; T-DM1: 6.7% vs 1.2%), Japan vs other Asian countries (T-DXd: 14.9% vs 9.6%; T-DM1: 6.7% vs 2.1%), and in pts with baseline moderate vs normal renal impairment (T-DXd: 14.3% vs 9.7%; T-DM1: 5.0% vs 1.0%). Adj DR ILD incidence was comparable across racial subgroups. In both arms, investigator-reported RP rates were higher in pts from Japan vs outside Japan (T-DXd: 47.1% vs 27.4%; T-DM1: 45.0% vs 27.3%). Most ILD/RP events recovered or were recovering with protocol-specific management. Recovery/resolution was observed in 64.5% vs 75.0% of adj DR ILD events and 38.2% vs 43.2% of RP events in the T-DXd and T-DM1 arms, respectively. **Conclusions:** Adj DR ILD and RP events were mostly low grade and reversible with protocol-specific management guidelines. Adj DR ILD rates were higher with T-DXd than T-DM1 and were influenced by country and baseline renal function, consistent with prior pooled analysis. These findings are consistent with, and further characterize, the safety profile of T-DXd in post-NAT HER2+ eBC. Clinical trial information: NCT04622319. Research Sponsor: This study is sponsored by Daiichi Sankyo, Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

International variation in diagnostic and treatment practices in patients with HER2+ EBC: The RWE PEARL-HER2 study.

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Background: Pts with HER2+ EBC achieving pCR post neoadjuvant chemotherapy (NACT) with trastuzumab (H) and pertuzumab (P) show favorable outcomes. Yet, management varies widely within healthcare systems, including access to continuation of adjuvant (adj) P. We compared diagnostic and treatment practices across countries. **Methods:** PEARL-HER2 is an international retrospective real-world cohort including pts with HER2+ EBC achieving pCR (ypTo/isNo) after NACT-HP (Jan 2014 to Dec 2023). This descriptive preliminary analysis (data cut-off Jan-2026) summarizes diagnostic and treatment data stratified by country. **Results:** 1345 pts with pCR were included. Significant heterogeneity in pts and disease characteristics was observed (Table 1). Diagnostic methods also varied: use of breast MRI ranged from 11-97% across countries (>85% in Spain/Portugal; Peru, 11%), while FDG-PET/CT ranged from 0-72% (overall 20%; Turkey, 72%; p<0.001). Anthracycline-based NACT varied from <20% in Argentina and Brazil to >85% in Portugal and Turkey (p<0.001). Adj P was administered to 33% of pts overall (0-97%; p<0.001), with high use in countries with public reimbursement and minimal in those without. Among ER+ pts, ET use was uniformly high (98%; p=0.590), but regimen selection varied substantially (p<0.001): tamoxifen (42%) and aromatase inhibitor (58%). Events occurred in 6% of pts (invasive/non-invasive relapses and death); median FU was 40 months (IQR 24-62). **Conclusions:** This analysis indicates marked cross-country variability in management of HER2+ EBC. Use of adj P closely aligned with national reimbursement policies, highlighting access as a major determinant of care beyond clinical risk and guideline recommendations. Research Sponsor: Association Jules Bordet.

Characteristics	Argentina (N=155)	Belgium (N=217)	Brazil (N=107)	Italy (N=52)	Peru (N=18)	Portugal (N=603)	Spain (N=110)	Turkey (N=83)	Total (N=1345)	P-value
Age, median (IQR)	47 (41-56)	54 (45-63)	46 (40-52)	53 (45-61)	45 (41-56)	52 (45-62)	53 (44-59)	51 (45-61)	51 (43-61)	<0.001
Pre-/perimenop., n (%)	96 (62)	91 (43)	72 (72)	26 (50)	13 (72)	286 (48)	52 (48)	38 (46)	674 (51)	<0.001
NST histology, n (%)	145 (95)	197 (91)	89 (83)	48 (94)	18 (100)	558 (93)	103 (95)	83 (100)	1241 (93)	<0.001
ER+, n (%)	77 (50)	95 (44)	61 (58)	16 (31)	5 (28)	277 (46)	57 (52)	44 (53)	632 (47)	<0.001
cN0, n (%)	58 (37)	28 (13)	43 (40)	24 (46)	2 (11)	267 (44)	50 (46)	21 (25)	493 (37)	<0.001
Breast MRI	123 (80)	126 (58)	73 (71)	13 (25)	2 (11)	521 (86)	102 (97)	35 (42)	995 (75)	<0.001
PET-CT, n (%)	114 (9)	163 (29)	127 (26)	113 (25)	10 (0)	170 (12)	121 (19)	160 (72)	1268 (20)	<0.001
Anthracycline-based NACT, n (%)	19 (12)	137 (63)	19 (18)	44 (85)	2 (11)	532 (88)	84 (76)	79 (95)	916 (68)	<0.001
ET use in ER+, n (%)	79 (98)	112 (95)	46 (98)	35 (97)	13 (100)	339 (98)	58 (100)	43 (98)	725 (98)	0.590
Adj P, n (%)	89 (57)	210 (97)	63 (59)	20 (39)	0 (0)	49 (8)	9 (8)	0 (0)	440 (33)	<0.001
Public adj P reimbursement	Yes, high risk	Yes, N+ only	No	Yes, since 2023	No	No	No	No	-	-

Percentages exclude missing data.

Neoadjuvant atimociclib plus letrozole versus letrozole alone in HR+/HER2–breast cancer: Results from FourLight-2, a randomized phase 2 window of opportunity study.

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Background: In the neoadjuvant setting, endocrine therapy is a standard of care option in patients (pts) with HR+ breast cancer (BC). Atimociclib (ATI, PF-07220060) is a potent and selective CDK4 inhibitor and has shown favorable tolerability and promising early activity as a first-line treatment in pts with HR+/HER2– metastatic BC. CDK4 selectivity is hypothesized to limit hematologic and gastrointestinal toxicities that may be dose-limiting; therefore, ATI may improve efficacy and tolerability. Ki-67 is a biomarker used to assess the antiproliferative activity of therapies. Complete cell cycle arrest (CCCA, defined as Ki-67-positive tumor cells $\leq 2.7\%$) in the neoadjuvant setting is correlated with less BC tumor recurrence. This phase 2 randomized global study evaluated the effects of ATI + letrozole (LET) and LET alone on Ki-67 expression in HR+/HER2– BC tumors after 14 days of treatment in the neoadjuvant setting (FourLight-2; NCT06465368). **Methods:** Postmenopausal women with HR+/HER2– BC and Ki-67 score of $\geq 10\%$ per local assessment, primary tumor ≥ 1.5 cm, no prior systemic therapy for BC, and ECOG PS ≤ 1 were enrolled. Eligible pts were randomly assigned to ATI (300 mg, orally BID) + LET (2.5 mg, orally QD) or LET alone (2.5 mg, orally QD), for 14 days. Baseline breast lesion biopsy and on-treatment biopsy on day 14 were obtained. The primary endpoint was centrally-assessed CCCA rate at day 14; secondary endpoints included Ki-67 expression change, safety, ctDNA assessments, and PK. **Results:** 121 pts were randomized to ATI + LET (n = 59) or LET alone (n = 62) arms; median age was 66 y and 63 y; 90% and 92% had Stage I/II disease, respectively. In Ki-67 evaluable pts (n = 51 and n = 56), 77% and 70% had Ki-67 $\geq 20\%$ at baseline (centrally assessed) and 71% and 80% had grade 1/2 tumor, respectively. At day 14, the proportion of pts who achieved CCCA was 88.2% (95% CI, 76.6–94.5) for ATI + LET and 17.9% (95% CI, 10.0–29.8) for LET alone, with median relative change of Ki-67 from baseline of -97.3% (range -99.8% , 34.0%) and -72.4% (range -98.3% , 139.9%) in each arm, respectively. CCCA was achieved at a higher rate with ATI + LET than LET alone across baseline subgroups (Table). The most common TEAEs with ATI + LET and LET alone, respectively, were diarrhea (19% and 2%), fatigue (15% and 10%), and nausea (14% and 5%) (all grade 1/2); no grade 3/4 treatment-related TEAEs or treatment discontinuations due to TEAEs were reported. **Conclusions:** ATI + LET demonstrated substantially greater antiproliferative effects than LET alone, with a tolerable safety profile in pts with HR+/HER2– BC, suggesting that ATI + LET may have value in early BC. Clinical trial information: NCT06465368. Research Sponsor: Pfizer Inc.

Subgroup Analysis with CCCA, n (%)	ATI + LET n = 51	LET alone n = 56
Tumor grade		
1/2	32 (89)	9 (20)
3/X	13 (87)	1 (9)
Primary tumor stage		
T1c	12 (80)	2 (11)
T2	28 (93)	7 (22)
T3/T4	5 (83)	1 (20)
Baseline Ki-67 (central assessment)		
<20%	9 (90)	4 (27)
$\geq 20\%$	35 (90)	6 (15)

Overall survival (OS) in premenopausal ER+/PR+, HER2– breast cancer (BC) treated with endocrine therapy (ET) ± chemotherapy (CT): A National Cancer Database (NCDB) analysis.

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Background: The comparative benefit of ET alone vs ET+CT in premenopausal women with stage I–III ER+/PR+, HER2– BC remains uncertain. Although Oncotype DX recurrence score (RS) guides CT use, management of premenopausal patients (pts) with low/intermediate RS remains challenging. The ongoing NRG-BR009 trial aims to clarify the relative benefit of CT but has faced accrual issues. To address this question, we evaluated OS difference by treatment among pts with No (n=0)/intermediate RS and N1 (n=1–3)/low–intermediate RS disease. **Methods:** NCDB data were analyzed for women <50 yrs with ER+/PR+, HER2–, stage I–III BC (2005–2022). Variables included tumor size, grade, nodal status (No/N1), stage, lymphovascular invasion, Ki67, Charlson–Deyo comorbidity score (CCS), RS category (low=0–17, intermediate=18–30) and treatments (ET, CT, surgery, radiation [RT]). OS was compared between ET+CT vs ET only groups using the log-rank test. Multivariable Cox models (MVA) were conducted to identify predictors of OS. **Results:** Median age was 45 yrs (18–49) among 15591 enrolled pts. In No/intermediate RS group, 3710 (42.5%) received ET+CT and 5022 (57.5%) received ET alone; 5-yr OS was 98.9% with ET+CT vs 98.7% with ET (p=0.40). In N1/low RS group, 1151 (26.2%) received ET+CT and 3242 (73.8%) received only ET; 5-yr OS was 98.5% with ET+CT vs 98.6% with ET (p=0.85). In N1/intermediate RS, 1718 (69.7%) received ET+CT and 748 (30.3%) received only ET; 5-yr OS was 96.2% with ET+CT vs 95.0% with ET (p=0.28). On univariable analysis, ET+CT did not improve OS in the No/intermediate RS, N1/low RS, or N1/intermediate RS groups (all p>0.05). MVA further confirmed ET+CT had no OS benefit compared to ET alone in all groups (all p>0.05, Table 1). Among No/intermediate RS pts, grade 3 disease was associated with worse OS (p<0.05). In N1/low RS subjects, CCS=2 predicted worse OS (p<0.05). In N1/intermediate RS pts, stage III disease and lack of RT predicted worse OS (p<0.05). **Conclusions:** In premenopausal women with early-stage ER+/PR+, HER2– BC, ET+CT yielded similar OS to ET alone in low/intermediate RS pts. Limitations include inability to assess ovarian function suppression and invasive disease-free survival. Larger studies are needed to validate the above findings and to investigate whether CT could be safely omitted in low–intermediate risk pts. Research Sponsor: None.

MVA for OS by RS and nodal status (HR, 95%CI).

	No, intermediate RS	N1, low RS	N1, intermediate RS
CCS (2 vs 0)	3.87 (0.52-29.00)	23.62 (4.63-120.46)	4.01 (0.43-37.77)
Grade (3 vs 1)	7.39 (1.45-37.62)	2.26 (0.26-19.57)	1.64 (0.26-10.35)
Stage (III vs I)	1.02 (0.21-4.99)	n/a	11.77 (1.90-73.04)
ET+CT vs ET	0.73 (0.33-1.62)	0.80 (0.25-2.51)	0.44 (0.14-1.35)
RT (yes vs no)	1.02 (0.48-2.19)	2.89 (0.65-12.82)	0.22 (0.08-0.66)

Socioeconomic and racial disparities in receipt of treatment among early-stage ER+/PR+ HER2- breast cancer: Insights from invasive breast cancer OncoDX recurrence score database.

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Background: Oncotype DX Recurrence Score (RS) predicts recurrence risk and potential benefit from chemotherapy (CT) in early-stage ER+ and HER2- breast cancer (BC). However, real-world CT decision patterns remain poorly understood. This work evaluated how socioeconomic, racial and clinical factors influence CT decisions beyond RS-guided recommendations.

Methods: We analyzed patients with early-stage ER+/PR+, HER2- BC in SEER OncoDX RS Database (2004-2019). Variables included age, rurality, poverty status, socioeconomic status (SES), RS, histology, tumor grade, nodal status, PR status, and CT receipt. Treatment disparities among patients with similar RS were evaluated using chi-square tests. Multivariable logistic regression model (MVA) identified independent predictors of CT utilization among patients with similar RS. **Results:** A total of 208,674 patients were included (median age 60). Median follow up was 4.9 years. Among postmenopausal (post-M, ≥ 50 yrs) women with RS ≥ 26 (CT indicated), lowest SES (60.6% vs 66.5% [highest], $P < 0.001$) and Hispanic ethnicity (63.2% vs 63.3% [White], $P = 0.016$) were associated with lower rate of CT. When CT was not indicated in post-M women (RS < 26), Black patients were more likely to receive treatment (9.0% vs 7.9% [White], $P < 0.001$). Among premenopausal (pre-M, < 50 yrs) women with No disease and RS > 15 , highest SES (41.0% vs 44.2% [lowest], $P = 0.032$) and White race (41.2% vs 46.8% [Black], $P < 0.001$) received less CT. Among pre-M women with N1-3 disease, rural residence (42.9% vs 47.1% [urban], $P = 0.004$) and White race (44.6% vs 50.1% [Black], $P = 0.042$) were associated with less CT. MVA showed that invasive ductal carcinoma, grade III tumor, PR-negative status and Black race increased the likelihood of CT irrespective of RS (Table 1). **Conclusions:** CT decisions were frequently influenced by socioeconomic, racial and clinicopathological factors beyond genomic guided recommendations. Our data highlights a gap between clinical guidelines and real-world practice. Future research should focus on understanding the underlying reasons for deviations in treatment selection and examining changes in practice patterns in the post-RxPONDER era. Research Sponsor: None.

MVA for CT decision by RS (OR, 95%CI).

	Pre-M, N0, ≤ 15	Pre-M, N0, > 15	Pre-M, N1-3	Post-M, < 26	Post-M, ≥ 26
SES (highest vs lowest)	-	0.88 (0.78-0.99)	-	-	1.34 (1.22-1.49)
Race (B vs W)	-	-	-	1.10 (1.01-1.19)	1.14 (1.03-1.26)
Histology (IDC vs ILC)	-	1.22 (1.11-1.33)	1.16 (1.01-1.32)	0.84 (0.80-0.88)	1.19 (1.09-1.28)
Grade (III vs I)	4.89 (3.72-6.42)	7.13 (6.42-7.93)	5.91 (4.96-7.04)	4.07 (3.80-4.36)	2.44 (2.21-2.71)
PR (pos vs neg)	-	0.49 (0.43-0.56)	0.44 (0.32-0.60)	0.53 (0.50-0.57)	0.82 (0.77-0.87)

Not statistically significant.

Associations between self-efficacy and symptom burden in young women with breast cancer initiating endocrine therapy (ET) on SWOG S2010.

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Background: Self-efficacy (SE) is the belief in one's ability to succeed in specific situations or accomplish a task, influencing motivation, behavior, and resilience. Both symptom (sx) burden at the time of ET initiation and lower SE for sx management are associated with ET non-adherence. The SWOG S2010 clinical trial enrolled premenopausal women starting adjuvant ovarian function suppression (OFS) plus ET for breast cancer. We examined associations between sx burden and self-efficacy at the time of ET initiation. **Methods:** All participants completed the FACT GP5 question evaluating bother from side effects of treatment, individual symptom PROMIS measures, and the PROMIS SE for managing sx and for managing medication (meds)/treatment (tx). GP5 is measured on a 5 point scale ranging from "Not at all" to "Very much." T scores were calculated for PROMIS measures (Table), with a mean score of 50 and higher scores reflecting more of the item being assessed. We evaluated associations between baseline sx and SE using logistic regression. **Results:** Of 528 participants with data, mean age was 44.1 years (SD 5.8), 23.5% were Hispanic, 5.5% Black, 6.4% Asian, and 77.7% White. The majority (69.9%) had received chemotherapy. On the FACT GP5 (n=503), only 31.6% reported no treatment side effect burden. Patients reporting a higher side effect burden from tx immediately prior to ET initiation had lower SE for sx (odds ratio (OR) 0.93 (95% CI 0.91-0.96, $p<.0001$)) and lower SE for meds & tx (OR 0.97 (95% CI 0.95-1.00, $p=.04$). Increased baseline sx and worse physical function were also statistically significantly associated with worse SE for managing both sx and meds & tx (Table). For example, patients with greater than average fatigue had lower SE for sx (OR 0.32 (95% CI 0.23-0.46, $p<.001$)). **Conclusions:** Symptom burden at the time of ET initiation is high for premenopausal women starting OFS plus ET, which may partially explain high rates of early ET discontinuation in this patient population. Lower SE was strongly associated with worse individual symptoms. Interventions to improve SE for sx and med management starting at or before ET initiation may improve ET adherence, which could thereby improve disease outcomes and quality of life for young women with breast cancer. Funding: NIH/NCI/NCORP grant UG1CA189974. Clinical trial information: NCT05568472. Research Sponsor: National Cancer Institute; UG1CA189974; National Cancer Institute; R01CA266012.

Associations between self-efficacy and symptoms.

PROMIS domain	PROMIS		Self		Efficacy Sx OR (CI)	P value (Chi square)	PROMIS		Self		Efficacy Meds OR (CI)	& Tx P value (Chi square)
	<50	≥50	<50	≥50			<50	≥50	<50	≥50		
Fatigue	<50	97	144	0.32 (0.23,0.46)	<.001	82	158	0.52 (0.36,0.74)	<.001	143	143	<.001
	≥50	194	93				143					
Anxiety/Fear	<50	56	105	0.30 (0.20,0.44)	<.001	42	118	0.36 (0.24,0.54)	<.001	183	183	<.001
	≥50	235	132				183					
Sleep disturbance	<50	85	120	0.40 (0.28,0.58)	<.001	69	135	0.54 (0.38,0.78)	.001	154	166	<.001
	≥50	206	117				166					
Physical function	<50	195	82	3.84 (2.67,5.51)	<.001	146	131	2.40 (1.68,3.42)	<.001	79	170	<.001
	≥50	96	155				170					

CI: Confidence intervals; OR: Odds ratio.

Tumor-associated macrophage (TAM) score as an independent predictor of recurrence in residual disease after neoadjuvant chemotherapy and for identification of high-risk patients for adjuvant escalation.

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Background: Tumor-associated macrophages (TAMs) drive immune evasion and chemotherapy resistance in breast cancer through tumor microenvironment reprogramming. We developed a composite TAM score integrating transcriptional programs with spatial IHC polarization markers to stratify recurrence risk and enrich macrophage-modulating trials, hypothesizing it would improve prognostic accuracy in treatment-naïve disease and predict neoadjuvant chemotherapy (NACT) response. **Methods:** TAM score was derived from scRNA-seq atlases (n=4), filtering survival-associated genes in METABRIC/TCGA (n=2,509), and weighting IHC markers CD163/CD206 normalized to CD68/CSF1R via Cox coefficients. Validation: treatment-naïve invasive carcinomas (n=83; follow-up 57 months; 24 events). Primary endpoint: recurrence-free survival (RFS); multivariable Cox adjusted for age, tumor size, nodal status, grade, subtype, treatment. Predictive utility assessed in matched primary/post-NACT residual tumors (n=45) correlating TAM dynamics with RCB. **Results:** High TAM score ($\geq$ median) independently predicted worse RFS (HR 3.8, 95% CI 1.6–9.1, $p<0.05$) and outperformed CD163/CD68 alone (HR 2.1, $p<0.05$); 5-year RFS was 68% vs 91% (TAM-high vs TAM-low). Prognostic value persisted in node-negative (HR 4.2, $p=0.02$) and luminal B (HR 3.5, $p=0.01$) subsets. In the NACT cohort, baseline TAM score inversely correlated with pCR (12% vs 38%, $p=0.04$). Among residual disease (RCB-II/III, n=34), persistent TAM-high post-NACT identified 3-year RFS 52% vs 85% in TAM-low/normalized cases (HR 4.1, $p=0.01$), independent of RCB; CD163+/CD206+ expansion occurred in 76% of RCB-III vs 29% of RCB-I ($p=0.008$). **Conclusions:** This TAM score predicts recurrence from pre-treatment tissue and identifies macrophage-driven resistance persisting post-NACT, nominating TAM-high residual disease for macrophage-modulating trials. Translational evidence supports this: CSF1R inhibition reduced immunosuppressive TAMs, increased M1-like programs, decreased PD-L1/PD-L2, and enhanced anti-PD-1 efficacy preclinically with ex vivo confirmation. Early-phase data (rebastinib plus chemotherapy in HER2-negative metastatic disease) demonstrate feasibility, supporting prioritization of TAM-high patients with residual disease for trials combining TAM modulation with checkpoint therapy. Research Sponsor: None.

TAM score performance in treatment-naïve and NACT cohorts.

Endpoint	TAM-High	TAM-Low	HR scores (95% CI)	p-value
Treatment Naïve cohort				
5 year RFS (Overall)	68%	91%	3.8 (1.6-9.1)	<0.05
RFS (node-negative)			4.0	0.02
RFS (luminal B)-			3.5	0.01
CD163/CD68 alone			2.1	<0.05
NACT Cohort (n=45)				
Baseline pCR rate	12%	38%		0.04
3-year RFS(RCB-II/III n=34)	52%	85%	4.1	0.01
CD163+/CD206+ expansion	76% (RCB-III)	29%(RCB-I)-		0.008

Chemotherapy, endocrine therapy, and cognitive impairment in long-term breast cancer survivors.

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Background: Chemotherapy and endocrine therapy have known neurobiological effects, yet evidence on their associations with long-term cognitive impairment remains limited. This study examined the relationship between prior chemotherapy, endocrine therapy, and cognitive impairment among long-term breast cancer survivors. **Methods:** Between July and September 2025, 1,338 participants from the Chicago Multiethnic Epidemiologic Breast Cancer Cohort were surveyed and completed the Functional Assessment of Cancer Therapy–Cognition (FACT–Cog), a validated self-report instrument assessing 4 specific domains: perceived cognitive impairment (PCI; scores 0–72), cognitive-related quality of life (QoL; scores 0–16), perceived cognitive abilities (PCA; scores 0–27), and comments-from-others (scores 0–16). Lower scores reflect worse cognitive function. Cognitive impairment was defined as a PCI score <54. Multivariable logistic regression was used to evaluate associations between chemotherapy and endocrine therapy with cognitive impairment. Multiple linear regression was used to assess associations with continuous FACT–Cog domain scores. All models were adjusted for age, race/ethnicity, radiotherapy, surgery history, and educational attainment. **Results:** The mean age at survey of the 1,338 study participants was 64.3 years (SD 11.7), and the median time from diagnosis to survey was 9.4 years (IQR 6.1–14.1). Overall, 299 (22.3%) met criteria for cognitive impairment. Additionally, 594 (44.4%) and 851 (63.6%) of the participants had prior chemotherapy and endocrine therapy, respectively. In adjusted analyses, chemotherapy (adjusted odds ratio [aOR] 1.39; 95% CI 1.03 to 1.89; $p=0.033$) and endocrine therapy (aOR 1.86; 95% CI 1.35 to 2.57; $p<0.001$) were significantly associated with cognitive impairment. Chemotherapy was associated with lower PCI (β -2.11; 95% CI -3.61 to -0.61; $p=0.006$), and lower QoL (β -0.60; 95% CI -1.01 to -0.19; $p=0.04$). Endocrine therapy was associated with lower scores in PCI (β -2.52; 95% CI -4.02 to -1.02; $p=0.001$), QoL (β -0.55; 95% CI -0.96 to -0.14; $p=0.009$), PCA (β -1.54; 95% CI -2.29 to -0.79; $p<0.001$), and comments-from-others (β -0.28; 95% CI -0.49 to -0.07; $p=0.008$). In joint models, those who received both chemotherapy and endocrine therapy (aOR 2.46; 95% CI 1.46 to 4.18; $p=0.001$) and those who received endocrine therapy alone (aOR 1.71; 95% CI 1.04 to 2.81; $p=0.035$) had significantly higher odds of cognitive impairment than participants who received neither therapy. **Conclusions:** In this multiethnic cohort of long-term breast cancer survivors, prior chemotherapy and endocrine therapy were independently associated with worse perceived cognitive functioning across multiple domains. These findings underscore the need for future studies to identify neuroprotective strategies and interventions to mitigate treatment-related cognitive sequelae. Research Sponsor: Breast Cancer Research Foundation; BCRF-20-071; National Cancer Institute; P20CA233307; Susan G. Komen; TREND21675016; National Institute on Aging; T32AG000243.

Adjuvant endocrine therapy omission in ER-positive breast cancer treated with neoadjuvant chemotherapy.

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Background: Adjuvant endocrine therapy (ET) decreases breast cancer (BC) recurrence and improves overall survival (OS) for patients (pts) with estrogen receptor positive (ER+) BC. Omission of adjuvant ET and nonadherence are major issues contributing to worse clinical outcomes. Recent data suggest that the number of pts who omit adjuvant ET may be increasing in Europe [1]. These data have yet to be evaluated in the U.S. We previously reported data from the National Cancer Database (NCDB) that ET omission was more likely in pts with ER+/HER2+ disease who achieved a pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) [2]. Herein we report an updated analysis with a larger cohort designed to examine trends in ET omission over time and the impact on OS in a group of pts at high risk of recurrence.

Methods: The NCDB was queried from 2010–2022 for pts with stage I–III ER+BC treated with NAC and surgery. pCR was defined as ypT0, ypN0. Use of adjuvant ET and the impact of adjuvant ET omission on OS in pts with and without pCR were assessed separately based on HER2 status. Adjuvant ET initiation by 1 year was summarized using the cumulative incidence estimate to account for the competing risk of death. OS was analyzed with ET as a time-dependent covariate using multivariable Cox proportional hazards regression. **Results:** We identified 130,438 pts with ER+BC (78,778 ER+/HER2–, 51,660 ER+/HER2+) who received NAC. Median follow-up was 5 years. Overall, pCR was achieved in 10.0% of ER+/HER2– and 35.9% of ER+/HER2+. On multivariable analysis, ET omission was significantly associated with worse OS in pts with residual disease (RD) [ER+/HER2– (HR 1.80 $p<0.001$) ER+/HER2+ (HR 1.66 $p<0.001$) and in those with a pCR [ER+/HER2– (HR 1.38 $p=0.002$) ER+/HER2+ (HR 1.42 $p<0.001$)]. Between 2010–2017, adjuvant ET omission was stable, with approximately 10.0% of pts not having initiated ET by 1 year after surgery. The proportion of pts omitting ET overall increased thereafter to 12.9% in 2018, rising to 24.4% in 2022. A sharp increase in ET omission was observed 2021–2022 in ER+/HER2– BC who achieved pCR, with 42.4% omitting ET compared to 25.1% for 2018–2020 and 18.8% for 2010–2017 ($p<0.001$). Adjuvant ET omission showed more modest but significant increases for other subgroups ($p<0.001$): ER+/HER2– with RD (8.5% 2010–2017, 12.3% 2018–2020, 18.7% 2021–2022), ER+/HER2+ with pCR (15.1% 2010–2017, 14.0% 2018–2020, 24.4% 2021–2022), and ER+/HER2+ with RD (9.5% 2010–2017, 12.5% 2018–2020, 22.2% 2021–2022). **Conclusions:** In ER+BC treated with NAC, omission of ET is increasing over time and associated with a higher risk of death, regardless of HER2, RD, or pCR status. These findings have substantial public health implications as they may result in a reversal of the 4-decade improvements in breast cancer mortality. Additional intervention is critical to improve adherence to guidelines. [1] Verreck et al. Breast 2025 [2] Choong et al. SABCS 2022. Research Sponsor: None.

Impact of *BRCA* pathogenic variants and novel targeted agents on ovarian reserve measured by anti-Müllerian hormone levels in young women with early breast cancer: A biomarker analysis of the PREFER study.

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Background: The impact of germline *BRCA* (*gBRCA*) pathogenic variants (PVs) and of novel targeted agents (anti-HER2 therapy, CDK4/6 inhibitors, or immunotherapy) on ovarian reserve in young women treated with chemotherapy (CT) for early breast cancer (BC) remains limited. This biomarker analysis of the PREFER study prospectively evaluated ovarian reserve using anti-Müllerian hormone (AMH) according to main patient and treatment characteristics. **Methods:** We included premenopausal women enrolled in the prospective PREFER study (NCT02895165) and candidates to (neo)adjuvant CT at the coordinating centre, the IRCCS San Martino Policlinic Hospital, Genoa, Italy. Serial serum AMH measurements were performed at baseline (prior to any CT initiation), during, and after systemic treatment. Longitudinal changes in centrally measured AMH were analysed using mixed-effects models on log-transformed values. Analyses explored the impact of patient (including age and *gBRCA* status) and treatment (CT alone or with anti-HER2 therapy, CDK4/6 inhibitors, or immunotherapy) characteristics on AMH levels over time. **Results:** Between 2012 and 2025, 309 premenopausal patients were enrolled at the coordinating centre, of whom 194 were included in the present analysis. Median age at diagnosis was 37 (IQR 33–40) years, with 146 patients (75.3%) aged ≤ 40 years and 48 (24.7%) 41–45 years. Overall, 85 patients (43.8%) had hormone receptor-positive/HER2-negative, 62 (32.0%) HER2-positive, and 47 (24.2%) triple-negative BC. In the entire cohort, AMH levels showed a marked decline during CT, followed by partial recovery during follow-up ($p < 0.001$), irrespective of patient and treatment characteristics. Younger women showed higher baseline values (2.31 vs 1.11 $\mu\text{g/L}$ for ≤ 40 years and 41–45 years) and greater post-treatment recovery ($p < 0.001$). Among patients with known *gBRCA* status ($n=147$), patients harbouring *gBRCA* PVs ($n=29$, 19.7%) showed lower baseline levels (1.60 vs 2.18 $\mu\text{g/L}$ for *gBRCA* carriers vs non-carriers) and a lower post-treatment recovery compared to non-carriers ($n=118$, 80.3%) ($p=0.01$). Regarding treatment exposure, 106 patients (54.6%) received CT alone, 62 (32.0%) CT plus anti-HER2 agents, 10 (5.2%) CT plus immunotherapy, and 16 (8.2%) CT followed by CDK4/6 inhibitors. No significant differences over time were observed according to treatment exposure ($p=0.41$); however, numerically lower mean AMH values after end of CT were observed among patients treated with CDK4/6 inhibitors and immunotherapy. **Conclusions:** In this PREFER biomarker analysis, older age and *gBRCA* PVs were associated with reduced ovarian recovery after treatment. Limited sample size precludes definitive conclusions on the gonadal impact of immunotherapy or CDK4/6 inhibitors; further analyses are urgently needed in this field. Research Sponsor: Associazione Italiana Ricerca sul Cancro (AIRC).

Impact of the Breast Cancer Index on extended endocrine therapy recommendations in patients from the BCI Registry study.

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Background: The Breast Cancer Index (BCI) test is an established genomic assay that provides individualized risks of overall and late distant recurrence and predicts the benefit from extended endocrine therapy (EET) in patients with early-stage, HR+ breast cancer. Previous findings from the large, prospective BCI Registry have shown that physicians changed their EET recommendation in over 40% of patients following BCI testing. This analysis investigates how physicians integrate prognostic and predictive BCI results in real care settings to decide whether or not to recommend extension of endocrine therapy. **Methods:** The BCI Registry study (NCT04875351) is evaluating the long-term clinical outcome, decision-impact and medication adherence in about 3000 patients. Pre- and post-BCI physician treatment recommendations were compared using McNemar's test. Clinicopathologic features of cases were correlated with BCI (H/I) predictive results and post BCI-EET recommendations using Fisher's exact test. Differences in mean BCI prognostic risk were assessed using analysis of variance (ANOVA). **Results:** Pre- and post-BCI testing physician questionnaires were completed for 2850 patients. The percentage of patients recommended for EET decreased from 54.6% before BCI testing to 41.2% after BCI testing, while those not recommended for EET increased from 44.9% to 58.0% ($p < .0001$). Among patients not recommended for EET pre-BCI, physicians cited low risk of recurrence (47.4%), osteoporosis risk (16.7%), side effects (8.6%), or multiple reasons (24.4%). Among BCI (H/I)-High patients ($N=1063$), recommendations for EET increased from 60.4% pre-BCI to 90.6% post-BCI, while EET non-recommendations decreased from 39.1% to 8.0%. Conversely, in BCI (H/I)-Low patients ($N=1787$), EET recommendations decreased from 51.1% to 11.8% and EET non-recommendations increased from 48.3% to 87.8%. Post-BCI, BCI (H/I)-High patients who were not recommended EET (8.0%) had more favorable clinicopathological features, including more T1 tumors (83.5% vs. 68.1%, $p = .009$), more G1 tumors (44.7% vs. 14.4%, $p < .0001$) and lower mean BCI prognostic risk compared to those for whom EET was recommended (4.4% vs 9.2%, $p < .0001$). Conversely, BCI (H/I)-Low patients who were recommended EET (11.8%) had a larger proportion of T2/T3 tumors (40.7% vs. 21.7%, $p < .0001$), more G2/G3 tumors (79.2% vs. 62.8%, $p < .0001$), more N+(1-3) cases (43.6% vs. 15.7%, $p < .0001$) and higher mean BCI prognostic risk (8.1% vs 4.7%, $p < .0001$). **Conclusions:** BCI results meaningfully inform physician recommendations for EET. Post-BCI, physician EET recommendations increased to 91% in BCI (H/I)-High patients and decreased to 12% in BCI (H/I)-Low patients, highlighting the important treatment guidance provided by BCI. Integration of both predictive and prognostic BCI results help further personalize patient care. Research Sponsor: None.

Platinum-based chemotherapy in early-stage, high-risk, triple-negative breast cancer: A systematic review and meta-analysis of randomized trials.

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Background: The clinical benefit of adding platinum agents to adjuvant chemotherapy for early-stage triple-negative breast cancer (TNBC) remains uncertain. A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to evaluate the impact of carboplatin-based adjuvant chemotherapy on survival outcomes in patients with early-stage, high-risk TNBC. **Methods:** RCTs comparing carboplatin plus standard adjuvant chemotherapy versus chemotherapy alone in early-stage, high-risk TNBC were identified through systematic searches of PubMed, Embase, Cochrane CENTRAL, and major oncology meeting proceedings. The primary endpoint was disease-free survival (DFS). Secondary endpoints included recurrence-free survival (RFS), distant disease-free survival (DDFS), and overall survival (OS). Hazard ratios (HRs) were pooled using random-effects models. Absolute survival differences at fixed timepoints were estimated using reconstructed individual patient-level data derived from published Kaplan-Meier curves. **Results:** Five randomized trials enrolling 3,153 patients were included; 1,576 (49.9%) received carboplatin-based chemotherapy. Median age ranged from 47 to 56 years, and most patients had grade 3 tumors and node-positive disease. Carboplatin-based chemotherapy significantly improved DFS compared with chemotherapy alone (HR 0.66, 95% CI 0.62–0.71; $p < 0.001$). Consistent proportional benefits were observed for RFS (HR 0.66, 95% CI 0.62–0.71; $p < 0.001$), DDFS (HR 0.66, 95% CI 0.62–0.71; $p < 0.001$) and OS (HR 0.66, 95% CI 0.62–0.71; $p < 0.001$), with no substantial between-trial heterogeneity ($I^2 < 25\%$ for all endpoints). Reconstructed survival analyses demonstrated increasing absolute benefit over time. At 3 years, carboplatin-based chemotherapy was associated with absolute improvements of approximately 4–6% in DFS and 3–5% in OS. At 5 years, absolute differences favored carboplatin by approximately 7–9% for DFS, 6–9% for RFS, 6–8% for DDFS, and 6–8% for OS (log-rank $p < 0.001$ for all comparisons). DFS benefit was observed across clinically relevant subgroups, including node-negative (HR 0.69, 95% CI 0.53–0.90) and node-positive disease (HR 0.57, 95% CI 0.37–0.86), as well as among patients with and without germline *BRCA1/2* mutations. Greater proportional benefit was observed in patients with grade III tumors and pT2–T3 disease. **Conclusions:** Across RCTs, the addition of carboplatin to standard adjuvant chemotherapy was associated with significant and durable improvements in DFS and OS in patients with early-stage, high-risk TNBC. Absolute survival gains increased with longer follow-up, supporting the clinical relevance of platinum-based adjuvant strategies in selected high-risk populations. Research Sponsor: None.

Real-world treatment patterns and adherence to adjuvant abemaciclib among patients with early hormone receptor–positive (HR+) breast cancer (BC).

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Background: Adjuvant abemaciclib (2 years) is approved in combination with endocrine therapy (ET) for node-positive high-risk early HR+ BC. Although it improves invasive disease-free and overall survival, its long duration and toxicities increase treatment complexity. As adjuvant regimens become more intensive, long-term adherence is critical for real-world effectiveness. However, data outside clinical trials are limited. We examined treatment patterns and factors associated with adherence to abemaciclib in a younger population of patients with early BC.

Methods: We conducted a retrospective cohort study using the Merative MarketScan Commercial Claims and Encounters database. Patients aged 18–64 years with early BC who received abemaciclib between 2017 and 2024 were identified. Index date was the date of the first abemaciclib claim. We included patients who underwent breast surgery within one year before the index date and had continuous enrollment for 6 months before and one year after index date. We excluded patients with metastatic disease prior to the index date. Medication adherence was assessed using the proportion of days covered (PDC), with adherence defined as PDC $\geq 80\%$. Multivariable logistic regression was used to examine factors associated with abemaciclib adherence at one and two years. **Results:** Among 640 patients (median age 51 years) treated with adjuvant abemaciclib (median follow up 1.5 years), 55% were adherent to therapy at one year. Adherence declined from 100% in month 1, to 66%, 57%, 55%, and 50% in months 2, 6, 12, and 24 ($p < 0.001$). Overall, 84.5% of patients initiated abemaciclib at 150 mg, and 47.2% had no dose adjustments during treatment. On multivariable analysis of one-year adherence, patients prescribed lower abemaciclib doses (50 or 100mg) were less likely to be adherent compared to those prescribed 150 mg (aOR=0.52; 95%CI 0.31–0.90). Adherence to ET was also associated with higher abemaciclib adherence (aOR=3.63; 95%CI 2.55–5.18). Polypharmacy was associated with reduced abemaciclib adherence among patients taking two (aOR=0.56; 95%CI 0.37–0.85) or ≥ 3 drug classes (aOR=0.51; 95%CI 0.34–0.78) compared with 0–1 drug class. Patients with high-deductible health plans (HDHP) had higher odds of adherence compared to those with PPO insurance (aOR=2.10; 95%CI 1.23–3.59). At two years ($n=213$), younger age and adherence to ET were significantly associated with greater abemaciclib adherence. **Conclusions:** Abemaciclib adherence was low, 55% in year 1, and 50% in year 2. Although lower abemaciclib doses and polypharmacy were associated with lower odds of adherence, ET adherence was associated with higher odds. Adherence in HDHP patients may reflect demographics (White, young, higher income). These findings highlight the need for close patient monitoring and strategies to support long-term adherence to adjuvant treatment. Research Sponsor: Susan G. Komen Foundation; The Breast Cancer Research Foundation; National Cancer Institute.

Chemotherapy (CT) use by Oncotype DX (O-Dx) recurrence score (RS) in hormone receptor–positive, HER2-negative (HR+/HER2-) invasive lobular carcinoma (ILC): A contemporary National Cancer Database (NCDB) analysis.

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Background: ILC has a distinct biology and is considered less chemosensitive than invasive ductal carcinoma (IDC). O-Dx RS can guide adjuvant CT decisions for patients with HR+/HER2- breast cancer (BC); however, pivotal trials largely included patients with IDC. Patients with high RS have been shown to benefit from CT. Whether this genomic risk threshold is applied to patients with ILC in real-world practice is not well understood. We evaluated contemporary CT use by O-Dx RS and its association with overall survival (OS) in patients with ILC. **Methods:** Patients ≥ 18 years with HR+/HER2- ILC diagnosed from 2018–2022 who underwent surgery, had pT1–T3, pN0–N1 disease, and known O-Dx RS were identified in the NCDB. Baseline characteristics were compared by RS groups: 0–10 (low), 11–25 (intermediate), and >25 (high). Multivariable logistic regression models identified factors associated with CT use in the overall cohort and stratified by RS. We evaluated the association between CT use and OS within each RS group, adjusting for covariates using propensity score matching (by year of diagnosis, age, pT, pN). **Results:** A total of 30,393 patients with early-stage HR+/HER2- ILC and O-Dx score were identified. Among them, 21% had low, 72% intermediate, and 7% high RS. Overall, 9.2% received CT, including 2.4% of those with low RS, 5.5% of intermediate RS, and 66% of high RS. CT use did not change over time ($p=0.47$). On multivariable analysis in all patients, higher RS was the key determinant of CT use (RS 11–25 vs 0–10: aOR=2.98, 95%CI 2.49–3.58; RS >25 vs 0–10: aOR=333.4, 95%CI 266.8–416.7), while older age was associated with lower CT use (aOR=0.91, 95%CI 0.91–0.92). In multivariable models stratified by RS, clinicopathologic features, including younger age, larger tumor size, higher nodal stage, and higher grade, were associated with CT use in low and intermediate RS groups (i.e., pN1 aOR=18.64 for RS 0–10; aOR=7.37 for RS 11–25; both $p<0.001$), whereas in high RS group, age had similar effect; however, tumor size and nodal status had significant but attenuated effects. In propensity-matched cohorts within RS groups, CT use was not associated with different OS in low RS (5-year OS 98% vs 100%, $p=0.29$) or intermediate RS (5-year OS 97% vs 97%, $p=0.68$) groups; however, in high RS group, CT use was associated with improved OS (5-year OS 96% vs 90%; $p=0.01$). **Conclusions:** In clinical practice, CT use in patients with ILC is guided by O-Dx RS but influenced by age and clinicopathologic risk. CT use conferred no OS benefit in patients with low or intermediate RS but was associated with OS benefit in high RS. Despite this, one-third of patients with ILC with high RS did not receive CT. These findings support RS-guided adjuvant CT decision-making in ILC and suggest that increasing CT use in patients with high RS may improve outcomes. Research Sponsor: Susan G. Komen Foundation; SAC150061, SAC220221; The Breast Cancer Research Foundation; BCRF-22-190, BCRF-23-190; The National Cancer Institute at the National Institutes of Health; P30 CA016672.

Pyrotinib plus nab-paclitaxel as adjuvant therapy for patients with N0/N1mi, HER2-positive early-stage breast cancer: 3-year iDFS results of the phase II PHAEDRA trial.

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Background: While dual anti-HER2 therapy is standard in the adjuvant setting for HER2-positive early breast cancer, treatment de-escalation is an attractive strategy for patients with low-risk disease. Previous studies (e.g., APT, ATEMPT) of adjuvant trastuzumab plus chemotherapy or T-DM1 monotherapy in this population reported 3-year invasive disease-free survival (iDFS) rates of 93.4%–98.7%. Pyrotinib, an irreversible pan-HER2 tyrosine kinase inhibitor, is effective in HER2-positive breast cancer; however, data supporting its use in the adjuvant setting for low-risk disease are limited. This study evaluated the efficacy and safety of adjuvant pyrotinib plus nab-paclitaxel in this population. **Methods:** This multicenter, single-arm, phase II trial enrolled women aged 18–75 with primary tumor size ≤ 3 cm and node-negative (N0) or micrometastases (N1mi), histologically confirmed HER2-positive early breast cancer. Patients received nab-paclitaxel (260 mg/m² IV, q3w) plus pyrotinib (400 mg PO, qd) for 12 weeks (4 cycles), followed by pyrotinib monotherapy (400 mg, qd) for one year. The primary endpoint was iDFS. Secondary endpoint was adverse events (AEs) graded by CTCAE v5.0. **Results:** From January 8, 2021, to September 21, 2023, 263 patients were enrolled and received treatment. Median age was 51 years; 60.8% (160/263) were hormone receptor-positive, and 97.7% (257/263) were node-negative. At the data cutoff (December 30, 2025), with a median follow-up of 36.2 months, 9 iDFS events were observed. The estimated 3-year iDFS rate was 96.8% (95% CI 93.4–98.5). One death occurred and overall survival data were immature. The most common grade ≥ 3 treatment-related AEs were diarrhea (50.6%), neutropenia (14.4%), and decreased white blood cell count (14.4%). No serious AEs were reported. Treatment interruption, dose reduction, and discontinuation due to AEs occurred in 12.2%, 3.4%, and 1.5% of patients, respectively. **Conclusions:** Adjuvant pyrotinib combined with nab-paclitaxel showed promising 3-year iDFS and a manageable safety profile in patients with low-risk, HER2-positive early breast cancer. This regimen represents a potential oral de-escalation strategy for this population. Clinical trial information: NCT 04659499. Research Sponsor: General Project of the 2025 Annual Beijing Municipal Education Science; No. CDDDB25233; National High Level Hospital Clinical Research Funding; 2025-PUMCH-A-148; Chronic Disease Management Research Project of National Health Commission Capacity Building and Continuing Education Center; No. GWJJMB202510041020.

Efficacy outcomes.

Efficacy outcomes	Pyrotinib + nab-Paclitaxel (n=263)		
Events, n(%)	9 (3.4)		
	24 months	36 months	48 months
iDFS rate, (95% CI)	98.77 (96.24, 99.60)	96.83 (93.42, 98.49)	93.17 (85.03, 96.96)
DDFS rate, (95% CI)	99.18 (96.76, 99.79)	98.77 (96.23, 99.60)	95.03 (86.00, 98.29)
LRFS rate, (95% CI)	99.18 (96.75, 99.79)	98.18 (95.18, 99.32)	94.47 (85.76, 97.92)

iDFS: invasive disease-free survival; DDFS: distant disease-free survival; LRFS: locoregional recurrence-free survival.

Real-world deployment of a multimodal artificial intelligence (AI) model for predicting response to neoadjuvant chemotherapy in early breast cancer.

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Background: Multimodal AI models integrate morphological information from H&E-stained images with clinical information, identifying subtle disease signatures beyond the perceptual limits of human experts. However, the clinical utility of AI tools in real-world settings remains underexplored. Here, we evaluated Ataraxis Breast (ATX), a multimodal AI test predicting response to neoadjuvant chemotherapy, in a prospective silent trial. **Methods:** We previously assembled an international dataset of whole slide images of H&E-stained biopsy specimens and clinical information to develop ATX as a biomarker of neoadjuvant response. To evaluate real-world clinical translation, we conducted a prospective silent trial of ATX in patients with early breast cancer treated with neoadjuvant therapy at our center. None of these patients were included in the original training, validation, or test datasets. The primary outcome was pathologic complete response (pCR). Area under the receiver operating curve (AUROC) analyses were conducted. **Results:** The study cohort included 50 female patients treated during 2025, with a median age of 53.8 years. Tumor subtypes comprised 30% (n = 15) triple-negative breast cancer (TNBC), 24% (n = 12) HER2-positive disease, and 46% (n = 23) hormone receptor-positive (HR+), HER2-negative tumors. Overall, 66% (n = 33) of patients had node-positive disease, and 60% (n = 30) had grade 3 tumors. Notably, all patients with TNBC received pembrolizumab, whereas patients with HER2-positive tumors were treated with chemotherapy combined with HER2-directed therapies. The overall pathological complete response (pCR) rate in this external validation cohort was 34%. ATX scores were significantly higher among patients who achieved pCR (p = 0.005). Moreover, when evaluated as a predictive biomarker across the entire cohort, ATX achieved an AUROC of 0.745 (95% CI, 0.58–0.89) for pCR. These findings were consistent across predefined subgroup analyses, including patients with HR+/HER2– disease (AUROC = 0.73) and TNBC (AUROC = 0.77). **Conclusions:** In this prospective deployment study, among patients with early breast cancer treated with neoadjuvant chemotherapy, higher AI-derived predictions were independently associated with improved neoadjuvant therapy response. Given the accessibility of H&E-slides, ATX may serve as a scalable predictive biomarker in real-world settings. Research Sponsor: Israel Ministry of Health.

Adjuvant antibody-drug conjugate (ADC) eligibility and corresponding prognosis in HER2+ early breast cancer (eBC): A US-based real-world comparison of KATHERINE and DESTINY-Breast05 populations.

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Background: The KATHERINE trial established adjuvant T-DM1 as standard of care (SoC) treatment for patients with HER2+ eBC and residual invasive disease (RD) following neo-adjuvant therapy. Recently, DESTINY-Breast05 (DB-05) demonstrated reduced recurrence risk with T-DXd vs. T-DM1 in a high-risk subset. While KATHERINE included any RD, DB-05 restricted eligibility to high-risk patients (inoperable at presentation or ypN+ at surgery). In this analysis, we aim to estimate the prevalence and associated outcomes of patients with HER2+ eBC and RD meeting eligibility for DB-05 vs. KATHERINE in a US real-world setting. **Methods:** This retrospective cohort study utilized the nationwide Flatiron Health electronic health record-derived de-identified database. We included patients diagnosed with stage I–III HER2+ eBC (Jan 1, 2011–Sept 30, 2025) who completed pertuzumab-based neoadjuvant therapy and surgery. RD status was determined via pathology reports. KATHERINE eligibility required any RD in breast/axillary nodes. DB-05 eligibility required high-risk RD: operable at presentation with node-positive disease at surgery (ypN1–3; “DB-05-operable”) or inoperable at presentation (cT4 or cT1–3/cN2–3; “DB-05-inoperable”). Distant recurrence-free survival (DRFS) and overall survival (OS) were estimated at 3 years post-surgery. The analysis was conducted on complete cases only. **Results:** The cohort included 9561 patients with HER2+ eBC and RD after neoadjuvant therapy. Overall, 9447 (99%) met KATHERINE eligibility. Conversely, only 4567 (48%) met DB-05 high-risk criteria: 3241 (34%) DB-05-operable and 1326 (14%) DB-05-inoperable. DB-05-ineligible patients mostly presented with cT1–3/cN0–1 disease and had RD confined to the breast (ypN0). In the overall study population, with a median follow-up for DRFS of 44 months, 3-year DRFS and 3-year OS were 88% and 94%, respectively. Patients eligible only for KATHERINE (i.e. DB-05-ineligible) experienced relatively favorable outcomes, with a 3-year DRFS of 94% and 3-year OS of 97%; conversely, DB-05-eligible patients experienced a 3-year DRFS of 82% and 3-year OS of 91%. Within the DB-05-eligible population, the poorest outcomes were observed if patients had inoperable disease at baseline, with a 3-year DRFS of 73% and 3-year OS of 86%. **Conclusions:** Approximately half of the patients with RD did not meet DB-05 high-risk criteria yet would have been eligible for KATHERINE. While T-DXd may become a new option for high-risk patients, T-DM1 remains a SoC for those with operable disease at baseline and node-negative RD at surgery. As ADCs were not widely available for eBC during the study period, these outcomes do not reflect ADCs’ treatment effect, and modern 3-year DRFS may possibly exceed 94% for this population. Research Sponsor: F. Hoffmann-La Roche Ltd.

A randomized phase II trial of folate receptor alpha peptide vaccine in early-stage triple-negative breast cancer.

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Background: Folate receptor alpha (FR α) is overexpressed in ~80% of triple-negative breast cancers (TNBC). We previously demonstrated that patients (pts) with breast cancer naturally mount immune responses to FR α . In prior Phase I and II studies, a GM-CSF-adjuvanted FR α peptide vaccine (FRPV) was safe and induced durable FR α -specific T-cell immunity in 83–90% of pts with breast and ovarian cancer. **Methods:** Eligible pts were women ≥ 18 years with TNBC (ER/PR $\leq 10\%$) with 1+ of the following: stage $\geq T1c$ disease, node-positivity, or residual disease after neoadjuvant chemotherapy. Pts were randomized 2:1 to receive FRPV or placebo (GM-CSF alone) every 28 days for cycles 2–7 and then every six months for 7 booster doses, with cycle 1 consisting of cyclophosphamide 50mg orally twice daily for days 1–7 and 15–21 (in both arms). Randomization was stratified by chemotherapy setting (adjuvant only vs neoadjuvant) and stage (I/II vs III). FR α expression was evaluated by immunohistochemistry. The study was designed to detect (at 30 months after the last pt enrolled) a disease-free survival (DFS) difference of 14% assuming a 3.5-year DFS rate of 70% in the control group and with 78% power. **Results:** 280 pts were enrolled (median age 52). The majority had stage I or II tumors (n = 219, 78%). There were numerically more node-positive tumors in the vaccine arm, 78 (41%) vs 27 (32%), p = 0.15. Median follow-up was 3.5 years, and 33 (FRPV: 25, placebo: 8) DFS events were observed; 3.5-year DFS rate was 88% with FRPV and 90% with placebo (HR 1.42, 95% CI 0.64–3.15; p = 0.39). Overall survival (OS) also did not differ by arm (HR 2.48, 95% CI 0.55–11.20; p = 0.22). Among node-positive pts (n = 105), DFS did not differ between arms (HR 0.95, 95% CI 0.34–2.66; p = 0.92). However, a numerical DFS event rate improvement (14% for vaccine vs. 26% for placebo) was observed in 61 patients with stage III disease (HR 0.51, 95% CI 0.16–1.68; p = 0.26). DFS did not differ by chemotherapy setting or by receipt of anthracycline, capecitabine, and/or an immune checkpoint inhibitor. FRPV was well tolerated, with predominantly grade 1–2 adverse events (AEs) and no vaccine-related grade ≥ 4 AEs. FR α expression was available from tumor in 230 pts, with 72% expressing > 0 . Overall, DFS was not significantly associated with FR α expression (0 vs > 0 ; HR 0.55, 95% CI 0.21–1.44; p = 0.21), and no significant differences in DFS by FR α expression were observed between treatment arms. **Conclusions:** FRPV following oral cyclophosphamide was safe, with no vaccine-related high-grade AEs. While no significant improvement in DFS or OS was observed overall, a numeric trend toward improved DFS was observed in pts with stage III TNBC. This finding is hypothesis-generating and supports further evaluation of FR α -targeted vaccination in higher-risk TNBC. Immune correlative analyses are ongoing to better define vaccine immunogenicity and its relationship to clinical outcomes. Clinical trial information: W81XWH-15-1-0293. Research Sponsor: U.S. Department of Defense; W81XWH-15-1-0293; U.S. Department of Defense; W81XWH-15-1-0292.

Disparities in utilization of genomic risk assays in early-stage hormone-positive breast cancer: A retrospective analysis using National Cancer Database (NCDB).

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Background: Prognostic genomic assays (GA) have become crucial in the management of early-stage hormone receptor positive breast cancer, particularly in guiding adjuvant chemotherapy decisions. Despite this, GA remain underutilized. This study aimed to identify predictors of GA utilization and associated survival outcomes. **Methods:** The 2023 NCDB PUF dataset was used to identify patients aged ≥ 18 years with HR positive, HER2 negative breast cancer diagnosed between 2010–2023. Patients with T1–T4, N0–N1 disease who underwent surgical resection were included, while those with T1aNo stage, M1 disease, unknown GA status, or receipt of BCI alone were excluded. Patients were stratified by the receipt of the GA. Descriptive and multivariable analyses were performed to identify factors associated with GA utilization, and survival was assessed using Kaplan–Meier (KM) analysis. **Results:** 594,872 patients were included in our study, of whom 63.12% (N=375,506) underwent GA testing. GA utilization increased over time from 52.7% in 2010–2015 period to 68.7% in 2021–2023 ($p < 0.001$). Using multivariable analysis, higher odds of GA testing were seen among Whites vs Blacks (OR 1.13 (1.11–1.16)), those with T2 tumors vs T1 (OR 1.26 95% CI 1.24–1.27), Grade 2 (OR 1.49 (1.47–1.51)) or Grade 3 (1.42 (1.39–1.45)) histology vs Grade 1, receiving regional lymph node surgery vs not (OR 2.47 (2.33–2.62)), hormonal therapy vs not (OR 2.39 (2.34–2.43)), radiation vs not (OR 1.32 (1.30–1.34)), and recent year of diagnosis, 2021+ vs 2010–2015 (OR 2.08 (1.99–2.18)). The odds of GA testing were lower for uninsured vs government insured patients (OR 0.86 (0.82–0.91)), those with higher T stages (T3: OR 0.63 (0.61–0.65) and T4: OR 0.26 (0.24–0.30)) vs T1, N1 disease vs N0 (OR 0.73 (0.72–0.74)) and increasing age with the lowest odds among patients aged >80 (OR 0.13 (0.13–0.14)) compared to 18–64 years old. KM analysis showed survival benefit favoring receipt of GA (HR= 0.4 (0.39–0.41), $p < 0.001$). **Conclusions:** Our study portrays low utilization of GA despite increasing use over time reflecting the impact of the TAILORx and RxPONDER trials. Significant disparities persisted by age, insurance status, race, and tumor characteristics. Older, Black and uninsured patients were substantially less likely to receive testing, despite an associated survival benefit, underscoring the need for more equitable implementation of guideline-recommended GA. Research Sponsor: None.

Preliminary injection site reaction immune response results from open-label arm of ongoing phase III study to evaluate the efficacy and safety of GLSI-100 (GP2 + GM-CSF) in patients with breast cancer with residual disease or high-risk PCR after both neo-adjuvant and postoperative adjuvant anti-HER2 therapy (Flamingo-01).

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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, 2026, issue of the *Journal of Clinical Oncology*.

Real-world post-APT trial adoption of de-escalated systemic therapy and outcomes in small HER2-positive breast cancer: An NCDB analysis.

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Background: The APT trial shifted adjuvant management of small HER2-positive breast cancer towards paclitaxel-trastuzumab, yet real-world uptake and outcomes of de-escalated single-agent chemotherapy (SC) plus anti-HER2 therapy (H) vs multi-agent chemotherapy (MC) plus H remain uncertain. **Methods:** Using NCDB (2013–2022), we identified patients with invasive HER2-positive pT1a–pT1c, pN0/N1mi, Mo disease treated with surgery without neoadjuvant therapy. We compared treatment patterns pre-APT (2013–2014) vs post-APT (2016–2022), excluding 2015 as a washout. Regimens were grouped as local therapy only, H only, chemo only, SC + H, or MC + H. Predictors of SC + H were assessed with multivariable logistic regression in post-APT chemo + H recipients. OS was evaluated using time-varying Cox models (time zero surgery; treatment exposure starting at recorded systemic therapy initiation), adjusted for demographic, tumor, and facility factors. In the overall cohort, each regimen (H only, chemo only, SC+H, and MC+H) was compared with local therapy only. For pT1a tumors, comparisons were limited to H only, chemo only, and any chemo + H vs local therapy. To evaluate whether de-escalation was associated with similar OS, SC + H vs MC + H was compared in separate Cox models restricted to chemo + H recipients in pT1b and pT1c. **Results:** Among 56,455 patients, SC + H use increased from 12.5% pre-APT to 40.3% post-APT, while MC + H decreased from 46.6% to 24.8% ($p < 0.001$). In the post-APT era among chemo + H recipients ($N = 24,867$), SC + H use increased with age (per 10-year OR 1.32, 95% CI 1.27–1.36) and hormone receptor-positive (HR-positive) status (OR 1.37, 95% CI 1.27–1.49), and less common with pT1c (OR 0.47, 95% CI 0.43–0.51) and N1mi (OR 0.21, 95% CI 0.17–0.24) tumors. In OS analyses of the entire cohort with available systemic start dates ($N = 51,078$; deaths = 3,246), SC + H (HR 0.62, 95% CI 0.57–0.67) and MC + H (HR 0.63, 95% CI 0.58–0.68) were associated with improved OS vs local therapy only. Additional independent predictors of mortality included Black race, older age, and higher tumor burden (T1c and N1mi), while HR-positive was linked to better OS. In pT1a cohort ($N = 10,212$; deaths = 461), any chemo + H was associated with improved OS vs local therapy (HR 0.83, 95% CI 0.70–1.00, $p = 0.049$), while H only (HR 0.85, 95% CI 0.51–1.42) and chemo only (HR 1.14, 95% CI 0.74–1.74) were not. Among chemo + H recipients, OS was similar for SC + H vs MC + H in pT1b (HR 0.96, 95% CI 0.80–1.16) and pT1c (HR 1.09, 95% CI 0.97–1.24) cohorts. **Conclusions:** Since APT, real-world care has shifted towards de-escalated SC + H regimens. Among treated pT1b and pT1c patients, OS was similar with SC vs MC backbones, supporting the feasibility of de-escalation in selected patients. In pT1a disease, the OS association for chemo + H was marginal ($p = 0.049$) and should be interpreted cautiously given non-random treatment selection and low event rates. Research Sponsor: None.

Adjuvant chemotherapy (CT) benefit in invasive lobular carcinoma (ILC) by Oncotype DX Recurrence Score and menopausal status.

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Background: The benefit of adjuvant CT in early-stage hormone receptor-positive (HR+) and HER2-negative (HER2-) ILC remains uncertain. The predictive utility of the Oncotype DX Recurrence Score (RS), widely used to guide CT decisions in HR+/HER2 BC, remains debated in ILC. To address these gaps, we analyzed the impact of adjuvant CT on overall survival (OS) across RS categories and by menopausal status. **Methods:** We queried the National Cancer Database for patients (pts) with early-stage HR+/HER2- ILC who had surgery between 2010 and 2021. Pts were grouped by receipt of adjuvant CT (CT+ vs CT-). Analyses were stratified by RS (low 0–15, intermediate 16–25, high ≥ 26) and menopausal status, using age (<50 vs ≥ 50 years) as a proxy. Overlap propensity score weighting (OPSW) balanced baseline covariates (race, ethnicity, comorbidities, clinical T and N stage, grade and radiation and hormone therapies), and OPSW Cox models assessed the association between time-varying adjuvant CT and OS. **Results:** Among 141,949 pts with ILC, 19.6% received adjuvant CT. The CT+ cohort was younger (median age 59 vs 67 years) and more often pre-menopausal (21.8 vs 9%), and had high grade tumors (8.7 vs 3.3%), advanced T stage (T2: 39.4 vs 21.8%; T3: 14.9 vs 3.4%), node-positive (N1–3: 22 vs 3.2%) disease and more frequently received radiation (74.6 vs 56.5%) and hormone therapy (93.3 vs 87.5%), all $p < 0.001$. RS testing was available in 38% of pts; CT+ cohort more often had high (9.2 vs 1.2%) or unknown RS (75.4 vs 57.9%), $p < 0.001$. In the high RS group, CT was associated with improved 5-year (93.3 vs 90.5%) and 10-year OS (79.4 vs 71.7%) and lower mortality (adjusted hazard ratio (aHR) 0.69, $p < 0.001$) (Table 1). Among postmenopausal pts, the survival benefit with CT was greatest in pts with high RS (10-year OS: 78.6 vs 69.2%; aHR 0.65, 95% CI 0.52–0.82, $p = 0.0003$). No OS benefit was observed in low (aHR= 1.16, $p = 0.31$) or intermediate (aHR= 1.07, $p = 0.39$) RS groups. Among premenopausal pts, CT benefit was limited to the intermediate RS group (10-year OS: 94.9 vs 91.3%; aHR 0.57, 95% CI 0.33–1.00, $p = 0.049$); no benefit was observed in low (aHR= 1.11, $p = 0.77$) or high (aHR= 1.50, $p = 0.55$) RS. **Conclusions:** In early-stage HR+/HER2- ILC, RS has limited clinical utility. Adjuvant CT benefit was restricted to pts with high RS, predominantly in postmenopausal pts, while RS did not reliably predict benefit in premenopausal pts. No OS benefit was seen in low RS disease, supporting a selective, biology-driven approach to CT use in ILC. CT decisions in pts with unknown RS appear largely driven by clinicopathologic factors. Research Sponsor: None.

10-year survival analysis of ILC patients based on CT receipt and RS.

RS group	OS (%; 95% CI) CT +	OS (%; 95% CI) CT -	aHR (95% CI) Reference: CT-	p-value
Low	87.6 (84.6-90.6)	88.9 (88.0-89.9)	1.13 (0.87-1.47)	0.36
Intermediate	86.2 (84.4-88.1)	86.5 (85.3-87.7)	1.02 (0.87-1.20)	0.78
High	79.4 (76.4-82.5)	71.7 (66.9-76.8)	0.69 (0.55-0.87)	<0.01

Overall survival association of adjuvant endocrine therapy (ET) after pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC) in ER+/HER2+ early-stage breast cancer.

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Background: In ER+/HER2+ early breast cancer, adjuvant ET is standard; however, its survival benefit for patients achieving pCR after NAC remains uncertain. As pCR is associated with favorable prognosis and may inform postoperative decision-making, it is unknown if pCR identifies a subset in whom the ET survival benefit is reduced. We evaluated ET use patterns and its association with overall survival (OS) in ER+/HER2+ patients with pCR after NAC. **Methods:** Using NCDB, we identified women with ER+/HER2+ Mo breast cancer treated with NAC and definitive surgery (2018–2022) who achieved pCR (ypT0/ypTis and ypNo). The primary end-point was OS. To reduce immortal time bias, we used a time-varying Cox model with ET initiation as a time-dependent exposure (time zero: surgery). A 6-month landmark analysis was performed as a sensitivity analysis. Multivariable models adjusted for demographic, clinicopathologic, treatment, and socioeconomic variables. Predictors of ET omission were assessed using multivariable logistic regression. Exploratory analyses evaluated ER-low (1–10%) and effect modification using an ET×ER-low interaction term. **Results:** Of 8,981 patients, 7,917 (88.2%) received ET and 1,064 (11.8%) did not. In the time-varying Cox model, ET receipt was associated with improved OS (HR 0.79, 95% CI 0.67–0.93). Worse OS was associated with older age (per 10 years: HR 1.17, 95% CI 1.10–1.24) and stage III disease (HR 1.39, 95% CI 1.16–1.67). In 6-month landmark analysis (n=8,756), ET benefit persisted (HR 0.58, 95% CI 0.39–0.86). There was no differential association by ER-low status (ET×ER-low interaction $p=0.73$), with similar ET associations in ER-high (HR 0.58) and ER-low (HR 0.63) groups. ET was omitted in 36.9% of ER-low patients compared to only 7.6% of ER-high patients. Logistic regression identified ER-low status as the strongest predictor of ET omission (OR 0.16, 95% CI 0.14–0.19). Omission was also more likely with older age (per 10-year increase: OR 0.92, 95% CI 0.85–0.99) and community facility treatment (OR 0.74, 95% CI 0.55–0.99), while ET receipt was more likely with PR-positivity (OR 1.54, 95% CI 1.32–1.79), radiation (OR 2.78, 95% CI 2.32–3.33) and HER2-targeted therapy (OR 2.62, 95% CI 2.03–3.38). **Conclusions:** In this NCDB cohort, adjuvant ET was associated with improved OS in ER+/HER2+ patients achieving pCR after NAC. The survival association did not differ by ER-low status, though event rates in this subgroup were limited. ER-low status was the strongest predictor of ET omission, highlighting a potential gap between real-world practice and outcomes. These findings support continued consideration of ET in post-pCR ER+/HER2+ patients, including the ER-low population. Research Sponsor: None.

Cohort	Total N	ET (%)	No ET (%)	Death (%)
Overall	8,981	7,917 (88.2%)	1,064 (11.8%)	152 (1.7%)
ER-low	1,316	831 (63.1%)	485 (36.9%)	32 (2.4%)

Three-monthly gonadotropin-releasing hormone agonist for ovarian function suppression in premenopausal breast cancer: A systematic review and meta-analysis.

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Background: Ovarian function suppression (OFS) with gonadotropin-releasing hormone agonists (GnRHa) is a cornerstone of endocrine therapy (ET) for premenopausal women with hormone receptor-positive (HR+) breast cancer (BC), most commonly administered on a monthly (1M) schedule. Three-monthly (3M) formulations have been proposed to improve convenience and adherence, but comparative efficacy and safety versus 1M regimens remain uncertain. **Methods:** PubMed, Cochrane, and Embase libraries were systematically searched for randomized clinical trials (RCTs) and non-randomized interventional studies comparing 3M versus 1M GnRHa regimens in premenopausal women with HR+ BC receiving ET. Outcomes included the incidence of ovarian escape (OE), mean estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels, disease-free survival (DFS), progression-free survival (PFS), and adverse events, with a minimum follow-up of 12 weeks. Random-effects models were used to estimate pooled risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI). Subgroup analyses were performed by estradiol assay type, and a sensitivity analysis restricted to RCTs was conducted. **Results:** Fifteen studies comprising 4,324 patients were included; 2,098 (48%) received a 3M regimen. The overall incidence of OE was low (10%) and did not differ between 3M and 1M schedules (RR 0.86; 95% CI 0.60–1.22). Ultra-sensitive assays revealed higher absolute OE rates (31%), without inter-regimen differences (RR 0.90; 95% CI 0.38–2.14). Mean E2 levels at 12 weeks were comparable across dosing strategies (MD 1.36 pg/mL; 95% CI –3.66 to 6.38), with no significant differences in mean FSH or LH levels; analyses restricted to RCTs yielded consistent findings (MD –1.77 pg/mL; 95% CI –5.71 to 2.17). DFS (RR 1.02; 95% CI 0.67–1.56) and PFS (RR 0.86; 95% CI 0.72–1.04) were similar between regimens. The most frequently reported adverse events were hot flashes, arthralgia, headache, and nausea, with no clinically relevant differences between dosing schedules. **Conclusions:** 3M GnRHa achieved OFS comparable to 1M dosing, with similar survival outcomes and safety profiles in premenopausal women with HR+ BC. Research Sponsor: None.

Real-world effectiveness and safety of adjuvant capecitabine in triple-negative breast cancer (TNBC) patients with residual disease following neoadjuvant chemotherapy.

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Background: The presence of residual disease in triple-negative breast cancer (TNBC) after neoadjuvant chemotherapy is associated with high recurrence risk and poor prognosis. The CREAT-X study demonstrated improved recurrence risk and survival outcomes with adjuvant capecitabine in this population [1]. We previously reported long-term outcomes in nonmetastatic TNBC, but the population is unselected, and the impact of adjuvant capecitabine is not assessed in the Indian scenario [2]. **Methods:** This single-center retrospective study included TNBC patients with residual disease after neoadjuvant chemotherapy treated between January 2020 and December 2024 with adjuvant capecitabine. Baseline clinicopathological characteristics were analyzed descriptively. Survival outcomes were assessed using the Kaplan–Meier method, and recurrence-free survival (RFS) and overall survival (OS) were estimated. Factors associated with survival outcomes were evaluated using univariate and multivariate Cox proportional hazards regression models. **Results:** Among 1548 patients diagnosed with Stage I–III TNBC, 1044 patients treated with neoadjuvant therapy underwent surgery; 671 patients had residual disease, out of which 315 patients who received adjuvant capecitabine were included in this retrospective analysis. The majority were premenopausal (66.3%), were older than 40 years (59.7%), and had stage III residual disease (71.4%). At a median follow-up of 25 months, the 2-year overall survival (OS) was 79.6%, with a median OS of 49.7 months. The 2-year recurrence-free survival (PFS) was 49.3%, with a median RFS of 23.9 months. On univariate analysis, higher nodal status ($P < 0.001$) and advanced stage ($P < 0.05$) were significantly associated with inferior RFS, while higher nodal status was also associated with inferior OS ($P < 0.05$). Multivariate analysis confirmed nodal status as an independent predictor of poor survival ($P < 0.01$). **Conclusions:** Adjuvant capecitabine demonstrated poor outcomes in our TNBC patients with residual disease compared to the randomized study; nodal status independently predicted poorer outcomes, emphasizing risk stratification and prospective validation. **References:** Toi M, Lee SJ, Lee ES, Ohtani S, Im YH, Im SA, Park BW, Kim SB, Yanagita Y, Takao S, Ohno S. Abstract S1-07: a phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X, JBCRG-04). *Cancer Research*. 2016 Feb 15; 76(4_Supplement): S1-07. Bajpai J, Kashyap L, Vallathol DH, Das A, Singh M, Pathak R, Rath S, Sekar A, Mohanta S, Reddy A, Joshi S. Outcomes of non-metastatic triple negative breast cancers: Real-world data from a large Indian cohort. *The Breast*. 2022 Jun 1;63:77–84. Clinical trial information: CTRI/2026/01/101798. Research Sponsor: None.

Chemotherapy use among women < 50 years with hormone receptor–positive breast cancer with low (≤ 15) Oncotype DX 21-gene recurrence score: A National Cancer Database (NCDB) analysis.

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Background: RxPONDER demonstrated a benefit to chemotherapy (CT) in premenopausal women with hormone receptor–positive (HR+) breast cancer (BC) with 1–3 pathological positive lymph nodes (pN1) regardless of Oncotype DX RS. Whether the benefit is due to the cytotoxic effects of CT itself or potentially from the CT-induced ovarian suppression remains to be determined. In the absence of large prospective data evaluating the predictive ability of RS in this population, including pN1mi, we sought to examine adjuvant CT use patterns among premenopausal women and low RS. **Methods:** This retrospective analysis queries the NCDB from 2018–2022 for patients (pts) with BC <50 years old (surrogate for premenopausal status) and clinically node negative disease at the time of diagnosis. Pts with stage I–III HR+ HER2–negative BC who underwent upfront curative breast surgery and had pathologically confirmed lymph node status (pN) were included. Oncotype DX RS was categorized as low if RS ≤ 15 . Multivariable binary logistic regression was used to examine associations between clinical–pathological factors and the receipt of adjuvant CT. **Results:** 6040 pts with Oncotype DX RS ≤ 15 met inclusion criteria. Most pts, 5090 (84.3%), had invasive ductal carcinoma, and high (>51%) ER and PR expression (>93% of patients). Among all low RS, 5081 (84.4%) had pN0 and 939 (15.5%) had pN1 or higher disease, 704 pts (76.6%) having 1 LN involved, of which 317 pts were pN1mi; 148 (16.1%) had 2 LN and 67 (7.3%) had 3+ LN. Accounting for all pts, 265 (4.4%) received CT: 64 (24.2%) were pN0, while 201 (75.8%) were pN1+. Among pts with pN1 BC, older age was associated with lower odds of receiving adjuvant CT (aOR 0.96, 95%CI 0.93–1.00, $p=0.03$). Other factors including higher pathologic tumor stage (pT3/T4 vs pT1/T2; aOR 4.46, 95% CI 2.34–8.51), higher pN involvement, specifically 2 LN (aOR 2.45, 95% CI 1.60–3.75) and ≥ 3 LN (aOR 4.65, 95% CI 2.54–8.51) compared to 1 positive regional LN, and poorly (vs well) differentiated tumor (aOR 2.36, 95% CI 1.14–4.88) had higher odds of receiving CT. Similarly, pts with pN0 and low RS that had pT3/T4 tumors (aOR 3.99, 95% 1.16–13.72) and higher grade (moderately and poorly differentiated tumors) had higher odds of receiving CT (aOR 1.84 95% CI 1.03–3.27 and 6.11 95% CI 2.58–14.44, respectively). **Conclusions:** Among women <50 years with low RS (≤ 15), CT receipt was strongly associated with clinicopathologic risk factors, including higher tumor stage, poorly differentiated grade and higher regional nodal involvement. These findings indicate that despite a low RS, young age and node positivity are associated with adjuvant CT recommendation. These results highlight the importance of ongoing trials such as OFSET, which aims to better answer the appropriateness of CT among premenopausal women. Research Sponsor: None.

Comparative effectiveness of adjuvant chemotherapy on survival in node-positive (N2/N3), stage III ER+/HER2– invasive lobular breast cancer (ILC) versus invasive ductal cancer (IDC).

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Background: ILC is characterized by loss of E-cadherin expression, with distinct biological and clinical features, and is often perceived to be less sensitive to chemotherapy compared with IDC. Oncologists and pts may face a treatment dilemma regarding the benefits of adjuvant chemotherapy in pts with lower biologic risk but higher anatomic risk (N2/N3), stage III ILC. In this study, we sought to compare the benefit of adjuvant chemotherapy in pN2/N3 ILC compared with IDC. **Methods:** We used the National Cancer Database (NCDB) to identify adults with primary, non-metastatic, ER-positive/HER2-negative invasive breast cancer diagnosed between 2010 and 2022 who underwent upfront surgery. Patients receiving neoadjuvant systemic therapy were excluded. Analyses were limited to pathologic stage I–III disease with known nodal involvement (N2–N3) and tumor category (T1–4). Propensity score matching (1:3, caliper 0.2; using R 4.5.1) was performed to balance age, sex, race, insurance status, grade, pathologic stage, nodal category, tumor category, Charlson-Deyo comorbidity score, and year of diagnosis. Overall survival (OS) was assessed using Kaplan–Meier methods and Cox proportional hazards models used to estimate hazard ratios (SPSS v28). **Results:** After propensity matching, we analyzed 28,115 pts with pN2/N3 disease (ILC 9,603 and IDC 18,512). Upstaging from cN0 to pN2/3 was higher for ILC than IDC (20.3% vs 13.3%, $p<0.001$). ILC pts were more likely to undergo mastectomy compared to IDC (80.2% vs 71.2%, $p<0.001$). Receipt of adjuvant chemotherapy for pN2/N3 disease was similar between IDC and ILC (78.0% vs 78.4%, $p=0.37$), as was use of adjuvant radiation and endocrine therapy. Among patients receiving chemotherapy, treatment was associated with a 65% reduction in death in ILC (HR 0.35, 95% CI 0.32–0.38, $p<0.001$) and a 73% reduction in IDC (HR 0.27, 95% CI 0.26–0.29, $p<0.001$), compared with no chemotherapy. 5-year OS among chemotherapy-treated patients was lower for ILC compared with IDC (HR 1.4, 95% CI 1.33–1.49; $p<0.001$, Table 1). In contrast, no OS difference was observed between ILC and IDC among patients who did not receive chemotherapy (HR 1.03, 95% CI 0.96–1.11; $p=0.38$). Chemotherapy was associated with higher 5-year OS in both IDC (87.7% vs 58.9%) and ILC (84.3% vs 59.2%). **Conclusions:** Adjuvant chemotherapy was associated with a substantial improvement in 5-year OS among patients with pN2/N3 disease in both IDC and ILC. Pts with ILC and extensive nodal involvement benefit from adjuvant chemotherapy. Research Sponsor: None.

5-year survival of IDC and ILC.

	IDC (18,512)		ILC (9,603)	
	No Chemotherapy (4,078)	Adjuvant Chemotherapy (14,434)	No Chemotherapy (2,071)	Adjuvant Chemotherapy (7,532)
pN2 (18,669)	62.8%	90.1%	64.4%	87.6%
pN3 (9,446)	48.3%	82.2%	51.4%	79.4%
pN2/pN3 Com- bined (28,115)	58.9%	87.7%	59.2%	84.3%

P <0.001, log rank.

AI-based pre-screening of *BRCA1/2* mutation likelihood from routine H&E histopathology in unselected breast cancer cases using peakPredictBRCA.

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Background: *BRCA1/2* mutation status is essential for precision oncology in breast cancer, directly guiding therapy decisions such as eligibility for PARP inhibitors. However, not all patients globally have reimbursed access to genetic *BRCA* testing, due to cost and a lack of uniform global implementation, leading to actionable mutations being missed. We developed a scalable artificial intelligence pre-screening algorithm that estimates *BRCA1/2* mutation likelihood from routine whole-slide H&E images, to enable systematic prioritization of patients for genetic testing. **Methods:** peakPredictBRCA, a deep learning-based algorithm, was developed to predict likelihood of *BRCA1/2* mutations from H&E whole-slide images of primary and metastatic breast cancer cases, independent of hormone receptor or HER2 status. Breast cancer images were collected from 6 institutions across 5 countries using different whole-slide scanners (Argentina, Brazil, Germany, Jordan, and USA), with slide-level *BRCA* mutation labels derived from clinical sequencing ($n=725$ images, 60% mutated). Training data was augmented with open-access TCGA datasets for breast, prostate, and ovarian cancer ($n = 1,633$ images), resulting in 2,358 total images (21% mutated). Model performance was evaluated on the collected breast cancer images using five-fold cross-validation. The model was trained end-to-end without manual annotations using multiple-instance learning. **Results:** On the breast cancer cohort, peakPredictBRCA achieved a mean AUC of 0.81 ± 0.13 . At a screening-oriented operating point, the model identified most *BRCA1/2* mutated cases (mean sensitivity 0.82 ± 0.23) while excluding a substantial proportion of non-mutated cases (mean specificity 0.56 ± 0.38), without additional calibration on held-out images. Additional analyses during development demonstrated that robust generalization to unseen data depends on appropriate tumor tissue detection and model architecture selection. **Conclusions:** Our results demonstrate that *BRCA1/2* mutation likelihood can be effectively triaged from routine H&E breast cancer histology with consistent performance across institutions, scanners, and slide preparations. Implementation of the peakPredictBRCA algorithm in routine pathology workflows could enable systematic prescreening of unselected breast cancer cases at diagnosis and prioritization for confirmatory genetic testing, particularly in resource-constrained settings. Ongoing work focuses on incorporating human-interpretable features and on prospective validation in real-world workflows. Research Sponsor: AstraZeneca International; Mindpeak GmbH.

Recurrence risk prediction using a large, multi-site observational dataset of patients with early breast cancer, including early-onset disease.

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Background: Accurate risk stratification in early breast cancer (eBC) is critical to guide adjuvant treatment intensity. In HR+/HER2- stage I-III disease, clinicians use clinical and genomic information to estimate recurrence risk, yet a comprehensive, real-world predictive model that synthesizes these inputs after curative-intent surgery is not established in routine practice. We developed a multimodal predictive survival model in a large, eBC cohort to predict recurrence-free survival (RFS) after surgery and derive risk groups to inform treatment escalation or de-escalation. **Methods:** This study used the US-based EHR-derived deidentified Flatiron Health Research Database (data cutoff: Sep 30, 2025). The cohort consisted of patients (pts) diagnosed with HR+/HER2- stage I-III eBC between Jan 1, 2016, and Jan 1, 2023, who received surgery and no neoadjuvant therapy. An Extreme Gradient Boosting (XGBoost) model was developed using 10-fold cross-validation, reserving 20% for testing, predicted time from surgery to recurrence or death. SHapley Additive exPlanations (SHAP) analysis was used to rank feature importance. Pts were classified into 3 risk groups by prediction percentile, and RFS by group was plotted in the test set using the Kaplan-Meier method. A second XGBoost model identified predictors specific to pts diagnosed with early onset (EO) eBC (age $\leq$ 45 yrs). **Results:** 158,111 pts qualified for the cohort, and the model C-index was 0.76. Top features that contributed to increased predicted hazard include age, higher tumor grade, higher stage, higher OncotypeDx score, longer time from diagnosis to surgery, ECOG score $\geq$ 2, and smoking history. Higher socioeconomic status (SES) decreased predicted hazard. Age had a non-linear association with predicted hazard; risk was elevated among pts <35 and >71 , with lowest prediction occurring at ages 46–51. The median RFS in the high-risk group was 8.5 yrs (IQR, 8.2–8.8) and was not reached in the medium and low-risk groups. In the early onset subgroup of 12,196 pts, the C-index was 0.71. Top features in the EO model that contributed to increased hazard also included higher tumor grade and stage, and younger age. Importance of race and Ki67 percent staining (PS) superseded that of ECOG and SES in the EO model. Pts of Black or African American race and pts with Ki67 PS $\geq$ 20% had higher predicted hazard. **Conclusions:** This analysis elucidated key predictors of RFS following surgery in pts with eBC, specifically in non-neoadjuvant-treated pts at higher risk for recurrence, and illustrated predictors that vary in younger pts. Predictors from this large, representative dataset are aligned with known associations with recurrence risk. These findings suggest real-world data models may complement established tools guiding adjuvant treatment intensity, though external validation and prospective evaluation are needed. Research Sponsor: Flatiron Health, Inc.

AI-driven large language models for multimodal prediction of homologous recombination deficiency using clinical features and histopathological whole-slide images.

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Background: Homologous recombination deficiency (HRD) implies the dysfunction of homologous recombination repair at the cellular level. The assessment of HRD status benefits making treatment plans and fertility counseling of breast cancer patients. Standard diagnostic tests for detecting HRD are expensive and not universally available. **Methods:** We trained a deep learning framework to predict HRD status by integrating routinely collected clinical records and histopathological imaging data, including hematoxylin and eosin (H&E)-stained whole-slide images, from primary breast cancer patients ($n = 397$) across three independent regional medical centers. The patient cohort was split into a training set (80%) and a validation set (20%). Clinical text as well as whole-slide images were encoded using large language model. This model integrated multimodal representation learning and was applied to generate robust HRD predictions. **Results:** Across breast cancer cohorts from three independent regional medical centers, the proposed approach demonstrated robust and consistent performance in predicting HRD. The reported AUC of 0.82 (95% CI, 0.79–0.84) represents the mean value over ten independent experiments with different random seeds. Notably, the model achieved a precision of 0.84 and a specificity of 0.92, indicating strong discriminatory power with a tendency towards cautious decision-making. **Conclusions:** Our model showed promising HRD predictive performance in breast cancers directly from routine multimodal data integrating clinical characteristics, imaging description with pathological slides. The HRD-positive predictions generated by this model show promise for clinical translation. Research Sponsor: National Natural Science Fund of China; No.82472749.

Prediction of pathologic response using a taxane-based gene expression signature in RNA-sequencing data from breast cancer patients receiving neoadjuvant therapy.

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Background: Taxanes are frequently used in both early and advanced breast cancer, but their use has not yet been guided by predictive biomarkers. We have previously validated a microarray-based 113-gene predictive signature for neoadjuvant taxane-based treatment across 6 independent cohorts, including I-SPY2. Here, we present our first validation of this signature in RNA-sequencing data. **Methods:** The study by Park et al. (2020; PMID: 33268821) enrolled 210 women with stage II–III invasive breast cancer, who received four cycles of neoadjuvant doxorubicin plus cyclophosphamide (AC) followed by four cycles of docetaxel (T) with trastuzumab (H) added for HER2-positive disease. We obtained pre-treatment TPM-normalized RNA-sequencing data from GEO (accession ID: GSE123845) for patients with available response data—pathologic complete response (pCR; $n = 34$) vs. residual disease (RD; $n = 62$)—following treatment completion ($n = 96$). To ensure compatibility between the RNA-sequencing data and microarray-based model, we performed frozen quantile normalization using the original training dataset for the model (GSE140494) as reference. We applied the signature on the normalized data to generate a response score for each patient in the range of 0–100 and evaluated the association between treatment response and patient score using logistic regression. **Results:** Increase in patient score was significantly associated with higher odds of pCR after adjusting for ER and HER2 status (one-sided $P = 0.003$), with a 50-point increase corresponding to an odds ratio of 3.44 (95% CI, 1.46–8.71), and an AUC of 0.74 for predicting pCR. Stratifying patients by median score revealed notable differences in pCR rates between low- and high-scoring patients. For ER+/HER2- patients ($n = 28$; median score = 26.6), the difference in pCR rates was 29% (0% vs. 29%) for patients below vs. above the median. Corresponding differences for triple-negative ($n = 35$; median score = 65.6) and HER2-positive patients ($n = 33$; median score = 51) were 13.8% (33.3% vs. 47.1%) and 39.4% (29.4% vs. 68.8%), respectively. **Conclusions:** We present the validation of a 113-gene predictive signature in RNA-sequencing data for achieving a pCR after taxane-based therapy. This is our first attempt at validating the signature in RNA-sequencing data, and the 7th successful validation overall across independent breast cancer cohorts. This result further highlights the signature's potential as a tool to support taxane-based treatment guidance. Research Sponsor: None.

Evaluating performance of an AI-based recurrence score in early breast cancer patients treated with chemoendocrine therapy: A secondary analysis of the UNIRAD trial.

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Background: Patients with node-positive HR+/HER2- early breast cancer are at high risk for relapse within 5 years of diagnosis, suggesting the potential need for treatment escalation. However, it is unclear which patients may experience worse recurrence-free outcomes and thus benefit from additional therapy. Ataraxis Breast (ATX) is an artificial intelligence (AI) test that integrates clinicopathologic variables with features extracted from whole-slide H&E images to estimate recurrence risk. Here, we perform a secondary analysis of the control arm of the UNIRAD trial, evaluating the ability of ATX to identify patients treated with standard-of-care therapy who may be candidates for treatment escalation. **Methods:** Clinical information and scanned H&E slides were sourced for 365 patients enrolled in the UNIRAD trial who were randomized to the control arm (standard-of-care therapy). ATX scores were generated using a locked model with pre-specified thresholds. No patients from UNIRAD were used in the training of ATX. Recurrence-free interval (RFI) was used as the primary endpoint. Kaplan-Meier estimators were used to predict the probability of meeting the RFI endpoint. To quantify relative differences in the hazard of experiencing an event contributing to the RFI endpoint associated with ATX scores, Cox proportional hazards models were fitted, from which hazard ratios (HRs) were estimated. The discriminative performance of ATX was evaluated using C-index. **Results:** Of the 365 patients randomized to the control arm of the UNIRAD trial with H&E slides available, 163 (45%) were classified as ATX low risk, and 202 (55%) as ATX high risk. Patients classified as ATX high risk had lower Kaplan-Meier-estimated probability of meeting the RFI endpoint (77%, 95% CI = 70-83%) than patients classified as ATX low risk (93%, 95% CI = 88-97%). Consistent with these findings, when modeled as a continuous variable, higher ATX scores were associated with a significantly higher hazard of an RFI-contributing event (HR = 1.57, 95% CI = 1.29-1.99, p-value < 0.001) and demonstrated strong discriminatory performance (C-index = 0.66, 95% CI = 0.59-0.72). This association remained significant after controlling for receipt of neoadjuvant therapy, tumor, and nodal stage (HR = 1.53, 95% CI = 1.05-2.23, p = 0.027). **Conclusions:** In the clinically homogenous UNIRAD trial cohort of patients with node-positive HR+/HER2- early breast cancer, ATX high risk patients treated with standard-of-care therapy had a significantly increased hazard of an RFI-contributing event. These findings suggest that AI-based risk stratification identifies biologically high risk patients who may derive benefit from adjuvant treatment escalation. Clinical trial information: NCT01805271. Research Sponsor: Ataraxis AI.

Estimating individual benefit from adjuvant chemotherapy in hormone receptor-positive breast cancer using causal multimodal artificial intelligence.

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Background: Adjuvant chemotherapy decisions in HR+/HER2- early breast cancer are often guided by prognostic gene expression assays. However, assessment of recurrence risk may not yield a predictive biomarker that accurately estimates treatment benefit. Here, we combine advances in deep learning and causality research to address this problem using routine histopathology and clinical data. We develop and validate a causal multimodal artificial intelligence (AI) model that predicts the patient-specific benefit of adding chemotherapy to endocrine therapy in HR+/HER2- early breast cancer. **Methods:** De-identified whole-slide histopathology images (WSIs) and clinical covariates from 9,269 patients across 12 observational cohorts were used to develop the Ataraxis Breast model (ATX). The locked model was then externally validated in a cohort from the University of Chicago (n = 435, stage I-III HR+/HER2- breast cancer, median age = 56, median follow-up = 7.2 years), grouped by adjuvant therapy received (endocrine therapy [ET] n = 322, chemoendocrine therapy [CET] n = 113). The primary endpoint was 5-year recurrence-free interval (RFI). WSIs were encoded via a pathology foundation model and integrated with clinical variables (including T/N stage, age, ductal vs lobular histology). ATX predicted counterfactual RFIs, assuming CET or ET, with the difference taken as the predicted treatment-benefit score. Discrimination was evaluated using Harrell's C-index. Multivariate Cox proportional hazards models were fitted, adjusting for clinicopathological factors (age and T/N stage), to estimate hazard ratios (HR). Subgroup differences were assessed using inverse-propensity-weighted Kaplan-Meier estimates and two-sided log-rank tests. **Results:** In the external validation cohort, ATX was significantly associated with the primary endpoint (adjusted HR = 1.65, 95% CI 1.05-2.6; p = 0.029), and demonstrated good discrimination at the patient-level (C-index = 0.704, 95% CI 0.588-0.821). Notably, ATX stratified patients into subgroups with differential chemotherapy effects: patients in the top tertile of predicted treatment benefit experienced improved RFI with CET (ET RFI = 0.744, CET RFI = 0.980; p < 0.001), with no difference observed in patients with low predicted treatment benefit (ET RFI = 0.975, CET RFI = 0.970; p = 0.85). The interaction between ATX and the magnitude of chemotherapy benefit, when adjusted for clinicopathological factors, was significant (p-interaction = 0.005). **Conclusions:** A causal multimodal AI model accurately estimates chemotherapy benefit for patients with HR+/HER2- early breast cancer, meeting the criteria for a predictive biomarker. The causal AI methodology presented here may provide a generalizable framework to optimize scalable, predictive biomarkers for other therapies and cancer types. Research Sponsor: Ataraxis AI.

Evaluating the prognostic performance of an AI-based model in clinically low-risk HR+/HER2– early breast cancer.

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Background: Accurate prediction of recurrence risk in early HR+/HER2– breast cancer remains central to adjuvant treatment decision making. Clinically approved prognostic models largely rely on genomic features, yet their performance remains insufficient for optimal clinical stratification. To address these limitations, AI-based approaches have increasingly been developed to improve risk prediction. Ataraxis Breast (ATX) is a multimodal artificial intelligence test integrating clinical information with morphological information from H&E-stained whole slide images for HR+/HER2– patients. Here, we evaluate ATX's ability to prognosticate recurrence risk in an external cohort of clinically low risk early breast cancer patients from Dordrecht, the Netherlands. **Methods:** Clinical information and H&E images were accessed for 887 patients with HR+/HER2– breast cancer. ATX scores were generated using a locked model and a prespecified cut-off was applied to classify patients into ATX high vs low groups. The primary endpoint was recurrence-free interval (RFI); recurrence-free probabilities were estimated for the two groups using a Kaplan-Meier estimator. Additionally, performance of ATX was assessed using C-index and hazard ratio (HR per 0.1 increase in ATX score). No patients from this dataset were used in the training of ATX. **Results:** The cohort of 887 patients was characterized by low clinical risk, where 631 tumors were classified as T1 and 239 as T2, and the majority of patients were node-negative (N0: n = 639). Tumors were predominantly low to intermediate grade (grade 1: n = 296; grade 2: n = 496), with relatively few high-grade cases (grade 3: n = 88). Histological analysis identified invasive lobular carcinoma in 131 patients. The median tumor size was 15 mm (interquartile range, 11–22 mm). Accordingly, most patients (n = 773, 87%) were classified as ATX low risk. Patients in the ATX high risk group had lower estimated 5-year probability of meeting the RFI endpoint (0.88, 95% CI = 0.80–0.93) than patients classified as ATX low risk (0.98, 95% CI = 0.96–0.98). When modeled as a continuous variable, ATX demonstrated strong discriminatory performance for recurrence risk (C-index = 0.740, 95% CI, 0.68–0.80) and was associated with a significantly increased hazard of an RFI-contributing event (HR = 2.68, 95% CI, 2.09–3.45; $p < 0.001$). To account for clinical confounding, we fitted a multivariate Cox proportional hazards model adjusting for T stage, N stage, grade, age at diagnosis, adjuvant endocrine therapy, adjuvant chemotherapy, and tumor size. We found that ATX score remained significant (HR = 1.99, 95% CI = 1.38–2.86, $p < 0.001$) and tumor size was the only other variable that was statistically significant ($p < 0.05$). **Conclusions:** ATX accurately prognosticates recurrence risk in a clinically low risk group of HR+/HER2– breast cancer patients from an external validation cohort. Research Sponsor: Ataraxis AI.

Standardized exam-style benchmarking of large language models in breast cancer clinical decision-making.

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Background: Large language models (LLMs) are increasingly used to support clinical reasoning in breast cancer (BC), yet reproducible benchmarking remains limited. In our prior work using complex breast cancer clinical scenarios (BCCS), OpenEvidence (OE) outperformed other LLMs; however, expert Likert-based grading may be influenced by subjective interpretation and human bias. Standardized, board-style multiple-choice questions—required even for expert clinicians—offer an objective framework to assess LLM accuracy and inform readiness for potential clinical decision support. We evaluated the accuracy of four LLMs on a standardized BC question set using binary grading and paired statistical testing. **Methods:** One hundred BC questions reflecting real-world clinical scenarios were submitted to four LLMs: ChatGPT-5.2 (GPT), Google Gemini 3 (Gemini), Claude Sonnet 4.5 (Claude), and OE. Questions were sourced from a hematology–oncology question bank and spanned major BC subtypes and treatment settings. Model responses were graded against bank-designated correct answers using binary scoring (1=correct, 0=incorrect). Overall accuracy with 95% confidence intervals (CI) was calculated. Pairwise comparisons were performed using McNemar’s test. **Results:** One hundred clinical scenarios were evaluated spanning all major BC subtypes and treatment settings, including early-stage and metastatic disease, and neoadjuvant and adjuvant therapy. Overall accuracy was highest for Gemini at 94.0% (95% CI, 87.4–97.8), followed by GPT at 90.0% (95% CI, 82.4–95.1), OE at 90.0% (95% CI, 82.4–95.1), and Claude at 89.0% (95% CI, 81.2–94.4). McNemar’s test showed no statistically significant differences between models. Compared with Gemini, GPT showed 4% lower accuracy ($p=0.289$), Claude 5% lower ($p=0.267$), and OE 4% lower ($p=0.289$). GPT and OE demonstrated equivalent accuracy (both 90.0%) with no significant difference ($p=1.000$). GPT vs Claude differed by 1% ($p=1.000$) and Claude vs OE differed by 1% ($p=1.000$). All models generated clinical reasoning, while OE was the only model providing citations. **Conclusions:** In standardized BC clinical scenarios, four widely used LLMs demonstrated high accuracy with no significant between-model differences. However, no model achieved 100% accuracy, reinforcing the need for ongoing refinement and clinician oversight prior to clinical use. Future studies should expand question volume, evaluate domain-specific error patterns, and incorporate question banks from multiple countries and geographic regions to improve generalizability before real-world clinical deployment. Research Sponsor: None.

Incremental prognostic value of an AI-derived histology signature beyond the 21-gene recurrence score: A prospective-retrospective validation in TAILORx.

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Background: The 21-gene recurrence score (RS) is a foundational tool for risk-stratifying HR+/HER2- early breast cancer (EBC). However, clinical outcomes vary within RS categories. RlapseRisk BC (RR), an AI pathology-based test, integrates features from H&E-stained whole-slide images with clinical data (age, tumor size, nodal status) and was developed using 7 retrospective cohorts totaling 6,039 patients. We evaluated the clinical validity of RR and its histology-only component (RR-H) beyond RS and standard clinicopathologic factors. **Methods:** The clinical validity of RR was established through a validation program of 4 cohorts and over 8,521 patients across diverse geographic regions and laboratory settings. This included 3 international cohorts (n=933) and a prospective-retrospective analysis of the TAILORx trial, where RR-H was evaluable in 7,585 (97.5% of analyzable patients). The primary endpoint was distant recurrence-free interval (DRFI). In TAILORx, we assessed the additive value of the RR-H score to a base model (composed of age, tumor size, histological grade and RS) using Cox proportional hazards models and C-index comparison. **Results:** Across international validation cohorts (median follow-up 7.5 years, 9.8% DRFI events), RR successfully stratified patients (HR=4.91; 95% CI: 3.13-7.71; $p < 0.00001$), and identified a low-risk population with a 97.5% (95% CI: 95.8%-98.5%) 5-year DRFI rate. In the TAILORx population (n=7,584), the RR-H score was a highly significant independent predictor of DRFI. Incorporating RR-H as a continuous variable to the base model (including RS) significantly increased the C-index from 0.6730 to 0.7007 ($p < 0.0001$). The estimated HR for a 1-point difference in RR-H was 1.108 (95% CI: 1.078-1.138; $p < 0.0001$). When analyzed by quartiles, patients in the highest risk group (Q4) exhibited a significantly higher risk of distant recurrence compared to the lowest risk group (Q1) HR= 2.656 (95% CI: 2.003-3.522). Concordance analysis revealed that RR-H is independent of stromal TILs ($R^2=0.01$). While RR-H correlated with increasing histological grade, substantial distribution overlap confirms intra-grade prognostic granularity. Furthermore, RR-H distributions were consistent across ILC and non-ILC. **Conclusions:** RR demonstrated robust and reproducible prognostic value across 8520 patients from diverse populations and settings establishing its clinical validity. Additional findings on TAILORx demonstrate that RR-H provides significant, independent prognostic value that complements existing prognostic tools (including genomic assays and clinicopathological factors), suggesting that integrating AI-pathology can refine precision risk assessment, and thus optimize adjuvant treatment in HR+ HER2- EBC. Research Sponsor: National Cancer Institute; U10CA180820, U10CA180794, UG1CA233329, UG1CA233247; U.S. Postal Service Breast Cancer Stamp Fund; Breast Cancer Research Foundation (USA); CONS-23-007.

Prognostic validation of artificial intelligence (AI)–based Stratipath breast risk stratification in TAILORx.

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Background: Stratipath Breast is an AI-based prognostic medical device for risk stratification of early-stage breast cancer using routine H&E-stained histopathology whole slide images (WSIs). AI-based analyses of histopathology slides offer an alternative to costly and logistically demanding genomic assays. In this study, the prognostic performance of Stratipath Breast was validated in the TAILORx trial (NCT00310180). **Methods:** WSIs from patients enrolled in TAILORx were analyzed by Stratipath Breast. After histopathology quality control and availability of clinical endpoints and WSIs, 5,519 patients were included. Stratipath Breast binary risk category, multi-level risk group, and continuous risk score were evaluated. The prognostic performance was analyzed by Kaplan–Meier statistic and log rank test, as well as concordance index (C-index). Multivariable Cox Proportional Hazard (PH) model adjusting for age, tumor size, histologic subtype and continuous Oncotype DX recurrence score (RS), both without and with histologic grade, was used to assess independent prognostic value. Recurrence-free interval (RFI) and distant recurrence-free interval (DRFI) were evaluated. **Results:** 53.9% (2,975/5,519) of patients were classified as Stratipath low risk and 46.1% (2,544/5,519) as high risk. A significant association of Stratipath risk category and group with RFI and DRFI was confirmed ($p < 0.05$). In multivariable Cox PH analyses, Stratipath high-risk category was an independent prognostic factor associated with worse outcomes (RFI HR = 1.54, 95%CI: 1.29–1.84, $p < 0.05$; DRFI HR = 1.61, 95%CI: 1.30–1.99, $p < 0.05$). Stratipath risk category remained significant in multivariable analysis when histologic grade was included, whereas grade did not. RS remained prognostic significant in multivariable analyses together with Stratipath Breast, indicating potentially complementary prognostic information. C-index improved with inclusion of Stratipath Breast together with clinical variables and RS, exceeding that of grade. **Conclusions:** In the TAILORx trial Stratipath Breast was found to provide significant prognostic value. Stratipath Breast also provided independent prognostic value in multivariable analysis adjusting for standard clinicopathologic factors and RS. These findings support the clinical relevance of AI-driven morphology-based biomarkers for breast cancer risk stratification. Research Sponsor: the National Cancer Institute of the National Institutes of Health; Breast Cancer Research Foundation; The U.S. Postal Service Breast Cancer Stamp Fund.

Deep learning–based classification of benign and malignant breast lesions on ultrasound using knowledge distillation with external validation and global deployment.

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Background: Breast cancer is the most common malignancy in women worldwide. Although breast ultrasonography is widely accessible, diagnostic accuracy remains limited by operator dependence and interobserver variability ($\kappa \approx 0.6-0.8$), contributing to delayed diagnosis and unnecessary biopsies. While deep learning has shown promise in ultrasound-based lesion classification, many models are computationally intensive and lack external validation, limiting clinical scalability. We developed a deployment-ready deep learning framework that balances diagnostic performance with computational efficiency using structured knowledge distillation. **Objectives:** To develop and externally validate a computationally efficient deep learning model for binary breast ultrasound lesion classification; to evaluate whether a distilled student model preserves clinically meaningful performance from a high-capacity teacher network; and to assess global clinical feasibility through independent radiologist evaluation. **Methods:** We analyzed 8,116 breast ultrasound images (4,074 benign; 4,042 malignant) independently annotated by two board-certified radiologists with consensus adjudication. A ResNet34 teacher network (21.8M parameters) was trained using ImageNet-pretrained weights. A lightweight ResNet18 student network (11.7M parameters; 46% reduction) was trained using structured knowledge distillation with confidence-aligned soft targets and KL-divergence regularization. External validation was performed on three independent ultrasound datasets not used during training. Performance metrics included accuracy, sensitivity, specificity, precision, F1 score, and AUROC. The model was deployed in a HIPAA-compliant cross-platform application and independently evaluated by physicians across six continents. **Results:** The student model achieved 91.9% accuracy on held-out test data with balanced performance (sensitivity 90.8%, specificity 93.0%, F1 score 0.918). External validation demonstrated stable generalization (accuracy 89–92%). In global clinical deployment, 94.2% of participating physicians rated the system clinically useful and suitable for integration into routine breast ultrasound workflows. **Conclusions:** Knowledge distillation enables substantial model compression while preserving diagnostic accuracy for breast lesion classification on ultrasound. This scalable, deployment-ready approach supports standardized interpretation across diverse clinical environments and warrants prospective evaluation for reducing unnecessary biopsies and improving diagnostic efficiency. Research Sponsor: None.

Prospective-retrospective HeCOG phase III trial validation of Polaris TME for the prediction of TILs from whole-slide images in high-risk early breast cancer.

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Background: Tumor-infiltrating lymphocytes (TILs) are an established prognostic and predictive biomarker in early breast cancer. However, manual histopathologic scoring can introduce interobserver variability and limit throughput in analyzing at scale in routine practice. Recent advances in artificial intelligence (AI) offer the potential to standardize TILs quantification and enhance reproducibility. Our aim is to evaluate whether deep learning-based tumor microenvironment (TME) quantification from digitized hematoxylin- and eosin (H&E)-stained slides can accurately classify TILs and assess their prognostic role in patients with early breast cancer. **Methods:** We conducted a prospective-retrospective external validation of Polaris TME, a deep learning model for TME quantification. The analysis included patients with high-risk early breast cancer treated with adjuvant contemporary dose-dense chemotherapy, spanning all histological subtypes, enrolled in four HeCOG trials conducted between 1997 and 2008 (3 randomized and 1 observational). Manual TILs scoring had been centrally performed by pathologists according to International TILs Working Group guidelines, enabling direct comparison between manual and AI-derived scoring. The Polaris foundation model was used for feature extraction, while model performance was assessed using correlation for continuous TILs scores using the Spearman ρ and discrimination for clinically defined TILs categories (thresholds: 5% and 50% using the Area Under the Curve (AUC) with 95% CI. The prognostic value of the model was assessed using the log-rank test for invasive disease-free survival (iDFS). **Results:** Overall, 1,214 patients with whole slide images, TILs quantification and follow-up data were included; median age 53 [22–79]; 638 (63%) were hormone receptor-positive/HER2-negative, 394 (32%) HER2-positive, 176 (14%) triple-negative breast cancer (TNBC), and 6 patients of unknown subtype. Median follow-up was 116.59 (53.45 –157.06) months. When blindly deployed on the external cohorts, the model showed a significant correlation with the manual TILs scoring ($\rho=0.60$, $p<0.001$). The model yielded an AUC of 0.78 (0.75–0.81) for $>5\%$ TILs and AUC of 0.92 (0.88–0.95) for the $>50\%$ TILs. Predicted low-TILs tumors were associated with significantly lower 10-year iDFS in TNBC (55.1% versus 70.9%, $p=0.034$), with a similar pattern observed in HER2-positive (55.3% versus 64.8%, $p=0.096$), whereas there was no difference in 10-year iDFS between the predicted TILs groups for luminal cancers. **Conclusions:** These results indicate that Polaris TME accurately quantifies TILs derived from digitized H&E slides and provides prognostic measure for long-term iDFS in high-risk early breast cancer. Prospective validation and harmonization efforts to facilitate clinical implementation are warranted. Research Sponsor: None.

AI-driven risk stratification for distant recurrence in node-positive HR+/HER2—early breast cancer: Independent validation in the NSABP B-28 trial.

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Background: Accurate prediction of risk of distant recurrence (DR) in HR+, HER2-negative early-stage breast cancer (EBC) is important for optimizing adjuvant therapy decisions, including treatment escalation with CDK4/6 inhibitors (CDK4/6i). Current guidelines recommend consideration of CDK4/6i for node-positive, clinically high-risk EBC, including N1 patients. However, it is not known which patients will benefit, and guideline recommendations suggest that the risks may outweigh benefits for patients with low risk of distant recurrence. Identification of these patients will help prevent over-treatment. RlapsRisk BC (RR) is an AI pathology-based test that integrates features from H&E-stained whole-slide images with clinicopathologic data (age, tumor size, nodal status) to assess risk of distant recurrence in HR+, HER2-negative EBC. The RR model was previously developed and validated using 7 retrospective cohorts totaling 6,039 patients. Here we report validation of RR in the NSABP B-28 cohort of HR+ HER2-negative N+ patients who received post-operative chemoendocrine therapy. **Methods:** This blinded independent validation study of the pre-specified RR included a subset of NSABP B-28 patients with HR+ and HER2-negative EBC (n=731) and digitized whole slide images from primary tumors. The primary endpoint was distant recurrence-free interval (DRFI). The objective was to validate the prognostic utility of RR score for DR. Univariable and multivariable Cox models were performed. **Results:** The evaluable cohort had a median follow-up of 11.1 years and included 504 (69%) patients with N1 disease, 87% grade 2/3 tumors, and a median tumor size of 21mm. Across the entire cohort, RR classified 58% of patients as low-risk and 42% as high-risk. RR (high vs low) was significantly associated with DRFI: HR=3.1 (95% CI: 2.3-4.3; $p < .001$). Estimated 10-year DR-free was 87.5% (95% CI: 83.9-90.4%) for low-risk vs. 65.0% (95% CI: 59.1-70.2%) for high-risk patients. In a multivariable Cox model, the histology-only score remained significant after adjusting for clinicopathologic data: HR=1.6 (95% CI: 1.4-1.9; $p < .001$). In the N1 subgroup, RR identified 65.7% of patients as low-risk with an estimated 10-year DR-free of 90.6% (95% CI: 86.9-93.4%), compared to 69.8% (95% CI: 62.2-76.2%) for high-risk. **Conclusions:** RR demonstrates robust prognostic performance in clinically high-risk N+, HR+, HER2-negative EBC patients from the NSABP-28 trial, in which the majority of patients had N1 disease. Our results demonstrate that approximately two-thirds of N1 patients, identified as low-risk by RR, exhibited favorable long-term outcomes with standard chemoendocrine therapies alone. As the clinical landscape shifts toward broader CDK4/6i use, RR could be used to identify N1 patients for whom the benefit of treatment intensification may be minimal. Research Sponsor: None.

Prognostic performance of a multimodal artificial intelligence histopathology-based tool versus the 21-gene recurrence score in early-stage breast cancer.

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Background: Genomic classifiers are widely used to assess risk of distant metastasis (DM) and inform chemotherapy (CT) benefit in patients with HR+/HER2- early breast cancer (EBC). While clinically validated, these assays are associated with high cost, long turnaround time, and tissue consumption. This study evaluates the performance of a histopathology based multimodal AI (MMAI) model in real-world institutional cohorts and compares its prognostic performance with the 21-gene recurrence score (RS). **Methods:** We conducted a retrospective analysis of 307 de-identified patients with node-negative HR+/HER2- EBC. Patients were treated at two institutions: Hoag Health System (n = 62) and the University of Virginia (n = 245). Median follow-up was 9.5 years. MMAI risk classifications (low vs. high) were compared to RS risk groups as defined in the TAILORx study (RS 0-10 (low), RS 11-25 (intermediate), RS $\geq$ 26 (high)). The endpoint was time to DM and was analyzed using Kaplan-Meier (KM) methods and Cox proportional hazards models, including univariable (UVA) and multivariable analyses (MVA) adjusting for clinicopathologic factors. **Results:** In this study, 64% of patients were classified as MMAI low risk and 36% as MMAI high risk. The majority of patients received endocrine therapy alone (86% with low RS and 77% with intermediate RS), while 79% of patients in the high RS group were treated with CT. KM analyses demonstrated significantly lower 10-year DM rates for patients classified as MMAI low risk (1.6%, 95% CI: 0.4%-6.8%) compared with patients classified as MMAI high risk (10.8%, 95% CI: 5.5%-20.6%). Among patients with low RS, the MMAI model classified 84% as low risk, with no DM events observed in this group. In contrast, 16% of patients classified as MMAI high risk within the RS low group experienced a 10-year DM rate of 20% (95% CI: 5.4%-60.0%). MMAI further stratified intermediate RS patients into distinct risk groups: 66% were classified as MMAI low risk and 34% as MMAI high risk, with 10-year DM rates of 2.6% (95% CI: 0.6%-10.9%) and 11.4% (95% CI: 4.5%-27.2%) respectively. In UVA analysis of the intermediate RS group, MMAI high risk classification was associated with DM risk (hazard ratio (HR) of 4.2 (95% CI: 1.1-16.1, p = 0.03). In MVA, adjusting for RS groups, adjuvant systemic therapy, and age, MMAI remained independently associated with DM risk (HR = 5.8, 95% CI: 1.7-19.8, p = 0.005). **Conclusions:** MMAI demonstrated prognostic risk stratification within RS groups, particularly among intermediate RS. Concordance between MMAI low risk and favorable outcomes among patients with low RS suggests MMAI may identify patients with low risk of DM without requiring additional tissue consumption. Further studies are needed to evaluate outcomes among MMAI risk groups within high RS to define the optimal clinical integration of MMAI with existing genomic assays. Research Sponsor: ArteraAI.

Prognostic value of an MRI-derived recurrence assay in women with hormone receptor-positive, HER2-negative breast cancer: A retrospective, multi-center analysis.

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Background: Patients (pts) with early stage hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer (BC) remain at both short and long term risk of recurrence. While clinico-pathological and gene-based biomarkers provide insight into early and late recurrence risk, additional prognostic tools are needed. We previously developed (Saha et al. *Clin Cancer Res*, 2025) a new breast MRI image-based artificial intelligence prognostic tool (TumorSight Risk) composed of both radiographic and clinical information. Here we sought to validate this tool in an independent cohort. **Methods:** In this multi-center, blinded, prospective/retrospective validation study, we sought to validate the 5-year recurrence-free survival (RFS) according to pre-defined risk scores (0-100) and categories ("high" or "low") via pre-specified cutoff (≥ 47) for pts with HR+/HER2- BC. Kaplan-Meier and Cox regression analyses were then used to assess the unadjusted and adjusted association between risk category/score and the 5-year RFS. **Results:** 2,129 pts with HR+/HER2- BC diagnosed between January 1, 2010, and December 31, 2024, who underwent breast MRI prior to surgery (no neoadjuvant therapy) were included from four institutions. Median age was 57 years, 16% were Black, 15% had grade 3 disease, 93% were clinical T1 or T2, and 85%/15% were clinical No/N1. At a median follow up of 6.24 years, the unadjusted hazard ratio (HR) for RFS comparing low (n=1808) and high risk (n=321) pts was 2.71 (95% CI = 1.95 – 3.76, $p = 3 \times 10^{-9}$). The estimated 5 year RFS rate according to risk score (low and high) was 95.5% (95% CI: 94.63 – 96.3%) and 89.6% (95% CI = 86.4 – 92.6%) while the 10 year RFS estimates were 88.9% (95% CI = 86.5 – 90.9%) and 69.6% (95% CI = 59.1 – 77.9%). Univariate subgroup analysis demonstrated that the risk score was prognostic by age (< 50 vs. ≥ 50 years), pathologic nodal status, grade, and surgery type, regardless of chemo-, endocrine, or radiation therapy administration. The observed continuous risk score was strongly associated with risk of recurrence, with a 22% increase in relative risk per 10-unit change in risk score (0-100), translating to a 2.4% (95% CI = 1.2 – 4.5%) and 25.5% (95% CI = 15.4 – 40.4%) risk of recurrence at 5-years for pts at the lowest (0-9) versus highest (90-100) risk score. The prognostic association between risk score and RFS remained after adjusting for pathologic T- and N-stage, grade, age, race, and treatment ($p = 0.002$). **Conclusions:** TumorSight Risk is a new image-based biomarker for HR+/HER2- BC that provides prognostic information independent of standard clinico-pathological parameters. Given the ready availability of breast MRI in most pts with BC, TumorSight Risk may be a convenient tool for estimating risk for recurrence. Research Sponsor: SimBioSys, Inc.

Association of the 70-gene assay and homologous recombination deficiency in patients with high risk 2 breast cancers.

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Background: Homologous recombination deficiency (HRD) is a biomarker for impaired DNA repair proficiency and genomic instability, associated with sensitivity to DNA-damaging agents. MammaPrint (MP), a 70-gene assay, stratifies early breast cancer (EBC) by UltraLow, Low, High Risk 1 (H1) or High Risk 2 (H2) of recurrence. Compared to patients (pts) with H1 tumors, pts with H2 tumors derive greater benefit from anthracycline-based chemotherapy. Here we analyze HRD signatures to assess whether MP gene expression profiling may detect pathway activity in H2 tumors indicating DNA repair deficiency. **Methods:** We analyzed tumors from pts enrolled in the FLEX study who consented to full transcriptome and clinical data collection, with available MP and Blueprint (BP; Luminal or Basal) results (N=1298). HRD status assessed using a 228-gene signature was further refined into a 26-gene panel (Jacobson et al., 2023). The R-package Limma was used to preprocess gene expression data. For each gene, the median expression value of probes mapping to the gene was calculated. Differences in HRD scores were compared across MP and BP groups using a t-test. **Results:** Pts with HR+HER2- EBC HRD scores differed significantly by both MP and BP. Using the 228-gene HRD signature, H2 tumors were associated with higher HRD compared with H1 cancers ($p < 0.001$). Luminal H2 tumors were also associated with higher HRD scores than Luminal H1 tumors ($p < 0.001$). Basal tumors were associated with higher HRD compared with Luminal tumors within both H1 and H2 (Luminal H1 vs Basal H1 and Luminal H2 vs Basal H2; both $p < 0.001$), and Basal H2 tumors had higher HRD scores than Basal H1 tumors ($p < 0.001$). Similar patterns were observed within the 26-gene HRD panel. H2 tumors were associated with higher scores than MP H1 tumors ($p < 0.001$), and Luminal H2 tumors were associated with higher scores than Luminal H1 tumors ($p < 0.001$). Basal tumors were associated with higher HRD than Luminal tumors within both MP risk groups (Luminal H1 vs Basal H1, $p = 0.002$; Luminal H2 vs Basal H2, $p < 0.001$). Basal H2 tumors demonstrated numerically higher scores than Basal H1 tumors using the 26-gene panel, but did not reach statistical significance ($p = 0.062$). **Conclusions:** In this real-world analysis, MP and BP identified differences in underlying HRD biology, with H2 tumors enriched for HRD and Luminal H1 tumors demonstrating relative homologous recombination proficiency. These findings may provide a biological rationale for the anthracycline chemotherapy and immunotherapy benefit observed in pts with H2 tumors and further evidence for MP as a tool for refined therapy selection. Additional research is warranted to examine MP as a biomarker for HRD-sensitive therapies such as PARP inhibitors and carboplatin. These results further highlight biological diversity within genomically high-risk tumors, uniquely detected by MP and BP. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

Predicting recurrence and survival in hormone receptor–positive (HR+)/HER2–negative (HER2–) early breast cancer (EBC) with machine learning models: Optimization of model complexity.

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Background: A machine learning model was previously developed to predict distant recurrence (DR) in endocrine therapy–treated patients with HR+/HER2– EBC, with high accuracy achieved using 10 variables (Howard FM, et al. *Clin Cancer Res.* 2026). Here, optimal performance, based on the number and identity of variables, of recurrence models that include survival events (distant relapse–free survival [DRFS], overall survival [OS]) was determined. **Methods:** Retrospective data from patients with stage I–III HR+/HER2– EBC (diagnosed 1 January 2011 to 30 April 2024) were extracted from the Flatiron Health US electronic health record–derived database. Elastic net–penalized Cox proportional hazards–based machine learning models were developed with 2, 5, 10, 15, or 20 variables identified by gradient boosting to predict DR, DRFS, and OS; DRFS was defined according to STEEP criteria v2.0. Model performance was assessed using the C-index and Brier score (BS). **Results:** With modeling based on 7842 patients, DR prediction accuracy plateaued (C-index, 0.857; BS, 0.046) (Table) with 10 variables (N status, T status, tumor grade, Ki-67 score, age, time from diagnosis to surgery, percent estrogen receptor–positive cells, menopausal status [post-], Oncotype DX Recurrence Score, and percent progesterone receptor–positive cells). The DRFS (C-index, 0.740; BS, 0.089) and OS (C-index, 0.781; BS, 0.075) prediction models showed high accuracy with 5 to 10 variables, and accuracy continued to increase with up to 20 variables. In contrast to the DR prediction model, the DRFS and OS prediction models included functional status (ie, Eastern Cooperative Oncology Group performance status, Charlson Comorbidity Index) among the most impactful variables. **Conclusions:** DR model performance plateaued with 10 tumor–intrinsic variables. In contrast, optimal DRFS and OS prediction required expanding the model to 20 variables, including functional and comorbidity domains necessary to capture non-cancer competing risks critical for survival prediction in real-world populations, despite the modest statistical impact. The machine learning model for predicting DR, a reliable proxy for survival in HR+/HER2– EBC, is based on a lower number of risk factors that are commonly accessible in real-world clinics and has good accuracy. Research Sponsor: Novartis Pharmaceuticals Corporation.

Model performance by outcome and number of variables.						
No. of variables	DR (C-index ^a)	DR (BS ^b)	DRFS (C-index ^a)	DRFS (BS ^b)	OS (C-index ^a)	OS (BS ^b)
2	0.812	0.044	0.667	0.093	0.611	0.081
5	0.849	0.046	0.718	0.092	0.770	0.075
10	0.857	0.046	0.736	0.089	0.774	0.075
15	0.858	0.046	0.737	0.089	0.776	0.076
20	0.851	0.047	0.740	0.089	0.781	0.075

^aConcordance index; scores span from 0.5 to 1; 1 = perfect.
^bBrier score; scores span from 0 to 0.25; 0 = perfect.

Gut microbiome characteristics in patients with hormone receptor–positive (HR+) HER2– breast cancer treated with adjuvant abemaciclib: Biomarker analysis of the TRADE trial.

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Background: Adjuvant abemaciclib reduces recurrence risk and improves overall survival in patients with high-risk node-positive early HR+/HER2– breast cancer. However, treatment-emergent diarrhea may lead to dose modifications, treatment discontinuation, and impaired quality of life. The gut microbiome influences treatment response and toxicity across multiple cancer therapies; its role in abemaciclib-associated diarrhea remains undefined. We evaluated features of the gut microbiome during the initiation of adjuvant abemaciclib and any association with diarrhea. **Methods:** 90 patients with HR+/HER2– early breast cancer enrolled in the TRADE trial (NCT06001762) and were treated with dose-escalated adjuvant abemaciclib (50 mg BID x 14 days, then 100 mg BID x 14 days, then 150 mg BID onwards) plus endocrine therapy. Stool samples were collected at baseline, cycle 2 day 1 (C2D1), and end of treatment (EOT). Whole-genome shotgun metagenomic sequencing was performed, and species-level profiles were generated using MetaPhlAn4. Diarrhea was analyzed as a binary outcome (ever vs none). Associations between microbiome features and clinical variables were evaluated using linear mixed modeling with a random effect for repeated samples from the same individual (alpha diversity) or per-timepoint using PERMANOVA (beta diversity) and MaAsLin3 (species and genes, with false discovery rate correction). Models were adjusted for age, cancer stage, and type of endocrine therapy. **Results:** A total of 142 samples were analyzed (77 baseline, 58 C2D1, and 7 EOT; 77 total subjects, 28 with diarrhea, 49 without). Treatment was associated with a consistent microbiome shift from baseline to C2D1, characterized by a decline in alpha diversity (-0.26 , 95% CI -0.39 to -0.14 , $p < 0.001$) and a phylum-level shift with increased Bacteroidota and decreased Firmicutes abundance ($p < 0.002$ and $p = 0.001$, respectively, paired T-test). When assessing by timepoint, having any-grade diarrhea was not associated with differences in beta diversity or alpha diversity, nor with individual microbial species; pathway-level enrichment suggested diarrhea-associated functional trends that did not meet FDR significance. Limited EOT samples suggested partial recovery following treatment. **Conclusions:** Adjuvant abemaciclib induced consistent, treatment-related shifts in gut microbiome composition, characterized by reduced diversity and a phylum-level shift from Firmicutes to Bacteroidota, suggesting an early broad ecological treatment effect from exposure to a CDK4/6 inhibitor. This pattern has been reported in patients with inflammatory bowel disease. A species-specific diarrhea signature or predictive relationship between microbiome signature and the development of diarrhea was not observed. Further evaluation of the microbiome's evolution at EOT is ongoing. Clinical trial information: NCT06001762. Research Sponsor: Eli Lilly.

Distinct late recurrence patterns and immune landscape of HER2-positive invasive lobular carcinoma (ILC): Analysis of NCCTG N9831 (Alliance) trial and real-world cohort.

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Background: HER2+ ILC is rare (~5% of ILC), with limited data on long-term adjuvant trastuzumab outcomes. We investigated late recurrence and immune landscapes of HER2+ ILC vs invasive ductal carcinoma (IDC) in the phase III NCCTG N9831 trial (NCT00005970) and a real-world cohort. **Methods:** We evaluated 3304 early-stage HER2+ breast cancer patients (pts) enrolled in N9831 (122 ILC, 3182 IDC). Recurrence-free survival (RFS) and overall survival (OS) were estimated (Kaplan-Meier) and compared using multivariable Cox regression adjusting for age, tumor size, grade, hormone receptor (HR), and nodal status. Findings were validated in a real-world cohort of HER2+ pts (Caris Life Sciences CODEai platform). Immune microenvironments were profiled by WTS deconvolution (Quantiseq). Real-world overall survival was calculated from trastuzumab start to last contact. **Results:** In N9831, ILC pts were older (median 54 vs 49 y), more ER+ (74.6% vs 51.4%), and had more N3 disease (25.4% vs 12.7%) compared to IDC. ILC pts derived a comparable magnitude of benefit from adjuvant trastuzumab compared to the overall population (HR 0.58 vs 0.67). However, long-term outcomes diverged: while the 5-year RFS was similar (77.1% vs 82.7%), ILC pts experienced a steep decline between years 5–15 (77.1% to 57.7%; ~20% decline) vs IDC (82.7% to 72.7%; ~10% decline) after multivariable Cox analysis (Table). In the real-world early/advanced cohort (n=1328; 26 ILC vs 1302 non-ILC [subset IDC n=595]) treated with trastuzumab-based therapy, ILC pts had worse mOS (33.7 vs 68.6 m, HR 2.01, 95%CI 1.00–4.07, p=0.04) compared to non-ILC. However, there was no statistically significant difference when compared specifically to IDC (HR 1.77, 95% CI 0.87–3.61, p=0.11). ILC had: i) numerically lower tumor mutation burden (TMB)–high (4.2% vs 9.5%, p=0.38); ii) higher infiltration of B cells, Tregs, and M2 macrophages (p<0.05); iii) upregulated MHC class II expression (HLA-DOA, p<0.05); and iv) downregulated proliferative and DNA repair pathways (E2F, G2M, MYC; FDR <0.25) compared to non-ILC. **Conclusions:** HER2+ ILC carries late recurrence risk despite initial trastuzumab benefit. The unique immune landscape (Treg/M2 macrophage enrichment and lower proliferative signatures) distinguishes HER2+ ILC from IDC, highlighting the need for tailored strategies. Research Sponsor: National Institutes of Health (NIH) / National Cancer Institute (NCI); U10CA180821, U10CA180882; Alliance for Clinical Trials in Oncology.

Long-term RFS and OS in HER2-positive ILC vs IDC (N9831 trial).

Population	N	5-year% (95% CI)	10-year% (95% CI)	15-year% (95% CI)
ILC	122	RFS 77.13% (69.9, 85.1) OS 84.04% (77.7, 90.9)	RFS 70.57% (62.7, 79.4) OS 76.0% (68.7, 84.2)	RFS 57.67% (44.2, 75.1) OS 65.22% (56.6, 75.2)
IDC	3182	RFS 82.71% (81.4, 84.1) OS 90.18% (89.1, 91.2)	RFS 77.45% (75.9, 78.9) OS 81.81% (80.4, 83.2)	RFS 72.68% (70.77, 74.6) OS 76.68% (75, 78.4)

Association of patient-reported stress and depression symptoms with ER-specific tumor transcriptional signatures in breast cancer (BC).

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Background: Psychological distress is common among women with BC, yet tumor-level biological correlates remain poorly defined. We used tumor transcriptomics to identify pathways associated with patient-reported stress and depression symptoms. **Methods:** RNA sequencing was conducted on FFPE tumor samples in 195 women with stage I-III BC (152 ER+, 43 ER-) from the Women's Health after Breast Cancer cohort. At diagnosis, participants completed Perceived Stress Scale (PSS-10) and Center for Epidemiologic Studies Depression (CES-D) Scale. High-low stress (PSS-10 >14 vs 0-14) and high-low somatic symptoms (CES-D somatic > 3 vs ≤ 3) were defined. Differential expression and gene-set enrichment analyses compared high-stress/low-somatic-symptom (HS/LSS) and low-stress/high-somatic-symptom (LS/HSS) groups with low-stress/low-somatic-symptom controls, stratified by estrogen receptor (ER) status, adjusted for age and education. Caris Life Sciences CODEai evaluated overall survival (OS) from tissue collection to last contact. **Results:** In ER+ BC, HS/LSS showed increased humoral-immune activity and checkpoint signatures, with reduced neuroendocrine activation. LS/HSS enriched for a neuroendocrine state, ribosome biogenesis, immune and cell-cycle pathways, with loss of epithelial regulatory programs. In ER- BC, HS/LSS showed growth-factor-driven proliferation with reduced epithelial differentiation and greater immune-checkpoint engagement. LS/HSS exhibited metabolic-stress features with loss of epithelial/immune programs and increased keratinization, consistent with impaired antigen presentation and altered differentiation. Table outlines key up- and down-regulated signatures. Using CODEai, in ER+ (n=11309), higher *PHOX2A* (41 m vs 38.4 m) and *TDGF1* (42 m vs 37.4 m), and in ER- (n=6402), higher *SCL5A11* (24 m vs 20.7 m) and *KRT40* (23.5 m vs 21.1 m) were associated with better OS, all $p < 0.01$. **Conclusions:** Patient-reported stress and depressive somatic symptoms map to distinct ER-specific tumor transcriptional signatures involving immune regulation, proliferation, metabolism and differentiation. Concordant survival associations support potential clinical relevance and warrant validation to identify actionable targets. Research Sponsor: NIH/NCI and NIH/NCATS; R03TR004607.

			ER+	ER-
HS/LSS	Genes (log ₂ FC)	Up	<i>IGLV3-16</i> (3.3), <i>IGHV3-30</i> (2.5)	<i>IGF2</i> (4.2)
		Down	<i>CHGA</i> (-21.5)	<i>KRT40</i> (-18.4), <i>PADI3</i> (-24.1)
LS/HSS	Pathways (NES)		Fcγ-receptor (2.7), B-cell receptor (BCR) (2.7), PD-1 co-inhibition (2.1)	PD-1 co-inhibition (2.4), MHC-I (2.1), ribosome (-2.1)
	Genes (log ₂ FC)	Up	<i>PCSK1</i> (4.0)	<i>IGFBP1</i> (7.6), <i>HSD11B1</i> (4.6), <i>OSGIN2</i> (3.0)
LS/HSS		Down	<i>PHOX2A</i> (-6.0), <i>TDGF1</i> (-5.4)	<i>IGHV7-41</i> (-18.9), <i>MUC2</i> (-21.5), <i>SCL5A11</i> (-21.1), <i>PADI3</i> (-22.3)
	Pathways (NES)		Ribosome biogenesis (3.1), IFNα (2.7), G1/S (2.7), G2/M (2.6), BCR (2.6)	Keratinization (2.7), cornified envelope (2.3), antigen presentation (-1.8), G1/S (-1.7)

Shared and distinct molecular signatures of resistance to different endocrine therapies (Alliance A011106).

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Background: Endocrine therapy (ET) resistance (ETR) remains a primary challenge in ER+ breast cancer. Analyzing pretreatment tumor transcriptomes across trials with early response endpoints can reveal shared and specific ETR signatures. This study utilizes baseline RNA data from the Phase III ALTERNATE trial (Alliance A011106, NCT01953588; Anastrozole [A], Fulvestrant [F], or AF) and the ACOSOG Z1031B trial (NCT00824941) to identify predictors of early Ki67 response in postmenopausal ER+/HER2- patients. **Methods:** ETR was defined as week-4 on-treatment Ki67 >10%. Baseline gene expression from ALTERNATE was analyzed to identify differentially expressed (DE) genes (Wilcoxon test, $P < 0.05$) and Hallmark pathways associated with ETR, both across and within individual treatment arms. Feature selection was performed using mixOmics. A Pan-Endocrine Therapy Signature (PETS) was developed by uniting DE genes identified across all three ALTERNATE arms and Z1031B. All statistical analyses were conducted in R ($P < 0.05$). **Results:** Overall ETR rate in the ALTERNATE RNA-seq cohort ($n=733$) was 26%. ETR was associated with high Risk of Recurrence (ROR), Oncotype RS, and Mammaprint scores (calculated from RNA-seq data in research setting). In luminal tumors ($n=649$), ETR was linked to chr 3q13.33, 8q24.13, and 20q13.12 cytoband upregulation and 17q21, 18q23, 3p21.1, and 10q24.32 cytoband downregulation. ETR tumors showed T-cell, E2F target, and interferon- γ enrichment; sensitive tumors favored early estrogen response and muscle differentiation. At individual gene level, high *MYBL2*, *PIF1*, *TROAP* and with low *HJURP* predicted ETR across all samples ($AUC > 0.70$). A deep learning model using all protein-coding genes achieved AUC 0.82 (training) and 0.79 (test) in predicting ETR. Cross-trial integration identified ETR-associated PETS, enriched for genomic instability. PETS performed comparably to established signatures and strongly correlated with *MYBL2* signature ($r=0.93$). Top ETR predictors were *MYBL2*, *AURKB*, and *EME1* for Arm A and *IL4I1*, *TNFAIP6*, and *ANLN* for Arm AF. AF-resistant tumors were enriched for systemic lupus and RIG-I-like receptor signaling; sensitive tumors favored PI3K-AKT, EGFR TKI resistance, AMPK, and insulin signaling. **Conclusions:** Baseline transcriptomics identify shared and therapy-specific ETR markers. The 15-gene PETS defines a convergent resistance signature, performing similar to established signatures in predicting ETR and correlating with *MYBL2*. Enrichment of cell-cycle and immune pathways in resistant tumors may suggest patient stratification approach for alternative or combinatorial strategies to overcome early ETR in ER+ breast cancer. **Acknowledgement:** <https://acknowledgments.alliancefound.org>. **Support:** U10CA180821, U10CA180882, U24CA1. **Clinical trial information:** NCT01953588. **Research Sponsor:** U.S. National Institutes of Health; U10CA180821, U10CA180882, U24CA196171; Susan G Komen; BCRF; AstraZeneca.

Spatial interactions between immune cells as a predictor of pCR to neoadjuvant chemotherapy (NACT) and nivolumab for ER+/HER2– breast cancer (BC): Analysis of the phase II GIADA trial.

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Background: Adding an immune checkpoint inhibitor (ICI) to NACT increases pathological complete response (pCR) rates in ER+/HER2– high-risk BC, at the cost of immune-related toxicity. Biomarkers are needed to improve patient (pts) selection. We here assess the association between immune cell spatial interactions and pCR in the GIADA trial (Dieci, CCR 2022). **Methods:** In the phase II GIADA trial, 43 premenopausal pts with stage II–IIIA ER+/HER2– Luminal B-like BC (Ki67 $\geq$ 20% and/or G3) received NACT with ECx3 followed by nivolumab (240mg q2w x8) and endocrine treatment. Tumor biopsies at baseline (T0) and after EC (T1) were assessed using multiplex immunofluorescence panels: (1) CD4, CD8, Granzyme B, FoxP3, CD20, pan-cytokeratin (CK), and DAPI; (2) CD3, CD68, CD163, PD-1, PD-L1, CK, and DAPI. Interactions were quantified using a count-within approach. The number of reference immune cells located in a ≤ 20 μ m radius of cells with a different phenotype (high probability of cell-cell contact) was calculated and normalized to number of reference cells. Association with pCR was assessed by binomial generalized linear models. **Results:** At baseline (T0), spatial interaction of tumor cells (CK+) with multiple immune cells (CD4+, CD8+, FOXP3+, CD68+), including cytotoxic, immunosuppressive and macrophagic subpopulations, was associated with pCR. Moreover, interaction of cytotoxic CD8+GranzymeB+ T-cells with regulatory FOXP3+ cells was associated with pCR. Interactions between PD-1+ and PD-L1+ cells were associated with pCR, mainly CK+PD-L1+/CD3+PD-1+ in tumor area and CD3+PD-1+/CD68+PD-L1+ in stroma. After chemotherapy (T1), only spatial interactions between tumor cells and CD8+ and CD4+ T-cells were associated with pCR. The role of cytotoxic CD8+GranzymeB+ T-cells appeared stronger as interactions with multiple immune subpopulations (CD4+, CD8+, CD8+GranzymeB+, FOXP3+, CD20+) were associated with pCR, overall (OR 1.06–1.73) and in stroma (OR 1.06–1.40). Interaction of CK+ tumor cells with PD-1+ cells in the tumor area and with CD68+ PD-L1+ macrophages in the stromal area was associated with pCR. **Conclusions:** Spatial immune profiling identifies distinct tumor-immune interaction patterns associated with pCR in high-risk ER+/HER2– BC treated with NACT and ICI. Clinical trial information: NCT04659551. Research Sponsor: Bristol Myers Squibb; Fondazione AIRC; 22759; Veneto Institute of Oncology IOV-IRCCS; NA.

Selected spatial interactions significantly associated with pCR.

	T0 overall	T0 tumor	T0 stroma	T1 overall	T1 tumor	T1 stroma
CK+ / CD4+	OR 1.08, p=0.034	OR 1.13, p=0.017		OR 1.07, p=0.038		
CK+ / CD8+	OR 1.21, p=0.005	OR 1.34, p=0.005	OR 1.06, p=0.049	OR 1.12, p=0.008	OR 1.16, p=0.021	OR 1.08, p=0.011
CK+ / FOXP3+	OR 1.21, p=0.017	OR 1.28, p=0.024				
CK+ / CD68+	OR 1.07, p=0.016		OR 1.09, p=0.007			
CK+PD-L1+ / CD3+PD-1+		OR 1.22, p=0.025				
CD3+PD-1+ / CD68+PD-L1+			OR 1.08, p=0.047			
CK+ / PD-1+ cells			OR 1.13, p=0.027	OR 1.27, p=0.015	OR 1.29, p=0.027	
CK+ / CD68+PD-L1+			OR 1.21, p=0.036			OR 1.44, p=0.030

Characteristics of cancer patients undergoing molecular residual disease testing with a tumor-informed assay.

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Background: Detection of circulating tumor DNA (ctDNA) is strongly associated with recurrence across a variety of cancers. The use of ctDNA testing to measure molecular residual disease (MRD) is still in its infancy, and understanding sample characteristics may help set expectations for oncologists and their patients. **Methods:** For the first thousand patients with MRD testing in Exact Sciences' commercial laboratory, the tumor and first plasma sample were used to record tumor type, tumor sample type (biopsy/surgical), tumor stage, MRD assay panel size (up to 200 variants), cfDNA levels, and ctDNA status (qualitative and quantitative), and, when data were available, presence of targetable alterations (TAs) were recorded. **Results:** A total of 1088 samples with valid results were included. Patients were mostly female (N=703, 64.6%) with a median age of 64 (range 17–97) years, and most had either breast (N=380, 34.9%) or colorectal (N=335, 30.8%) cancer. Most (N=632, 58.1%) tumor samples were surgical, and average number of variants for MRD assays from 86 in ovarian cancer to 189 in melanoma. Plasma cfDNA yield ranged from 15 ng (the minimum required) to 10,709 ng and was significantly higher in 412 ctDNA+ (median 86.1 ng, mean 239.7 ng) compared to ctDNA– (median 73.5 ng, mean 114.6 ng) samples ($p<0.001$). In 13 cancers with at least 10 patient samples, only breast cancer showed a difference in the average number of identified variants between sample types (biopsy: 129.1 versus surgical: 101.5), stage IV cancers had more cfDNA than stage I, range of ctDNA+ samples was from 27% in melanoma to 65% in gastroesophageal cancers, and ctDNA+ proportion tended to increase with stage: 26 (14.2%) of 183 stage I, 84 (32.1%) of 262 stage II, 140 (38.9%) of 360 stage III, and 140 (65.1%) of 215 stage IV. ctDNA+ samples had levels between 2.6 and $\geq 352,000$ parts per million (PPM), with 27 (6.6%) samples below 15 PPM, 40 (9.7%) between 15 and 50 PPM, and 345 (83.7%) above 50 PPM. Genomic profiling was performed on 158 samples, most from breast (N=50, 31.6%) and colorectal (N=17, 10.8%) cancer patients. The mean number of TAs per sample was 4.6, with little difference between the 114 ctDNA+ patients (mean = 4.4, range 0–24) and 44 ctDNA– patients (mean = 5.1, range 1–29). TAs were present in 83 (72.8%) and 36 (81.8%) tumors in ctDNA+ and ctDNA– patients, respectively. Of note, both high microsatellite instability and high tumor mutational burden tumors had numerically higher proportion in ctDNA– (15.9% and 9.1%, respectively) compared to ctDNA+ (5.3% in both) patients. **Conclusions:** ctDNA+ frequency varied by cancer type and cfDNA yields and ctDNA+ proportion increased numerically with stage, though where patients were in their treatment cycles was unknown. Of patients with profiling results, a large proportion of patients had TAs regardless of ctDNA status, indicating a potential for immediate consideration of matched therapies in ctDNA+ patients. Research Sponsor: Exact Sciences.

mTOR activation and racial disparity in early breast cancer survival.

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Background: Black women have lower survival rates following a diagnosis of estrogen receptor-positive (ER+) early breast cancer (EBC) compared with White women, with 80% higher mortality and more frequent genomically high-risk tumors (Hoskins et al, JAMA Oncol, 2021). A whole-transcriptome comparison of 412 luminal tumors from Black women with EBC and age-matched White women showed increased mTOR signaling in tumors from Black patients (Hoskins et al. J Clin Oncol 2021, 39:15_suppl, 1009-1009), suggesting a molecular driver of the survival disparity. This study aimed to confirm increased mTOR pathway activation at the protein level in Black patients with an independent cohort, and to explore factors responsible for racial differences in luminal tumor biology. **Methods:** A breast tumor tissue microarray (TMA) comprising primary tumor cores from diverse patients with EBC was analyzed with multiplex immunofluorescence staining to quantify protein markers of mTOR pathway activation (pS6K and pAkt). Image segmentation was performed with pan-cytokeratin staining to delineate tumor cells from stromal cells. Halo HighPlex image analysis software was used for automated digital image analysis to calculate an H-score for each tumor core. Ancestry admixture analysis was performed with ancestry informative markers that are located within coding regions of genes using RNAseq data generated from tumors represented on the TMA. Data on contextual factors was obtained by geocoding patients' residential address at the time of diagnosis and linking to a census tract-level measure of neighborhood disadvantage (Area Deprivation Index-ADI). mTOR pathway activation levels were compared by self-identified race, proportion of African ancestry, body mass index (BMI), insurance status, and ADI. One-sided t-tests evaluated mean H-scores for pS6K and pAkt in tumor cells for various comparisons. **Results:** Analysis of 70 ER+ primary tumors from Black patients and 43 tumors from White patients showed mean pS6K staining in pan-cytokeratin-positive cells was significantly higher in tumor cores from Black compared with White patients (p-value = .05). Ancestry admixture analysis (dichotomized by the proportion of African ancestry > 0.4 vs. < 0.4) showed significantly increased pS6K staining in patients with greater proportion of African ancestry (p-value = .04). There was no association with ADI (p-value = .30). Analyses of association with insurance status and BMI, multivariable analyses, and survival analyses are ongoing and results will be presented, along with data on pAkt staining. **Conclusions:** This study demonstrated increased mTOR pathway activation at the protein level in Black women with ER+ EBC, confirming the result of a prior gene expression analysis. The underlying cause of this racial difference is unknown, but findings support development of clinical trials targeting the mTOR signaling pathway to mitigate racial disparity in EBC survival. Research Sponsor: None.

Evaluation of whole-exome and whole-genome sequencing tumor-informed circulating tumor DNA MRD assays in patients with early triple-negative breast cancer (TNBC) receiving neoadjuvant chemotherapy (NAC) with or without olaparib: A prospective sub-study of the PARTNER trial.

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Background: Detection of molecular residual disease (MRD), using circulating tumor DNA (ctDNA), following treatment for early-stage TNBC is associated with a high risk of recurrence. ctDNA clearance in response to NAC has shown potential for predicting pathologic complete response (pCR) and improving the prognostic ability of pCR status. PARTNER is a prospective, phase II-III, randomized controlled clinical trial, which recruited early-stage basal TNBC BRCA1/2 wild-type patients (Nature April 2024). Control regimen was neoadjuvant carboplatin–paclitaxel followed by anthracycline-based NAC. Experimental arms added olaparib to the platinum-taxane backbone. A sub-study of serial blood samples for ctDNA analysis during NAC and post-op were analyzed with 2 tumor informed MRD assays using primary tumor and germline sequencing: 1) whole-exome sequencing (WES) to select ≤ 200 variants and 2) whole-genome sequencing (WGS) to select 400–5000 variants for the two bespoke MRD assays, respectively. Both assays were independently used to assess available plasma samples collected for the presence or absence of ctDNA. **Methods:** This prospective sub study included TNBC patients enrolled within PARTNER with serial blood collections at baseline (prior to NAC), mid-NAC, post-NAC, 2–4 weeks post-op, 3 months post-op and 12 months post-op. Germline and somatic DNA were provided via the Personalised Breast Cancer Program. The primary objective was to determine the association of ctDNA positivity post-op with distant recurrence-free interval (DRFI). The distribution of DRFI by ctDNA status was compared using the log-rank test. The Cox proportional hazards regression model was used to estimate the strength of the relationship between ctDNA positivity and DRFI. **Results:** Median WES MRD assay panel size was 159 variants (range 47 – 200). At baseline ctDNA was detected in 50 of 55 patients (91%). After NAC, 4 of 63 patients had detectable ctDNA. 24 of 28 non-pCR patients were ctDNA negative and 0 of 35 pCR patients were ctDNA positive. Of 61 post-op patients available to assess DRFI distant recurrences developed in 8 patients (13.1%) within a median follow up of 5 years. Post-op 5 patients were ctDNA positive and 3 developed distant recurrences (log-rank $p < 0.0001$, HR = 20.2, 95% CI = 4.3, 95.1). In addition, 56 were ctDNA negative and 51 (91%) were distant recurrence free. Median WGS MRD assay panel size was 2962 variants (range 552 – 5000). At baseline ctDNA was detected in 46 of 47 patients (98%). Additional WGS MRD results are being generated and will be presented at the meeting. **Conclusions:** Post-op detection of ctDNA using a WES MRD assay was highly prognostic for distant recurrence in TNBC patients following NAC. WGS MRD improved baseline detection. Research Sponsor: Exact Sciences.

Molecular profiling of male breast cancer in Brazil: Comprehensive genomic characterization of a Latin American cohort.

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Background: Male breast cancer (MBC) is a rare disease, accounting for < 1% of all breast cancers. Current treatment recommendations are largely extrapolated from female breast cancer data, which may not reflect the distinct biological features of MBC. Notably, MBC is associated with higher mortality rates than female breast cancer. Molecular data from Latin America are scarce. This study aimed to characterize the clinicopathological and molecular features of MBC in a Brazilian cohort, addressing an important knowledge gap in an under-represented population. **Methods:** Medical records of 106 men diagnosed with breast cancer at three Brazilian cancer centers between 2000 and 2022 were reviewed. Tumor samples from 48 patients were available for molecular analysis after centralized histopathological review. FFPE samples with $\geq 10\%$ tumor cellularity were included. DNA and RNA were extracted using the AllPrep kit (Qiagen). Libraries were prepared using the Oncomine Focus Assay (Thermo Fisher Scientific) and sequenced on the Ion S5 platform. Bioinformatic analysis for single nucleotide variants (SNVs), insertions/deletions, copy number variations (CNVs), and gene fusions was performed using Ion Reporter software. **Results:** The median age at diagnosis was 58.5 years (range: 33–84). A family history of cancer was reported in 64% of patients, including female breast cancer in 32%. Most tumors were invasive ductal carcinomas (87.7%), high grade (grades 2–3; 90%), and hormone receptor–positive (93%). HER2+/HR– and triple-negative subtypes accounted for 0.9% and 3.9%, respectively. Most patients (88.5%) presented with localized or locally advanced disease. The most frequent pathogenic variants were PIK3CA (28%), followed by MAP2K1, BRAF, and AKT1 (6% each), and EGFR, JAK3, and MTOR (3% each). The most common CNV amplifications involved MYC (24%), FGFR1 (20%), CCND1 (16%), and ERBB2 (4%). No gene fusions were identified. Pathway analysis revealed alterations in PI3K/AKT/mTOR (37%), Cell Cycle (40%), FGF signaling (20%), and MAPK (12%) pathways. Overall, 46% of patients harbored potentially actionable SNVs, and 24% harbored potentially actionable CNVs. **Conclusions:** This is the first comprehensive molecular characterization of MBC in Brazil. Our findings confirm PIK3CA as the most frequent alteration, consistent with international cohorts, supporting the central role of the PI3K/AKT/mTOR pathway in MBC. Additional alterations in Cell Cycle and FGF signaling pathways highlight distinct oncogenic drivers. The high prevalence of potentially actionable genomic alterations suggests that molecular profiling may inform treatment selection for a substantial proportion of patients. These findings underscore the limitations of extrapolating treatment guidelines from female breast cancer and support biomarker-driven clinical trials for men with breast cancer in Latin America. Research Sponsor: None.

Functional domain disruption to define the molecular and clinical spectrum of germline *RAD51* family variants in hereditary breast cancer (BC).

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Background: RAD51 paralogs (RAD51C, RAD51D, XRCC2) and RAD50 are crucial in DNA repair. Germline pathogenic variants (PVs) increase hereditary breast/ovarian cancer risk, but domain-specific impacts remain unclear. **Methods:** Retrospective cohort study (2019–2025) of breast cancer patients undergoing multigene testing. PVs were mapped to functional domains. Tumor features included histology, stage, grade, TILs, and molecular subtype. Associations were assessed using Fisher's exact test. **Results:** Among 495 patients, 23 (4.6%) had RAD51 family PVs (RAD51C = 16, RAD51D = 4, RAD50 = 1, XRCC2 = 1). Median diagnosis age was 49. Synchronous malignancies were significantly more frequent in RAD51 carriers vs. BRCA1 carriers (34.8% vs.; OR 3.51, 95% CI 1.09–11.26). Most variants (22/23) were truncating (11 nonsense, 9 frameshift, 1 splice-site, 1 exon deletion). Domain mapping revealed disruption of critical regions: RAD51-like core domain truncations (RAD51D p.Arg186; RAD51C p.Arg193), RAD51C C-terminal truncations removing essential regions for complex integrity, and early RAD50 truncation predicted to abolish MRN complex function. Tumors were predominantly early-stage (65.2% stage I). Histology showed invasive carcinoma of no special type (69%) and invasive lobular carcinoma (25%), with strong enrichment of lobular histology in RAD51C carriers ($p < 0.001$). RAD51C tumors were basal-like or luminal A, while the RAD50 tumor was luminal B HER2-positive. RAD51C tumors often had high nuclear grade (77.3%) but low TILs (71%). **Conclusions:** RAD51 family PVs are primarily truncating, disrupting key HRR domains and supporting loss-of-function as the main mechanism. Domain location correlates with distinct clinicopathological features, refining genotype–phenotype correlations for improved risk assessment. Research Sponsor: None.

Multi-omic profiling to identify RNA-protein concordance and post-transcriptional dysregulation in HER2+ breast cancer.

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Background: Standard HER2 testing relies on single-modality assays, such as immunohistochemistry (IHC) for protein overexpression and in situ hybridization (ISH) for gene amplification. These tests may fail to capture the regulatory complexity underlying HER2 biology, including post-transcriptional modulation, which may result in RNA-protein discordance and potentially drive therapeutic resistance. We performed a multi-omic analysis to characterize functional HER2 biology and uncover regulatory mechanisms not captured by standard diagnostic testing. **Methods:** We utilized Panakeia's multi-omics platform to analyze a set of 475 breast cancer samples with a complete set of *ERBB2* RNA and protein expression values from the Cancer Genome Atlas (TCGA). HER2+ (n=79) and HER2- (n=396) cohorts were defined using clinical HER2 status assessed via IHC/ISH. Transcriptomic and proteomic over-expression states were binarized by thresholding RNA/protein expression values. RNA-protein concordance was assessed to define four molecular states of the tumor: coordinated activation (RNA+/Protein+), coordinated inactivation (RNA-/Protein-), translation blocks (RNA+/Protein-), or post-transcriptional upregulation (RNA-/Protein+). **Results:** A strong correlation was measured between RNA and protein over-expression (Pearson's correlation $r=0.752$, $p<0.001$) with 93.7% concordance (445/475). Molecular patterns with respect to HER2 clinical status were observed as follows: (1) coordinated activation (n=48, 10.1%) with 95.8% HER2+ concordance (46/48), validating HER2 over-expression; (2) coordinated inactivation (n=397, 83.6%) with 95.2% HER2- concordance (378/397), confirming HER2 inactivity; (3) RNA+/Protein- translation blocks (n=29, 6.1%) where *ERBB2* RNA was over-expressed but not translated; (4) RNA-/Protein+ (n=1, 0.2%). Among 79 HER2+ patients, only 46 (58.2%) showed functional translation (RNA+/Protein+), while 19 (24.1%) had complete molecular negativity (both inactive) and 14 (17.7%) exhibited translation blocks. Multi-omics profiling identified actionable changes in 35/475 cases (7.4%): 19 potential over-treatment candidates, 14 potential treatment resistance cases, and 2 potential under-treatment cases that are clinically HER2- but exhibit coordinated molecular activity. **Conclusions:** Integrative multi-omic analysis of the HER2 molecular landscape enabled assessment beyond standard-of-care assays, identifying non-responders to HER2-targeted therapy by capturing post-transcriptional dysregulation not detected by single-modality testing. Overall, multi-omic profiling can support precision stratification by confirming active HER2 signalling, identifying potential over-treatment, refining patient selection and guiding treatment decisions. Research Sponsor: None.

Exploring diversity and composition of sulfidogenic gut bacteria in breast cancer.

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Background: Sulfidogenic bacteria produce hydrogen sulfide, the excess of which is genotoxic and proinflammatory and is absorbed through the GI tract into the systemic circulation. The role of sulfidogenic bacteria in BC has not been explored. In this study, we aimed to evaluate sulfidogenic bacterial abundance and diversity in BC. We hypothesized that there will be lower alpha and beta diversity in BC groups. We also hypothesized that there will be a higher relative abundance of sulfidogenic bacteria in BC vs. controls. **Methods:** We used high throughput sequencing of the *dsrA* gene in stool samples of female participants with BC and controls without BC (n=283). Controls were further delineated into normal mammogram, abnormal mammogram with no evidence of BC (e.g. cysts, etc), and controls without BC but with a first degree relative who has BC. To process the sequences, QIIME2 bioinformatics pipelines were used with taxonomy assigned using the SILVA database. We performed alpha diversity analyses with nonparametric statistics, and beta diversity analyses using the Bray-Curtis and weighted/unweighted UniFrac metrics. Differential abundance of sulfidogenic bacteria at the genus level was calculated in R using the DESeq2 package. In the same samples, we used sequencing of the V3-V4 region of the 16S rDNA gene to compare relative abundance of total sulfidogenic bacteria between BC samples and controls in R using the DESeq2 package. **Results:** Using the Chao1 metric, we found higher sulfidogenic alpha diversity in BC vs. all controls ($p < 0.001$), BC vs. controls who have a first degree relative with BC ($p = 0.005$). as well as within controls with a normal mammogram vs. abnormal mammogram without BC ($p = 0.037$). We did not find significant differences in beta diversity between BC vs. controls. When analyzed visually using PCoA of unweighted UniFrac distances, there were two clusters within all patient groups, indicative of two enterotypes across all subjects. We did not find a significant difference in the relative abundance of overall sulfidogenic bacteria as identified by the 16S rDNA gene between BC and controls. However, *Desulfovibrio* was enriched in BC compared to normal mammogram samples with a log fold change of 1.69 ($p = 0.013$). **Conclusions:** These results suggest altered sulfidogenic gut bacterial community composition in individuals with BC, particularly in organisms with lower relative abundance. *Desulfovibrio* appears as a predominating organism in BC. This is supported by prior research, which suggests *Desulfovibrio* becomes less abundant in participants exposed to agents that inhibit BC cell proliferation. We propose that there are two enterotypes of sulfidogenic gut bacteria in women. Research Sponsor: NIH (National Institutes of Health); University of Illinois.

Beyond convolution: Attention-driven vision transformer modeling for breast cancer detection on mammography.

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Background: Breast cancer is the most commonly diagnosed malignancy among women worldwide, and screening mammography remains central to early detection and mortality reduction. Despite standardized reporting systems, mammographic interpretation is challenged by tissue overlap, subtle lesion morphology, and interobserver variability. Convolutional neural networks (CNNs) have demonstrated strong performance in automated mammography analysis but rely on localized receptive fields that may limit modeling of global spatial relationships critical for detecting architectural distortion and diffuse malignancy. Vision Transformers (ViTs) employ self-attention mechanisms that enable global contextual modeling across entire images. We evaluated the performance of a Vision Transformer for breast cancer classification on mammographic imaging. **Methods:** We analyzed over 8,000 anonymized mammography images obtained from publicly available Kaggle datasets curated and annotated by expert radiologists. Images included malignant and non-malignant breast findings and were preprocessed and resized to 224×224 pixels. Data were split into training and validation cohorts using stratified sampling at the patient level to prevent data leakage. A Vision Transformer B/16 model pretrained on ImageNet was fine-tuned for binary classification. Images were divided into non-overlapping 16×16 patches, embedded into token sequences with positional encodings and a learnable class token, and processed through 12 transformer blocks with multi-head self-attention. Model performance was evaluated using accuracy, sensitivity, specificity, F1 score, and area under the receiver operating characteristic curve (AUROC). **Results:** The ViT-B/16 model achieved high diagnostic performance, with validation accuracy approaching approximately 96% and AUROC exceeding 0.98. Sensitivity for malignant lesions remained robust across dense and non-dense breast tissue. Attention-based global processing reduced misclassification of lesions with diffuse margins, asymmetric density, and architectural distortion—patterns that are challenging for purely convolutional approaches. Performance was comparable to state-of-the-art CNN models, though achieved with higher parameter count and computational cost. **Conclusions:** Vision Transformer-based modeling enables accurate breast cancer detection on mammography by capturing global contextual relationships through self-attention. While computationally heavier than optimized CNNs, ViT offers complementary strengths in modeling complex spatial patterns and provides interpretable attention maps aligned with radiologic reasoning. These findings support further evaluation of transformer architectures in large-scale breast cancer screening and diagnostic workflows. Research Sponsor: None.

ILCness to stratify lobular-like breast cancer biology and as an outcome independent of *CDH1* mutation in early ER-positive/HER2-negative breast cancer.

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Background: Invasive lobular carcinoma (ILC) represents a distinct histological subtype of breast cancer; however, its underlying molecular basis remains incompletely defined. Although loss-of-function mutations in *CDH1* are considered a hallmark genetic event, substantial biological heterogeneity persists that cannot be fully explained by histology or mutation status alone. **Methods:** To address this limitation, we developed a continuous transcriptional framework, termed the ILCness score, to quantitatively capture lobular-like tumor biology. A tightly constrained principal component-based model was trained in the METABRIC cohort and fully fixed without retraining, enabling reproducible projection across independent datasets and expression platforms. **Results:** Unsupervised transcriptomic analyses demonstrated that invasive ductal carcinoma (IDC) and ILC did not form discrete expression clusters but instead distributed along a continuous molecular spectrum. The ILCness score robustly captured this continuum, with mixed-histology tumors occupying intermediate positions. Importantly, lobular-like transcriptional programs quantified by ILCness showed limited concordance with *CDH1* mutation status. Across tumors, higher ILCness was consistently associated with reduced DNA repair and E2F target activity (Spearman $|\rho| > 0.4$, $P < 0.001$), whereas epithelial-mesenchymal transition displayed a context-dependent pattern. Tumor microenvironment analyses revealed that stromal and immune cell infiltration correlated more strongly with ILCness than with *CDH1* mutation status. These associations were reproducibly validated in independent cohorts without model recalibration. Clinically, ILCness stratified prognostically distinct subgroups within histologically defined tumors, including IDC, independent of *CDH1* mutation (disease-specific survival, $P < 0.01$). Across multiple neoadjuvant and systemic therapy datasets, higher ILCness showed consistent directional associations with reduced pathological complete response to chemotherapy and differential response patterns to immune checkpoint inhibition and endocrine therapy. **Conclusions:** These findings establish lobular breast cancer as a continuum of transcriptional states rather than a discrete entity defined by histology or single-gene alterations. The ILCness score provides a scalable RNA-based framework for integrating molecular heterogeneity with tumor biology and clinical behavior, with potential implications for biologically informed patient stratification. Research Sponsor: None.

Neighborhood disadvantage and correlation with differences in somatic mutations in a real-world breast cancer cohort.

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Background: African compared to European genetic ancestry is associated with lower prevalence of clinically actionable alterations despite comparable overall prevalence of driver alterations by ancestry group. This likely contributes to breast cancer (BC) disparity. A limitation of prior ancestry studies is lack of neighborhood-level disadvantage (ND) data, a contributor to BC disparity. The objective of this study was to investigate associations between ND and somatic mutations in a real-world BC cohort. **Methods:** Somatic mutations from primary and metastatic BC samples and genetic ancestry data were identified from MSK IMPACT (FDA-authorized sequencing panel). Samples sequenced between 2015–2025 were annotated and linked with census-tract level socioeconomic status (Yost Index 1–100; higher reflects increasing ND). Multivariate logistic regression analyzed associations between ND and somatic mutations, adjusting for covariates (FDR $p < 0.05$). **Results:** 6703 samples (62% primary, 38% metastatic) were analyzed. Mean age was 60 (SD 13). Mean Yost was 26 (SD 24). 67% had ER+/HER2- disease, 9.7% had ER+/HER2+, 5.1% had ER-/HER2+, and 19% had ER-/HER2-. Adjusting for age, BMI, ancestry, and subtype, patients from ND had lower odds of CDH1 (OR 0.99, 95% CI 0.98–0.99, $p < 0.001$), BRCA1 (OR 0.96, 95% CI 0.94–0.99, $p = 0.021$), and AKT1 (OR 0.98, 95% CI 0.97–0.99, $p = 0.006$) somatic mutations in metastatic samples. **Conclusions:** We identify novel associations between ND and somatic mutations. Notably, patients with ND had lower odds of actionable BRCA1 and AKT1 mutations. This highlights the importance of ensuring patients of diverse ancestry and ND have equitable inclusion in clinical sequencing workflows to improve identification of actionable mutations in all populations. Research Sponsor: None.

Genetic ancestry (GA) and somatic mutational frequency by Yost.

	Total N=6703 ¹	Yost 1-20 (Most Advantaged) N=3601 ¹	Yost 21-40 N=1539 ¹	Yost 41-60 N=826 ¹	Yost 61-80 N=477 ¹	Yost 81-100 (Most Disadvantaged) N=260 ¹	p-value ²
European GA*	0.75 (0.36)	0.83 (0.30)	0.72 (0.38)	0.64 (0.39)	0.58 (0.39)	0.42 (0.35)	<0.001
African GA*	0.12 (0.27)	0.04 (0.16)	0.15 (0.30)	0.21 (0.34)	0.25 (0.36)	0.44 (0.38)	<0.001
East Asian GA*	0.05 (0.21)	0.05 (0.21)	0.06 (0.22)	0.06 (0.21)	0.07 (0.23)	0.04 (0.17)	<0.001
South Asian GA*	0.06 (0.16)	0.06 (0.17)	0.05 (0.15)	0.06 (0.17)	0.04 (0.12)	0.03 (0.08)	<0.001
Native American GA*	0.03 (0.10)	0.01 (0.07)	0.03 (0.10)	0.04 (0.12)	0.06 (0.16)	0.08 (0.17)	<0.001
Mutational Frequency, metastases	N=2536 ¹	N=1403 ¹	N=584 ¹	N=311 ¹	N=165 ¹	N=73 ¹	p-value ^{2A}
CDH1	341 (13%)	220 (16%)	66 (11%)	26 (8.4%)	18 (11%)	11 (15%)	<0.001
AKT1	127 (5.0%)	74 (5.3%)	34 (5.8%)	12 (3.9%)	4 (2.4%)	3 (4.1%)	0.006
BRCA1	21 (0.8%)	13 (0.9%)	7 (1.2%)	1 (0.3%)	0 (0%)	0 (0%)	0.021

*Calculated using >3,000 common SNP markers.

^AMVA, control for age, BMI, ancestry, subtype.

¹Mean (SD), n (%).

²Pearson's Chi² test; Kruskal-Wallis rank sum test; Fisher's exact test.

Does surgery improve breast cancer–specific survival in low-grade DCIS?: A 20-year population-based analysis by nuclear grade.

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Background: Active surveillance is increasingly discussed for low-risk ductal carcinoma in situ (DCIS), yet randomized trials report only short-term outcomes. Long-term survival data stratified by nuclear grade remain limited. We evaluated the association between cancer-directed surgery and long-term breast cancer–specific survival (BCSS) and overall survival (OS) in DCIS. **Methods:** We conducted a retrospective population-based cohort study using SEER 17 registries, including patients diagnosed with DCIS between 2000 and 2019 with follow-up exceeding 36 months. Exposure was cancer-directed surgery (yes vs no). Outcomes were BCSS, analyzed using cause-specific Cox models, and OS. Prespecified covariates included age, year of diagnosis, race, tumor size, nuclear grade, estrogen and progesterone receptor status, median household income, and residence type. Missing data were handled using multiple imputation. Confounding was addressed using inverse probability of treatment weighting with stabilized weights. Analyses were stratified by nuclear grade (Grades 1–3). **Results:** Among 51,637 patients, 50,346 (97.5%) underwent surgery and 1,291 (2.5%) did not. Median follow-up was 120 months. In the overall cohort, surgery was associated with improved BCSS (hazard ratio [HR] 0.13; 95% CI, 0.09–0.19) and OS (HR 0.65; 95% CI, 0.56–0.75). Outcomes differed substantially by nuclear grade. In Grade 1 DCIS, surgery was not associated with improved BCSS (HR 0.57; 95% CI, 0.05–6.16), with 20-year BCSS exceeding 99% regardless of treatment, although OS favored surgery. In Grade 2 DCIS, surgery reduced breast cancer–specific mortality (HR 0.22; 95% CI, 0.10–0.45) without an OS benefit. In Grade 3 DCIS, surgery conferred marked improvements in both BCSS (HR 0.10; 95% CI, 0.06–0.15) and OS (HR 0.49; 95% CI, 0.40–0.60). **Conclusions:** In this large population-based study with up to 20 years of follow-up, omission of surgery in low-grade DCIS was not associated with worse breast cancer–specific survival, whereas clear survival benefits were observed in intermediate- and high-grade disease. These findings support risk-adapted management strategies and provide long-term survival context for active surveillance approaches in DCIS. Research Sponsor: None.

Wire-guided versus radio-guided localization for non-palpable occult lesion in breast tissue: A systematic review and meta-analysis.

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Background: Accurate preoperative localization of non-palpable breast lesions is crucial for successful breast-conserving surgery. Wire-guided localization (WGL) has traditionally been the standard technique; radio-guided localization (ROLL) has emerged as an alternative approach with potential benefits in surgical precision and workflow. Current evidence comparing the efficacy and safety of these two techniques remains inconsistent. This systematic review and meta-analysis evaluates WGL versus ROLL for non-palpable breast lesions with respect to surgical and oncological outcomes. **Methods:** A systematic literature search was conducted on electronic databases from inception until January 2026. Outcomes included re-excision rates, margin involvement, specimen volume and weight, accurate localisation of lesions and operative time. We employed risk ratios (RRs) with 95% Confidence Intervals (CIs) for dichotomous outcomes. Mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs were computed for continuous outcomes using Review Manager V.5.4. Quality assessment and risk of bias were assessed using the Cochrane Risk of Bias Tool 2 on all included RCTs. **Results:** This systematic review and meta-analysis included 13 studies with a total of 5,318 patients. There was no statistically significant difference in the re-excision rates between the two interventions (OR = 1.44; 95% CI: [0.73, 2.83], $p = 0.143$). Localization time (SMD = 1.75; 95% CI: [-1.01, 4.51], $p = <0.0001$) and length of operation time was significantly shorter in the ROLL group (SMD = 0.22; 95% CI: [0.10, 0.34], $p = 0.028$). There was no statistically significant difference in the margin involvement between the two groups (OR = 0.61; 95% CI: [0.37, 0.99], $p = 0.063$). ROLL was associated with significantly smaller volume of specimen (SMD = 0.16; 95% CI: [-5.41, 5.73], $p = <0.0001$). **Conclusions:** ROLL and WGL demonstrate comparable oncological outcomes, with no significant differences in the re-excision rates or margin involvement. However, ROLL is associated with significantly shorter localization and operative times, suggesting procedural efficiency over WGL. Research Sponsor: None.

Intraoperative precision margin assessment in breast-conserving surgery using handheld fluorescence microscopy.

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Background: Breast-conserving surgery (BCS) is the standard treatment for early-stage breast cancer and is increasingly preferred by younger patients. The key challenge in BCS is ensuring complete tumor removal while preserving healthy breast tissue. Surgical margin assessment plays a crucial role in reducing the risk of local recurrence. Traditional intraoperative frozen sections (FS) are time-consuming, limit sampling, and may cause tissue damage. This study evaluates the performance of EndoScell, a handheld fluorescence microscopy system, as a rapid and efficient alternative for intraoperative margin assessment. **Methods:** EndoScell provides real-time, high-resolution imaging of tissue margins during surgery. This system rapidly stains and scans tissue, allowing for micron-level visualization of cellular features. In this study, EndoScell was used to scan marked surfaces of breast tissue during surgery. The surgeon performed an initial assessment, while images/videos were recorded. Specimens were then sent for intraoperative FS analysis for comparison. If FS identified positive margins, the area was re-excised by 3–5 mm, and the process was repeated. Routine paraffin pathology served as the gold standard, with blinded side-by-side reading of ES images to evaluate consistency. **Results:** As of December 31, 2025, 300 patients undergoing BCS were included. EndoScell demonstrated high diagnostic accuracy with a sensitivity of 96.4%, specificity of 95.1%, and AUC of 0.953, showing strong agreement with paraffin pathology. Notably, the time required for EndoScell imaging was significantly shorter than FS, with an average of 3.14 ± 1.48 minutes compared to 37.50 ± 13.34 minutes for FS ($P<0.001$), leading to substantial improvements in surgical efficiency. **Conclusions:** This study confirms the feasibility and non-inferiority of EndoScell for intraoperative margin assessment in breast-conserving surgery. The system enables real-time decision-making, reducing secondary surgeries, improving outcomes, and enhancing surgical safety. Its significant clinical and social value supports further development and implementation. Research Sponsor: None.

Key metrics related to diagnostic accuracy and time efficiency between EndoScell and traditional frozen section methods.

Metric	EndoScell (ES)	Frozen Section (FS)
Positive Margin	54	56
Negative Margin	246	244
Sensitivity	0.964	1.000
Specificity	0.951	1.000
AUC	0.953 (95% CI: 0.912–1.003)	1.000
Imaging Time (min)	3.14 ± 1.48	37.50 ± 13.34
p-value	<0.001	N/A
Cohen's d	-3.64	N/A

Impact of time-to-surgery on survival outcomes in Korean breast cancer patients: A nationwide population-based cohort study.

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Background: The increasing incidence of breast cancer and the resulting surgical workload in South Korea have led to concerns regarding surgical delays. While the clinical impact of time-to-surgery (TTS) remains debated, defining an optimal threshold is crucial for health policy and patient outcomes. This study aimed to investigate the impact of TTS on overall survival (OS), disease-free survival (DFS), and breast cancer-specific survival (BCSS) using nationwide claims data. **Methods:** This study utilized a merged dataset from the National Health Insurance Service and Korean Statistical Information Service database. We identified 11,683 women newly diagnosed with Stage I-III primary breast cancer in 2016, excluding prior history or concurrent malignancies. TTS was defined as the interval from breast cancer diagnosis to the definitive surgical procedure. To determine the optimal clinical cutoff, the Contal and O'Quigley method was applied. Multivariable Cox proportional hazards models were used for OS. To account for competing risks, the Fine-Gray subdistribution hazard model was employed for DFS and BCSS, with non-breast cancer death treated as a competing event. Covariates included physical activity, type and region of institution, systemic treatments, income decile, and Charlson Comorbidity Index (CCI) score. **Results:** Initial analysis using 30-day and 60-day thresholds showed significant differences in survival outcomes. The Contal and O'Quigley method identified 68 days as the optimal cutoff for TTS. Patients with TTS > 68 days exhibited significantly worse OS compared to those with TTS ≤ 68 days (adjusted Hazard Ratio [HR], 3.396; 95% CI, 2.402-4.802; $p < 0.001$). In the competing risk regression, TTS > 68 days was associated with inferior DFS (adjusted subdistribution HR [sHR], 1.496; $p = 0.001$) and BCSS (adjusted sHR, 5.868; $p < 0.001$). The negative impact of delayed surgery remained consistent across various subgroups regardless of income level or comorbid status. **Conclusions:** Delays in surgery exceeding 68 days are significantly associated with poorer survival outcomes in Korean breast cancer patients. These findings suggest that every effort should be made to perform surgery within 68 days of diagnosis to optimize long-term prognosis. Clinicians should prioritize streamlining the diagnostic-to-treatment pathway to minimize surgical wait times. Research Sponsor: None.

Can robotic surgery better preserve sensory function?: The significance and strategy of nerve preservation in axillary lymph node dissection.

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Background: Conventional axillary lymph node dissection (C-ALND) carries a high risk of damaging the intercostobrachial nerve (ICBN), which remains a critical clinical issue affecting both psychological recovery and quality of life in breast cancer patients. While advancements in minimally invasive surgery provide improved visualization and precision, evidence supporting its clinical benefit in preserving sensory function is lacking. **Methods:** A retrospective analysis was conducted on breast cancer patients who underwent robotic-assisted axillary lymph node dissection (R-ALND, $n = 53$) and endoscopic-assisted axillary lymph node dissection (E-ALND, $n = 58$) between 2021 and 2025 (total $n = 111$). The anatomical integrity of the ICBN (T1-3) was systematically identified and recorded during surgery. Additionally, a blinded evaluator performed standardized bedside sensory testing (BST) on four key ICBN areas (medial upper arm, axilla, upper chest, and lateral chest wall) three months postoperatively, using a scoring system adapted from the ISCIPS consensus group for the current study. A multivariate linear regression model was applied for analysis. **Results:** Compared with E-ALND, R-ALND demonstrated a significantly higher ICBN-trunk preservation rate (77.4% vs. 63.1%, $p = 0.033$) and a greater proportion of areas with normal sensation at three months postoperatively (89.2% vs. 74.6%, $p = 0.025$). Multivariate linear regression revealed that T2-ICBN trunk preservation was the strongest independent predictor of sensory recovery at three months ($\beta = 0.571$, 95% CI 0.477–0.664, $P < 0.001$), with an effect size (standardized $\beta = 0.720$) far exceeding other factors. Patients with T2-ICBN preservation achieved a 77.4% rate of completely normal sensation across all four key ICBN areas at three months. After adjusting for variables including T2-ICBN preservation, tumor stage, age and so on, robotic surgery showed a tendency to be an independent protective factor for sensory recovery at 3 months postoperatively compared with endoscopic surgery. ($\beta = 0.110$, $p = 0.016$). **Conclusions:** Through three-dimensional visualization and tremor-filtering technology, R-ALND significantly reduces the risk of iatrogenic ICBN injury and outperforms E-ALND in preserving short-term postoperative sensory function recovery. In the early phase with a limited learning curve, preserving the ICBN trunk (particularly the T2-ICBN) is recommended to retain most of the patient's sensory function. Research Sponsor: None.

Synergistic efficiency of methylene blue and carbon nanoparticles for sentinel lymph node biopsy in early breast cancer: A large-scale real-world cohort study of 1,355 patients.

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Background: Sentinel lymph node biopsy (SLNB) using radioisotopes and fluorescence imaging is the gold standard but remains inaccessible in many resource-limited regions due to high costs and the lack of nuclear medicine infrastructure. Methylene blue (MB) is a globally available, low-cost tracer, but often lacks consistent nodal yield. This study evaluates a radiation-free, dual-tracer protocol combining MB with carbon nanoparticles (CN) to provide a highly accessible and reliable axillary staging method for diverse clinical settings. **Methods:** In this single-center retrospective cohort study, 1,355 female patients with cT1-2N0Mo breast cancer (May 2019 to December 2022) were stratified into the MB group (n=675) or the MB+CN group (n=680). Primary endpoints were the SLN detection rate and mean node retrieval (MNR). Sensitivity analyses adjusted for confounders, including Ki67 status, using multivariate regression. The goal was to determine if this dual-dye approach could match the reliability of high-cost methods without specialized equipment. **Results:** The MB+CN group achieved a comparable detection rate to MB alone (96.32% vs. 96.44%; P=0.905). Crucially, the dual-tracer protocol significantly increased the MNR (2.43±1.64 vs. 2.10±1.35; P<0.001). Adjusted linear regression confirmed a robust increase in node count (β=0.36, 95% CI: 0.19–0.52, P<0.001). Subgroup analysis demonstrated enhanced utility in aggressive molecular profiles, with significantly higher node retrieval in high-Ki67 (P=0.002), T2 stage (P=0.032), and ER-positive (P<0.001) cohorts. No significant differences in detection rates were observed across any clinicopathological subgroups. **Conclusions:** The MB+CN dual-tracer strategy significantly enhances nodal yield while maintaining high detection rates. By eliminating the need for radioactive tracers and expensive imaging hardware, this approach offers a precise, safe, and cost-effective SLNB solution. It is particularly suited for large-scale implementation in developing countries and rural healthcare systems, bridging the gap in breast cancer surgical standards globally. Research Sponsor: None.

Comparison of SLNB outcomes between MB and MB+CN groups.					
Outcome	MB Group (n=675)	MB+CN Group (n=680)	Univariate P	Adjusted Estimate (95% CI)	Multivariate P
Detection Rate, % (n ₁ /n)	96.44% (651/675)	96.32% (655/680)	0.905	OR: 0.83 (0.64–1.09)	0.182
Mean Node Retrieval (SD)	2.10 (1.35)	2.43 (1.64)	<0.001	β: 0.36 (0.19–0.52)	<0.001

Oncological safety of oncoplastic breast conservation surgery: Experience of over a decade in early and locally advanced breast cancer from a tertiary care cancer center in India.

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Background: Oncoplastic breast conservation surgery (O-BCS) is the norm. O-BCS improves cosmetic outcomes by restoring the shape, size, contour and symmetry of the breast and hence, quality of life. Carefully selected patients with locally advanced breast cancers (LABC) can be offered O-BCS after systemic therapy. We retrospectively evaluated our prospective dataset for oncological outcomes of patients who had O-BCS. **Methods:** Patients undergoing O-BCS between January 2013 and December 2023 were included. They received (neo)adjuvant chemotherapy, targeted and radiotherapy along with endocrine treatment as per standard institutional protocol and decision of Breast Cancer-Disease Management Group (BC-DMG). Clinico-pathological characteristics, type of oncoplastic procedure and follow-up details were updated from Electronic Medical Records. Data was collected and analyzed in SPSS-V29. **Results:** A total 1483 patients underwent O-BCS during the study period. The median age of the cohort was 45 (21–86) years. Of 1483, 670 (45.2%) were operated upfront and 573 (38.6%) post-chemotherapy whereas 240 (16.2%) had had prior excision biopsy elsewhere. Clinically, 939 (63.3%) were early (EBC-T1/2, N0/1), 518 (34.9%) locally advanced (LABC-T3/4, N2/3) and 26 (1.8%) oligometastatic breast cancers. 1016 (68.5%) were HR+, 289 (19.5) TN and 396 (26.7%) HER2+. Median pT in upfront versus post-chemotherapy operated patients was 3 cm (0.1–8.5) and 2.7 cm (1–10) respectively. Upfront, 45.8% patients were node positive (median-2 {1–54}) and post-chemotherapy 38.3% (median-3 {1–38}). The median specimen volume was 432 cm³ (56.8–3528) in upfront and 270 cm³ (3–2875) in post-chemotherapy operated patients. The overall margin positive rate was 5.5% (81/1483). Of 1483, 573 (38.6%) patients had type-1 oncoplastic parenchymal closure, 377 (25.4%) had local dermo-glandular flaps, 344 (23.2%) a latissimus dorsi myo-cutaneous flap, and 189 (12.7%) bilateral reduction mammoplasty. At median follow-up of 47 months, there were 245 (16.5%) recurrences—77(5%) local and 211(14%) distant—and 153 (10.3%) deaths, and the disease-free survival (DFS) and overall survival (OS) were 84.1% and 89.5% respectively. The local recurrence rate in EBC was 4% and LABC 7.4%. The 5-year DFS was 82.1%(95%CI-79.75%-84.84%) and OS was 88.5%(95%CI-86.54%-90.46%) across the whole cohort. On Cox regression, high clinical nodal stage (HR-1.47, 95%CI-1.04-2.08, p=0.03) and histological grade 3 (HR-1.87, 95%CI-1-07-3.29, p=0.03) were predictors of poor DFS whereas type of O-BCS did not have impact on survival. **Conclusions:** The local recurrence rate in O-BCS was 5.3% in our setting which is reassuring considering that 1/3rd patients had locally advanced disease. A longer follow-up of this cohort of patients and future PROMs and QOL studies will be consolidatory. Research Sponsor: None.

Surgical outcomes and postoperative complications of robotic versus conventional nipple-sparing mastectomy in breast cancer: A meta-analysis.

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Background: Breast cancer is the most common type of cancer, affecting millions of women worldwide. Nipple-sparing mastectomy has emerged as a technique that leaves most of the healthy breast skin, areola, and nipple. This technique is widely used but there is little evidence comparing conventional and robotic nipple-sparing mastectomy. This meta-analysis aimed to compare the efficacy, safety, and postoperative complications of conventional and robotic nipple-sparing mastectomy. **Methods:** A systematic search of PubMed, Scopus, Web of Science, and the Cochrane Library was conducted to identify studies comparing robotic and conventional nipple-sparing mastectomy. The primary outcome was nipple and skin necrosis; secondary outcomes included operative time and Clavien–Dindo Grade III complications. Pooled estimates were calculated using a random-effects model, and heterogeneity was assessed using the I^2 statistic. **Results:** A total of nine studies encompassing 1,220 participants (423 in the robotic group and 797 in the conventional group) were included in the final analysis. Robotic nipple-sparing mastectomy (RNSM) was associated with a significantly lower risk of nipple and skin necrosis compared to conventional nipple-sparing mastectomy (CNSM), with a pooled odds ratio of 0.47 (95% CI: 0.26–0.86; $P = 0.01$) and low heterogeneity ($I^2 = 20.5\%$). Conversely, RNSM was associated with a significantly longer operative time, with a weighted mean difference of 52.86 minutes (95% CI: 20.28–85.43; $P = 0.001$) and substantial heterogeneity ($I^2 = 96\%$). Regarding safety, there was no statistically significant difference in Clavien–Dindo Grade III complications between the two techniques (OR = 0.60; 95% CI: 0.35–1.05; $P = 0.07$; $I^2 = 0\%$), although the results showed a trend favoring the robotic approach. **Conclusions:** Robotic nipple-sparing mastectomy demonstrates a superior safety profile regarding ischemic complications, significantly reducing the risk of nipple and skin necrosis compared to the conventional approach. However, it is associated with longer operative times. The incidence of major complications (Grade III) is comparable between both techniques. Research Sponsor: None.

Evaluation of a novel diagnostic kit using the semi-dry dot-blot method with an automated reader for detecting breast cancer metastases in sentinel lymph nodes: A combined analysis of two multicenter prospective studies in Japan.

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Background: The semi-dry dot-blot (SDB) method is a diagnostic procedure for detecting lymph node (LN) metastases using an anti-cytokeratin (CK) antibody, based on the premise that epithelial components such as CK protein are not present in normal LNs. Thus, the presence of CK protein in the lavage fluid of sectioned LNs indicates metastasis. Because this method does not involve loss of LN tissue, it can be used in parallel with conventional histopathological diagnosis. We developed a novel diagnostic kit utilizing the SDB method and a newly developed anti-CK19 antibody to detect macrometastases over 2.0 mm in diameter. Two multicenter prospective studies were conducted to evaluate the diagnostic performance of this kit, and we herein report a combined analysis of the two studies. **Methods:** A total of 825 sentinel LNs were dissected between January and December 2021, and 909 LNs between August 2023 and November 2024, at seven institutions in Japan from 880 patients with breast cancer. Patients who received neoadjuvant chemotherapy or endocrine therapy were excluded. LNs were sliced at 2-mm intervals and washed with phosphate-buffered saline. Cells in the lavage fluid were centrifuged and lysed, and the extracted proteins were applied to the SDB kit. Absorbance was measured using an automated reader to determine the presence of metastases. The washed LNs underwent blinded intraoperative and permanent histopathological examination. Diagnostic performance of the SDB kit was compared with permanent histology, with primary endpoints being sensitivity, specificity, and overall concordance for detecting macrometastases. **Results:** Of the 1,734 LNs analyzed, 199 were diagnosed as macrometastases and 1,535 as non-macrometastases, including 64 micrometastases measuring more than 0.2 mm and not up to 2.0 mm in diameter, based on permanent histopathology. Using a CK absorbance cutoff of 11.9, the SDB kit correctly identified 185 of the 199 macrometastatic LNs and 1,496 of the 1,535 non-macrometastatic LNs. This corresponded to a sensitivity of 93.0%, specificity of 97.5%, and overall concordance of 96.9%. Additionally, the kit enabled diagnosis within approximately 20 minutes, at a cost of under \$30 per test and less than \$3,000 for the reader device. **Conclusions:** The novel SDB kit with an automated reader demonstrated high accuracy, rapid turnaround, and cost-effectiveness in detecting breast cancer LN metastases, while preserving LN tissue. It proved particularly effective in identifying macrometastases. Commercial availability of the kit and reader is planned in the near future. Research Sponsor: None.

Distant recurrence-free survival in invasive lobular carcinoma (ILC) with isolated tumor cells: Does pN0(i+) behave like node-negative or node-positive disease?

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Background: ILC is a distinct breast cancer subtype with unique biology and clinical behavior compared with invasive ductal carcinoma. The prognostic significance of isolated tumor cells (ITCs; pN0(i+)) in ILC remains unclear, creating a management gap regarding whether patients with ITCs should be risk-stratified and treated similarly to node-negative (pN0) or node-positive (pN1) disease. **Methods:** We performed a retrospective analysis of patients with ILC treated at The University of Texas MD Anderson Cancer Center (Protocol PA20-0040). Distant recurrence-free survival (DRFS) was assessed using Kaplan-Meier methods and compared using log-rank testing. Univariate and multivariable Cox proportional hazards models evaluated associations between clinicopathologic and treatment variables and DRFS. The multivariable model included age, pathologic nodal stage, grade, HER2 status, histologic subtype (classical vs non-classical), and receipt of endocrine therapy, chemotherapy, radiation therapy, and definitive surgery. **Results:** The cohort included 4,217 patients (mean age 56.8 years). Most tumors were classical ILC (89.1%). ITCs were present in 169 patients; comparator groups included pN0 (n=1,799) and pN1 (n=1,040). In univariate analysis, there was no evidence that pN0(i+) were associated with worse DRFS versus pN0 (ITC negative) (HR 0.71, 95% CI 0.45-1.13; p=0.135), whereas pN1 was associated with inferior DRFS versus pN0 (HR 1.85, 95% CI 1.62-2.10; p<0.001). In multivariable analysis, there remained no evidence that pN0(i+) were associated with inferior DRFS versus pN0 (HR 0.661, 95% CI 0.404-1.081; p=0.099), while pN1 was independently associated with worse DRFS versus pN0 (HR 1.922, 95% CI 1.589-2.326; p<0.0001). **Conclusions:** In this large ILC cohort, pN0(i+) (ITCs) did not confer inferior DRFS compared with pN0, and outcomes were clearly distinct from pN1 disease. These findings support prospective validation and may inform nodal-status-driven risk stratification and treatment de-escalation strategies for pN0(i+) patients with ILC. Research Sponsor: None.

Key DRFS comparisons (reference = pN0).

Comparison	Univariate HR (95% CI)	Univariate p-value	Multivariable HR (95% CI)	Multivariable p-value
pN0(i+) vs pN0	0.71 (0.45-1.13)	0.135	0.661 (0.404-1.081)	0.099
pN1 vs pN0	1.85 (1.62-2.10)	<0.001	1.922 (1.589-2.326)	<0.0001

Can we omit surgical axillary staging in early-stage invasive lobular carcinoma?: Results from a large multicenter retrospective cohort study.

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Background: The SOUND, INSEMA and BOOG 2013–08 randomized trials demonstrated that, in selected patients with clinically node-negative (cN0) early-stage breast cancer, omission of sentinel lymph node biopsy (SLNB) results in non-inferior disease-free and invasive disease-free survival. However, invasive lobular carcinoma (ILC) was under-represented in these three studies, and the safety of this approach in ILC remains uncertain due to concerns about a potentially higher axillary nodal burden and risk of undertreatment. We evaluated the axillary nodal burden in ILC patients who met the trials eligibility criteria. **Methods:** This retrospective multicenter study included patients with cT1–2 cN0 ILC, undergoing upfront surgery between 2012 and 2025 across three high-volume Italian institutions. All patients underwent preoperative axillary ultrasound (US), with needle biopsy performed for US-suspicious lymph nodes. Uni- and multivariable logistic regression analyses identified factors associated with advanced nodal disease (pN2/3). **Results:** A total of 1886 patients (median age 65 years) were included. The median radiologic tumor size was 16 mm (IQR 11–23). Most patients underwent SLNB (84%), while the remaining were treated with axillary dissection. The overall rate of pN2/3 disease was 2.5% (48/1886). On univariable analyses, a palpable mass on physical exam (OR 3.59; $p < 0.001$), the presence of US-suspicious axillary nodes (OR 8.19; $p < 0.001$), tumor size > 2 cm (OR 2.96; $p = 0.002$), multicentric disease (OR 4.5; $p < 0.0001$), high tumor grade (OR 2.15; $p = 0.03$), the presence of lymphovascular invasion (LVI) (OR 3.25; $p = 0.001$) and HER2 positivity (OR 3.81; $p = 0.022$) were significantly associated with pN2/3 disease. On multivariable analysis, tumor size > 3 cm ($p = 0.003$), the presence of US-suspicious axillary nodes (OR 6.29; $p = 0.002$), the presence of LVI (OR 3.65; $p = 0.006$), multicentric distribution (OR 5.19; $p < 0.0001$), and HER2 positivity (OR 3.86; $p = 0.041$) were independently associated with pN2/3 disease. **Conclusions:** In this large real-world cohort of SOUND/INSEMA eligible patients with ILC, the rate of pN2/3 disease was 2.5%, higher than that reported in the aforementioned trials. Omission of axillary surgical staging in patients harboring high risk features may result in understaging, with potential implications for adjuvant treatment decisions and oncologic outcomes. Meticulous selection is critical to identify patients who are not at risk of potential undertreatment. Research Sponsor: None.

Changes in metastatic breast cancer (MBC) bone lesions and SREs/fractures via a single intratumoral injection for a first-of-its-kind drug: Preliminary phase 2a results.

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Background: Lytic bone metastases develop in ~70% of breast cancer patients that lead to pain, functional decline, and skeletal-related events (SREs) that reduce quality of life (QoL) and survival. Prophylactic denosumab/bisphosphonate treatment offers limited protection, and current local palliative interventions, EBRT and surgery, don't reverse lytic destruction. Zeta-BC-003 is a first-in-class intratumoral (IT) injectable biomaterial infused with N-allyl noroxymorphone, a small molecule drug that acts through the p21 pathway to drive bone healing and local tumor control. Reports on two Compassionate Use patients (7 lesions, 2-yr follow-up; Palma et al, Pain Manag 2023) showed no SREs/fractures or tumor activity coupled with neo-trabecular bone regeneration and therapeutic spread to other lesions within treated bone, which align with these Phase 2a results. **Methods:** ZGMBC (NCT05280067), an open-label Phase 2a study, enrolled women (N=10; 8/23–3/25) with MBC lytic lesions and a Spinal Instability Numeric Score (SINS) ≥ 3 – ≤ 9 . A single intratumoral (IT) Zeta-BC-003 injection was administered via fluoroscopic guidance. CT & MRI were obtained at Days 0, 84, and 180. Primary endpoints: SREs/fractures; defect volume; pain via the Numeric Rating Scale (NRS); post-op pain control via the Morphine Equivalent Dose (MED); and AE/SAEs. Secondary endpoints: QoL (SF-12v2); SINS; and tumor response. **Results:** Subjects (mean age 52) had the following MBC subtypes: HR+ (N=6), HR+/HER2+ (N=2), HER2+/HR- (N=1), and TNBC (N=1). Breakthrough lesions were seen in 5 subjects despite bisphosphonate therapy and 1 subject died from pleural edema prior to study end. Zeta-BC-003 was injected into 10 subjects with 11 lesions with additional therapeutic effect seen in 4 adjacent untreated lesions. A CR was shown for all lesions and there were no SREs/fractures. The bone defect volume decreased 65.4% ($\pm 20.5\%$; $p=0.0003$) and 84.1% ($\pm 13.1\%$; $p<0.0001$) at Days 84 and 180. NRS pain scores decreased 4.2% ($p<0.05$) and MED decreased $\geq 33\%$ in opioid-treated subjects. SINS scores improved 18.5% ($p<0.05$), indicating increased stability. Increased PCS (24%) and MCS (12%) scores showed increased QoL. There were no treatment emergent SAE/AEs. **Conclusions:** Zeta-BC-003 prevented SREs/fractures in all lesions, reduced lytic defect volume, improved spinal stability, decreased pain/opioid use, improved QoL, ceased tumor activity, and demonstrated therapeutic spread to untreated lesions in the same vertebral body. These findings contrast with historical SRE rates of 53% in MBC and align with the durable CR seen in our Compassionate Use patients. Zeta-BC-003 may represent a first-of-its-kind intratumoral drug that ceases lytic activity, stimulates neo-trabecular bone growth, and improves QoL by eliminating SREs/fractures while also increasing overall survival. Clinical trial information: NCT05280067. Research Sponsor: Zetagen Therapeutics; National Institutes of Health, National Cancer Institute; R44 CA221553; National Institutes of Health, National Cancer Institute; R43CA221553; National Institutes of Health, National Cancer Institute; R44 CA221553; National Institutes of Health, National Cancer Institute; R43CA221553.

National real-world adoption of 5-fraction breast radiotherapy in the United States (2020–2023).

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Background: The landmark FAST-Forward trial demonstrated that ultra-hypofractionated whole-breast irradiation with 26 Gy in 5 fractions over 1 week was non-inferior to 40 Gy in 15 fractions for local control (HR 0.67, 95% CI 0.38–1.16), with similar normal tissue effects at 5 years. In response, major international guidelines incorporated 26 Gy in 5 fractions as a standard approach or recommended option for selected patients. Despite robust randomized evidence and guideline endorsement, U.S. real-world adoption patterns and equity of uptake across patient populations remain incompletely characterized. This study evaluated national trends in 5-fraction breast radiotherapy and sociodemographic differences from 2020 to 2023. **Methods:** The National Cancer Database radiotherapy fractionation fields were used to identify radiotherapy (RT) courses with evaluable fraction counts, and a binary indicator for 5-fraction RT (yes/no) was created. Temporal trends by diagnosis year (2020–2023) were assessed, and associations between 5-fraction RT and sociodemographic factors (primary insurance, urban or rural status, neighborhood income quartile, and race) were examined using chi-square testing. **Results:** Among 536,783 RT courses with complete data from 2020 to 2023, use of 5-fraction RT increased substantially over time: 4.3% in 2020, 8.1% in 2021, 12.7% in 2022, and 17.4% in 2023, resulting in an overall adoption rate of 10.7% ($p < 0.001$). In the subset eligible for fractionation (5, 15–16, 25–28 fractions; $N = 31,448$), 5-fraction RT accounted for 11.7% and differed significantly by insurance type ($p < 0.001$): Medicare 17.4%, Private 7.6%, Medicaid 5.9%, and Uninsured 6.9%. Geographic variation was notable ($p < 0.001$), ranging from 7.3% in mid-size metropolitan areas (250,000–1 million population) to 17.7%–18.1% in more remote or non-adjacent areas; large metropolitan areas (≥ 1 million) had 12.8% uptake. Neighborhood income showed a gradient ($p < 0.001$): 10.1% in the lowest quartile compared to 12.5% in the highest. Race was also associated with uptake ($p < 0.001$), with lower use among Black patients compared to White patients (9.4% vs 12.2%). **Conclusions:** In routine U.S. practice, adoption of 5-fraction breast RT increased rapidly from 2020 to 2023, with the most pronounced growth after 2021, reflecting the swift translation of trial evidence into clinical practice. However, uptake varies by insurance, geography, income, and race, indicating that diffusion is not uniform. Given the potential benefits of ultra-hypofractionation in reducing treatment burden and supporting timely completion, targeted implementation strategies, such as provider education, reimbursement alignment, and facility-level operational support, may be necessary to ensure equitable access as 5-fraction regimens become more widely adopted and potentially become the standard of care. Research Sponsor: None.

A response-adapted and genomically informed strategy to optimize neoadjuvant chemotherapy versus endocrine therapy plus CDK4/6 inhibition in high-risk HR+/HER2– breast cancer.

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Background: Premenopausal patients with locally advanced hormone receptor–positive, HER2–negative (HR+/HER2–) breast cancer are routinely recommended neoadjuvant chemotherapy (NAC) despite heterogeneous and often limited response. In advanced disease, endocrine therapy (ET) plus CDK4/6 inhibition has replaced chemotherapy as first-line treatment. Whether patients with poor early response to NAC may benefit from chemotherapy-sparing strategies remains unclear. We conducted a prospective response-adapted study integrating early chemosensitivity assessment with exploratory genomic profiling to guide neoadjuvant treatment selection. **Methods:** A total of 116 premenopausal patients with stage II–III HR+/HER2– breast cancer received two initial cycles of TAC chemotherapy (docetaxel, doxorubicin, and cyclophosphamide). Radiologic response was assessed after two cycles. Patients achieving partial response (PR) continued TAC. Patients with stable disease (SD) were randomized to either continue TAC (NAC) or switch to 16 weeks of ET consisting of dalpiciclib (CDK4/6 inhibitor), exemestane, and goserelin (NET). Whole-exome sequencing was performed in an exploratory subset. The primary endpoint was objective response rate (ORR). **Results:** After two cycles of TAC, 30 patients achieved PR, while 86 exhibited SD and were subsequently randomized. Among evaluable patients, the ORR was 68.3% in the NET group (41 evaluable patients) compared with 48.7% in the continued NAC group (39 evaluable patients), indicating a higher response rate with NET in tumors demonstrating poor early chemosensitivity. Exploratory genomic analyses further showed that NET-sensitive tumors were predominantly TP53 wild-type and lacked PIK3CA or AKT alterations, consistent with a highly endocrine-dependent biology. In contrast, nonresponders to NET frequently harbored TP53 mutations, often in combination with PIK3CA/AKT pathway alterations, whereas patients who responded to continued chemotherapy commonly exhibited TP53 or TTN mutations, suggesting a chemotherapy-responsive but endocrine-refractory phenotype. **Conclusions:** Taken together, our findings indicate that in premenopausal patients with stage II–III HR+/HER2– breast cancer who demonstrate suboptimal early response to intensive neoadjuvant chemotherapy, continued cytotoxic treatment may not be optimal for all patients. A response-adapted strategy integrating early functional assessment with genomic features, particularly TP53 and PI3K/AKT pathway status, distinguishes endocrine-sensitive from chemotherapy-sensitive disease. These results provide a biologically informed framework for neoadjuvant treatment selection and support biomarker-enriched randomized trials evaluating chemotherapy-sparing strategies in selected patients. Clinical trial information: NCT06009627. Research Sponsor: None.

Impact of age on breast cancer outcomes in the neoadjuvant I-SPY2 trial.

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Background: Historically, young women with early-stage breast cancer (EBC) have had worse outcomes than older women. This is based largely on population-based or adjuvant studies, with limited neoadjuvant data. **Methods:** Patients (pts) with Stage 2–3 EBC treated with neoadjuvant chemotherapy +/- immunotherapy (Cx-IT) on the I-SPY2 trial between 2010–2022 were included (data cutoff 07/2025). Pts were stratified by age at trial screening (<40 vs ≥40 yrs), and clinical/molecular subtypes, including ImPrint, an immune signature predictive of Cx-IT response. Pathologic complete response (pCR), residual cancer burden (RCB), and event-free survival (EFS) were evaluated by age and disease subtypes using Kaplan–Meier methods and Cox proportional hazard ratios (HR). **Results:** Among 2117 evaluable pts, 510 (24%) were <40 yrs and 1607 (76%) were ≥40 yrs. Overall, 43% of tumors were HR+/HER2–, 35% HR–/HER2– (TN), 22% HER2+. 34% / 66% were ImPrint +/- (27% / 73% for HR+; 44% / 56% for HR–), with similar rates of ImPrint +/- between age groups. Rates of pCR (31% vs 35%) and RCB 0/1 (48% vs 51%) were similar between pts <40 and ≥40. Overall, pts <40 had worse EFS ($p < 0.01$) vs pts ≥40; however, in pts who achieved pCR, there was no difference in EFS in all biologic subgroups (HR 0.90, $p=0.77$). In contrast, in pts with residual disease, those <40 had worse EFS than pts ≥40 (HR 0.72, $p<0.01$). The worse EFS in pts <40 with residual disease was limited to pts with ImPrint– disease, in both HR+/HER2– (HR 0.64, $p=0.02$) and TN (HR 0.62, $p=0.04$) subtypes, where response rates were lower. In ImPrint+ pts, no differences in EFS by age were observed (HR 1.01, $p=0.98$). Similar results were seen for pts with HR+/HER2– disease when stratifying by RCB (RCB 0/1 vs 2/3). There was no difference in EFS by age for pts with RCB 0/1 disease in any subtype (HR 0.66, $p=0.09$). For ImPrint–, pts <40 with RCB 2/3 disease had worse EFS than pts ≥40 (HR 0.61, $p=0.01$). For HR+/HER2–, 64% of tumors were MammaPrint (MP) High 1 vs 36% MP High 2, and 74% were Luminal. When stratifying by pCR or RCB 0/1, similar age-related EFS differences were observed in HR+/HER2– Luminal or MP High 1 tumors, as in ImPrint– tumors. **Conclusions:** Overall, young pts <40 yrs with high-risk EBC in the I-SPY2 trial had worse 5-yr EFS than pts ≥40; however, when taking response into account, there were no age-related EFS differences for pts who had an excellent response to neoadjuvant Cx-IT (i.e. pCR or RCB 1). The EFS difference was driven by pts with residual disease, specifically in the subset with ImPrint– disease, which is associated with less response to Cx-IT. Whereas, for pts with ImPrint+ disease, there was no difference in EFS by age, regardless of pCR or RCB. This highlights the unmet need for more effective therapies for immune-negative tumors. Our results reinforce the importance and prognostic value of neoadjuvant therapy, particularly in our youngest pts, to better risk-stratify and optimize treatment based on tumor biology and response to therapy. Clinical trial information: NCT01042379. Research Sponsor: None.

Pathologic complete response in rare histologic subtypes of early-stage triple-negative breast cancer in the era of immunotherapy.

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Background: The addition of immunotherapy (IO) to chemotherapy has improved outcomes in early-stage triple-negative breast cancer (eTNBC). Rare histologic subtypes, like lobular and metaplastic, are managed using the same treatment algorithms as ductal TNBC but historically have been associated with worse outcomes. Whether the benefits of IO extend to these rare subtypes in real-world practice remains unclear. **Methods:** We used the National Cancer Database to retrospectively identify patients diagnosed with stage II–III TNBC who received neoadjuvant therapy from 2021 to 2022, after FDA approval of IO for eTNBC. TNBC was categorized as ductal, lobular, metaplastic or other. Logistic regression was used to assess pathologic complete response (pCR) stratified by IO use. All models were controlled for key demographic and clinicopathologic factors. **Results:** We identified 17,006 patients with stage II–III TNBC (mean age 55.0 years). Most patients had ductal histology (91.1%), with smaller proportions of metaplastic (2.5%), and lobular (1.9%). Overall, 11,132 (65.5%) patients received IO and achieved a higher pCR rate than those who did not receive IO (45.2% vs 33.1%). pCR rate differed significantly by histologic subtype treated with neoadjuvant chemotherapy, both with and without IO. Among patients who received IO, pCR rate was highest in ductal TNBC (47%) and was significantly lower in lobular (18.9%) and metaplastic (17.6%) tumors ($p < 0.001$). Similarly, in patients who did not receive IO, ductal TNBC had the highest pCR rate (34.6%) with metaplastic and lobular subtypes having lower pCR rates (12.5% and 14.3%, respectively; $p < 0.001$). After covariate adjustment, all non-ductal subtypes had significantly lower odds of pCR compared to ductal TNBC regardless of receipt of IO. This was most notable for metaplastic TNBC with an odds ratio [OR] of 0.19 (95% CI 0.10–0.33) with IO and OR 0.13 (95% CI 0.04–0.44) without IO. Lobular TNBC was also associated with significantly lower odds of pCR in IO-treated patients (OR 0.50, 95% CI 0.28–0.90) with similar trends observed in patients treated without IO. **Conclusions:** In this national real-world cohort, we demonstrate that despite the adoption of neoadjuvant IO for eTNBC and improved pCR rates overall, rare histologic subtypes continue to experience inferior treatment outcomes. Metaplastic and lobular TNBC had persistently low pCR rates, regardless of IO use. These results highlight the urgent need for novel therapeutic strategies and dedicated clinical trials for these rare histologic subtypes. Research Sponsor: National Institute on Aging; T32AG000243.

Association of immunotherapy infusion timing with outcomes in early-stage triple-negative breast cancer.

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Background: Circadian regulation of immune function has been shown to influence the efficacy of immune checkpoint inhibitors (IO) in several malignancies. However, the clinical relevance of IO infusion timing in breast cancer remains unclear. We evaluated the association between IO timing, baseline characteristics, pathologic complete response (pCR), and recurrence outcomes in patients with early-stage triple-negative breast cancer (TNBC). **Methods:** We conducted a retrospective cohort study of 139 patients with early-stage TNBC treated at Manhattan and Mineola campuses alongside with four sites in Queens, Brooklyn, and Long Island using a KEYNOTE-522-based neoadjuvant regimen including pembrolizumab, chemotherapy, and surgery between July 2021 and June 2025. IO infusion timing was dichotomized using the cohort median time (12:22 PM); patients receiving all first three IO infusions after this cutoff were classified as late. Baseline characteristics including age, body mass index (BMI), race, ECOG performance status, clinical T/N stage, and chemotherapy backbone were compared between groups. pCR was defined as absence of residual invasive disease. Recurrence outcomes included local recurrence, distant recurrence, or death. Multivariable analyses adjusting for baseline clinical factors were performed. **Results:** Amongst our 139 patients, 108 received early IO and 31 received late IO. Patients receiving early IO were younger (mean age 55.9 vs 63.5, $p = 0.025$) and had lower BMI (27.4 vs 30.6, $p = 0.017$), while ECOG performance status 0-1 (early: 98.1% vs late: 90.3% respectively, $p = 0.075$), non-white race (52.5% vs 56%, $p = 0.825$), clinical T/N stage ($T \geq 2$: 88.7% vs 90.3%, $p = 0.999$; $N \geq 1$: 37.4% vs 38.7%, $p = 0.999$), carboplatin/paclitaxel chemotherapy backbone distributions (93.5% vs 90.3%, $p = 0.693$) were similar between groups. pCR occurred in 63% of patients receiving early IO and 45.2% receiving late IO ($p = 0.098$). Recurrence outcomes occurred in 3.7% of the early IO group and 16.1% of the late IO group ($p = 0.026$), driven primarily by distant recurrence (0.9% vs 12.9%, $p = 0.009$). After adjusting for age, BMI, and clinical T/N stage, late IO remained associated with distant recurrence (adjusted odds ratio 16.1; 95% CI, 1.39–186.4; $p = 0.026$). **Conclusions:** In this retrospective analysis, early IO infusion timing was associated with significantly lower recurrence risk, particularly distant recurrence. While pCR rates were not statistically significant between early vs late IO, we observed a numerical difference favoring early IO. These findings may suggest that circadian timing of IO may influence long-term outcomes beyond pathologic response. Given the retrospective design and limited number of events, these results are hypothesis-generating and warrant prospective validation. Research Sponsor: The Betty Ajces grant (philanthropy fund), NYU Langone Long Island Grossman School of Medicine, Perlmutter Cancer Center.

Neoadjuvant chemotherapy combined with toripalimab for triple-negative breast cancer: A prospective, single-arm, multi-center study (NEOTORCH-BREAST02).

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Background: Neoadjuvant de-escalation chemo-immunotherapy with abbreviated cycles remains unclear. We aimed to assess the efficacy and safety of toripalimab, a novel PD-1 antibody, combined with an abbreviated course of epirubicin–cyclophosphamide (2 cycles) followed by nab–paclitaxel (2 cycles), as a neoadjuvant regimen for early-stage TNBC patients. **Methods:** This phase II trial, conducted from 2024 to 2025, involved stage II–III TNBC. The neoadjuvant regimen included epirubicin, cyclophosphamide, and toripalimab for 2 cycles, followed by nab–paclitaxel and toripalimab for another 2 cycles. Patients achieving a pathological complete response (pCR) received up to 13 cycles of adjuvant toripalimab, while those with residual disease received additional chemotherapy and toripalimab. Whole-exome sequencing (WES) and circulating tumor DNA (ctDNA) monitoring were also performed. The primary endpoint was the total pCR (tpCR) rate (ypT0/is ypN0). Secondary endpoints included breast pCR (bpCR; ypT0/is), residual cancer burden (RCB 0–1), objective response rate (ORR), and event-free survival. This trial was registered with ClinicalTrials.gov (NCT06682195). **Results:** As of January 20, 2026, 48 patients were enrolled, and 40 underwent surgery (median age: 48 years; 87.5% stage II). WES analysis in 37 patients identified BRCA1 mutations in 12 (32.4%). Baseline ctDNA was positive in 32 of 34 (94.1%) patients, and 24 (75%) achieved ctDNA negativity after neoadjuvant therapy. Among 40 surgical patients, tpCR, bpCR, RCB 0–I, and ORR rates were 55%, 60%, 70, and 92.5%, respectively. Subgroup analyses showed tpCR rates of 25% for CPS <1, 58.3% for CPS ≥1, 72.7% for CPS ≥10, and 80% for CPS ≥20. For TILs <10, tpCR was 25%, increasing to 66.6% for TILs ≥10, 82.3% for TILs ≥30, and 85.7% for TILs ≥50. Among BRCA1 mutation carriers, 75% achieved tpCR, and 62.5% of patients with ctDNA negativity also achieved tpCR. Grade ≥3 AEs occurred in 6 (15%) patients, most commonly vomiting (7.5%) and leukopenia (7.5%). Hypothyroidism was the most frequent immune-related AE (17.5%, all grade 1–2). **Conclusions:** Preliminary findings indicate that this 4 cycles de-escalation neo-adjuvant strategy is effective and safe for early-stage TNBC, warranting further investigation in randomized trials. Clinical trial information: NCT06682195. Research Sponsor: None.

Response endpoints for the entire cohort (N = 40).		
Efficacy endpoint	N (%)	95% CI(%)
tpCR(ypT0/is, ypN0)	22(55.0)	38.5–70.4
bpCR(ypT0/is)	24(60.0)	43.3–75.0
Miller–Payne (MP) grades		
MP score 1	2 (5.0)	0.6-23.2
MP score 2	3 (7.5)	1.6-27.3
MP score 3	7 (17.5)	7.3-34.7
MP score 4	4 (10.0)	2.8-23.7
MP score 5	24 (60.0)	43.3.-75.0
Residual cancer burden (RCB) class		
RCB class 0–I	28(70.0)	53.3–83.4
RCB class II	6 (15.0)	5.7-31.9
RCB class III	6 (15.0)	5.7-31.9

Abbreviations: tpCR, total pathological complete response; bpCR, breast pathological complete response; CI, confidence interval.

Application of a neoadjuvant 21-gene breast recurrence score assay to redirect surgical and systemic treatment pathways in early breast cancer: A multicenter prospective study.

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Background: The 21-gene Oncotype DX Breast Recurrence Score assay is well established for determining use of adjuvant chemotherapy in hormone receptor (HR)-positive, HER2-negative breast cancer patients. However, the role of the 21-gene assay in the neoadjuvant setting has yet to be established. We previously reported the impact of the 21-gene assay in the neoadjuvant setting in node-negative breast cancer patients, which led to a reduction in the recommendation of chemotherapy in about one-third of patients. Here, we report the impact of the assay on neoadjuvant treatment pathways including surgery, endocrine therapy, and chemotherapy, in addition to overall costs. **Methods:** We performed a multicentre, prospective observational trial of HR-positive, HER2-negative breast cancer patients with T2-T3 disease and clinically negative axillary lymph nodes. Physicians completed questionnaires prior to and after Recurrence Score (RS) results, indicating their treatment choice for neoadjuvant endocrine or chemotherapy, or upfront surgery. Data was also collected at 6 months after initiation of therapy, to verify treatment received. The primary and secondary objectives were to evaluate impact of RS results on physician's treatment decisions and on drug (anti-emetics and pre-medication), and nursing (counselling and infusion time) costs, respectively. **Results:** A total of 70 patients were enrolled in the study as part of five hospital centers of the McPeak Sirois Group in the province of Quebec from 2018–2021. Feasibility of the 21-gene assay from core biopsy samples was 98.6%. At 6-month follow-up, the 21-gene assay led to a change in treatment decision in 52.2% of patients, including de-escalation from neoadjuvant chemotherapy to either upfront surgery in 21.7%, or to neoadjuvant endocrine therapy in a further 21.7%. The use of upfront surgery changed from 10.0% at baseline to 33.3% at 6-month follow-up ($p = 0.0004$). Use of neoadjuvant endocrine therapy also changed from 12.9% to 29.0% ($p = 0.02$). Among patients treated with upfront surgery or neoadjuvant endocrine therapy, 52.2% and 55.0% of patients, respectively, had a $RS \geq 16$. At baseline, for all patients, total chemotherapy-associated drug costs were \$190,656 CAD, and nursing-associated costs were \$96,918 CAD. RS-guided treatment recommendation reduced chemotherapy-associated drug costs by 32.3% and nursing resource utilization by 44.1%. **Conclusions:** The use of the 21-gene assay reclassified treatment pathways in 52.2% of patients, including shifting patients from neoadjuvant chemotherapy toward upfront surgery or neoadjuvant endocrine therapy, while reducing chemotherapy-related resource utilisation. These data support the use of the 21-gene assay as a clinical decision-making tool in the neoadjuvant setting. Additional information: Coauthor André Robidoux, MD, died in July 2020. Research Sponsor: Exact Sciences; Scotiabank Chair in the Diagnosis and Treatment of Breast Cancer, University of Montreal.

Evaluation of a taxane mRNA-based profile in neoadjuvant therapy across I-SPY2 investigational arms.

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Background: Neoadjuvant chemotherapy is standard in early-stage breast cancer (eBC), enabling tumor downstaging and treatment tailoring. Taxanes are a core component of standard neoadjuvant regimens across breast cancer subtypes, and biomarkers of taxane response may inform treatment strategies. In I-SPY2, high-risk eBC patients (pts) were randomized to standard taxane-anthracycline-cyclophosphamide (T-AC) or investigational regimens (IRs). A 113-gene model has been validated in multiple cohorts and in the I-SPY2 T-AC arm. Here, we extend these analyses to nine I-SPY2 IRs, which all include a T-AC backbone. **Methods:** Agilent gene expression data from 987 high-risk eBC pre-treatment tumors (GSE194040) were analyzed from pts treated with T-AC $\pm$ nine IRs. Pts were scored on a scale from 0-100 and association of score (per 50-point increase) with pCR was assessed using logistic regression. For benchmarking, the raw score was Z-scaled, and OR was calculated per 1 standard deviation increase (OR/1SD) to enable comparison with published I-SPY2 biomarkers. **Results:** In a pooled multivariable logistic model including all treatment arms (N = 987), a 50-point increase in score was strongly associated with higher odds of pCR after adjusting for treatment arm, hormone receptor (HR) and HER2 (OR = 2.99, p = 7.93e-13). Allowing for treatment-specific score effects did not reveal statistically significant interactions. The score was benchmarked against 27 I-SPY2 qualifying biomarkers using OR/1SD increase. In the full cohort (N = 987), it ranked among biomarkers with the largest effect sizes for pCR. When analyses were stratified by treatment arm, the score was the top-ranked biomarker by effect size in the T-AC arm (N = 210) and trebananib arm (N = 134), while effect estimates in other arms were directionally consistent but not uniformly statistically significant. Furthermore, the score provided independent predictive information beyond I-SPY2 Response Predictive Subtypes (RPS). In multivariable models adjusting for RPS, the score remained significantly associated with pCR in the full cohort and the T-AC arm. As an illustrative example, using score quartiles defined in the full cohort, pCR rates among HR+/HER2- pts (N = 379) increased from 6.0% (8/134) in the lower quartile to 43.1% (28/65) in the upper quartile. Similarly, among TN pts (N = 363), pCR rates increased from 16.7% (5/30) in the lower quartile to 48.7% (77/158) in the upper quartile. **Conclusions:** A taxane-specific gene expression score was strongly associated with pCR across all taxane-containing I-SPY2 regimens and provided information beyond established response predictive subtypes. These findings suggest that taxane sensitivity contributes substantially to treatment response across I-SPY2 therapies and highlights the potential value of incorporating additional drug-specific biomarkers to further refine response prediction. Research Sponsor: None.

Efficacy and safety of neoadjuvant disitamab vedotin (DV) in combination with toripalimab (Tor) and concurrent/sequential chemotherapy (chemo) in patients with HR-negative, HER2-low breast cancer: A randomized multicenter phase 2 study.

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Background: For patients (pts) with triple-negative early breast cancer (BC), recommended neoadjuvant regimens include chemo with or without immunotherapy, which achieve a modest rate of pathological complete response (pCR). Emerging data suggest that anti-HER2 antibody-drug conjugates (ADCs) have antitumor activity in HER2-low advanced BC. Notably, DV (anti-HER2 ADC) has shown encouraging efficacy both as monotherapy and in combination with Tor (PD-1 inhibitor) in pts with HER2-low advanced disease. We evaluated the efficacy and safety of neoadjuvant DV-containing regimens in pts with hormone receptor (HR)-negative HER2-low BC in a randomized phase 2 trial. Here, we report results from the pts receiving DV plus Tor combined with concurrent/sequential chemo. **Methods:** Eligible pts were aged ≥ 18 years with untreated histologically confirmed HR-negative and HER2-low (centrally confirmed as IHC 1+, or IHC 2+/ISH-) BC (T1cN1-2Mo or T2-3N0-2Mo as per AJCC 8th edition) who were planned to undergo curative-intent breast cancer surgery. Pts randomized to group A received DV (2.0 mg/kg Q2W) + Tor (3.0 mg/kg Q2W) + carboplatin (AUC 3 Q2W or AUC 1.5 QW) for 18 weeks. Pts randomized to group B received DV + Tor for 12 weeks followed by epirubicin (90 mg/m² Q3W) + cyclophosphamide (600 mg/m² Q3W) + Tor for additional 12 weeks. Stratification factors were PD-L1 status (positive or negative) and clinical staging (stage II or III). After neoadjuvant treatment, surgery was performed. Enrollment in group B was closed after 28 pts had been randomized to this group, while enrollment in group A continued. The primary endpoint was total pCR (tpCR, defined as ypTo/TisNo) rate; secondary endpoints included breast pCR (bpCR, defined as ypTo/Tis) rate, objective response rate (ORR), and safety. **Results:** 40 pts were enrolled in group A (median age: 46.0 years; clinical stage III: 37.5%; clinical N+: 82.5%; IHC 1+: 72.5%; PD-L1 CPS < 10: 37.5%) and 28 in group B (54.0%; 42.9%; 82.1%; 67.9%; 32.1%). The tpCR was achieved in 25 pts (62.5% [95% CI: 45.8–77.3]) in group A and 14 pts (50.0% [31.9–71.3]) in group B. The bpCR rate was 65.0% (95% CI: 48.3–79.4) and 53.6% (35.3–74.5) for groups A and B, respectively. The corresponding ORR was 92.5% (95% CI: 79.6–98.4) and 75.0% (55.1–89.3), respectively. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 29 (72.5%) of pts in group A and 23 (82.1%) in group B. Serious TRAEs occurred in 6 (15.0%) and 7 (25.0%) of pts, respectively. Immune-related adverse events occurred in 3 (7.5%) of pts in group A and 7 (25.0%) in group B. No grade 5 TRAEs occurred. **Conclusions:** Both treatment regimens showed manageable safety profiles; DV + Tor + carboplatin showed numerically better efficacy in pts with previously untreated, HR-negative, HER2-low, early BC. Clinical trial information: NCT06227117. Research Sponsor: RemeGen Co., Ltd.

Efficacy and safety of a short-course (12-week) de-escalated neoadjuvant regimen (weekly paclitaxel/trastuzumab/pertuzumab) in early HER2-positive breast cancer: Interim analysis of a prospective study.

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Background: Standard neoadjuvant regimens for HER2-positive early breast cancer (EBC), such as 6 cycles of TCHP, achieve high pathological complete response (pCR) rates but carry significant toxicity risks. De-escalation strategies aiming to reduce treatment intensity and duration without compromising efficacy are clinically relevant. We present the interim analysis of a prospective study evaluating a shortened (12-week), carboplatin-free and anthracycline-free regimen (THP). **Methods:** We enrolled patients (pts) with histologically confirmed HER2-positive (IHC 3+ or ISH+) EBC, clinical stages T0–1N1M0 or T2–3N0–1M0. Pts received a de-escalated regimen consisting of 12 weekly infusions of paclitaxel (80 mg/m²) combined with trastuzumab and pertuzumab administered every 3 weeks for 4 cycles (12 weeks total). The primary endpoint was pCR rate (ypT0/is ypN0). Secondary endpoints included safety and treatment adherence. This interim analysis reports data from the first 70 pts who completed surgery. **Results:** Median age was 50 years. The cohort included 69% stage IIA and 31% stage IIB pts; 57% were cN0. 60% had HR-positive and 40% had HR-negative disease. Treatment compliance was excellent: 100% of pts completed the full 12-week course. The overall pCR rate was 60.0% (42/70). Efficacy was strongly associated with hormonal status: the pCR rate reached 82.1% (23/28) in the HR-negative subgroup, compared to 45.2% (19/42) in the HR-positive subgroup. The safety profile was exceptionally favorable compared to historical TCHP data. Grade ≥3 neutropenia occurred in only 4% of pts. No cases of febrile neutropenia or symptomatic cardiotoxicity were observed. Grade ≥3 non-hematological toxicity (diarrhea/rash) was limited to 8%. Peripheral neuropathy was predominantly grade 1, with occasional grade 2 events; no grade ≥3 neuropathy occurred. **Conclusions:** The short-course (12-week) de-escalated THP regimen demonstrated high efficacy, particularly in HR-negative/HER2-positive pts (pCR 82.1%), comparable to longer, more toxic multi-agent regimens. With a 0% rate of febrile neutropenia and 100% completion rate, this regimen represents a promising "chemo-light" option for selected patients, potentially guiding future de-escalation strategies in personalized oncology. Research Sponsor: None.

Baseline characteristics and clinical outcomes (N=70).

Characteristic / Endpoint	N (%) or Median (Range)
Median Age, years	50 (29–75)
Node-positive disease (cN+)	30 (43%)
HR-negative / HER2-positive	28 (40%)
Completed full 12-week NACT	70 (100%)
Breast-conserving surgery	34 (49%)
Pathological Complete Response (Total)	42 (60.0%)
pCR in HR-negative subgroup	23/28 (82.1%)
pCR in HR-positive subgroup	19/42 (45.2%)
Grade 3-4 Neutropenia	3 (4%)
Febrile Neutropenia	0 (0%)

Neoadjuvant penpulimab combined with taxanes and carboplatin in triple-negative breast cancer: Updated efficacy and safety results from the phase II NeoTAPPL study.

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Background: The KEYNOTE-522 and IMpassion031 trials established that adding immune checkpoint inhibitors to neoadjuvant chemotherapy significantly improves pathologic complete response (pCR) rates and survival outcomes in triple-negative breast cancer (TNBC). In our previously reported phase II NeoTAPPL trial, an anthracycline-free neoadjuvant regimen of penpulimab (anti-PD-1 antibody), carboplatin, and taxanes demonstrated promising efficacy and manageable safety. Here, we present updated efficacy and safety outcomes from the full trial cohort. **Methods:** In this open-label, multi-center phase II study, patients with untreated, histologically confirmed TNBC in stage II-III were enrolled. Patients received 6 cycles of neoadjuvant therapy with penpulimab (200 mg, d1, q3w) plus taxanes (docetaxel 75 mg/m² or nab-paclitaxel 260 mg/m², d1, q3w) and carboplatin (AUC=6, d1, q3w). Patients who either completed or discontinued the neoadjuvant treatment would undergo breast surgery. Adjuvant chemotherapy and immunotherapy were at the discretion of the treating physician, and radiation therapy was per standard of care. The primary endpoint was the rate of pCR based on the definition of ypT0/Tis ypN0. Secondary endpoints included residual cancer burden (RCB), event free survival (EFS), overall survival (OS), adverse events (AE), and immune response biomarkers. **Results:** 64 patients were enrolled, all of whom received neoadjuvant treatment and underwent surgery. The median age was 53 years (range, 32-73). At diagnosis, 54 patients (84.4%) had stage II disease. pCR was achieved in 41 of 64 patients (64.1%; 95% CI, 51.1%-75.7%), and 50 patients (78.1%; 95% CI, 66.0%-87.5%) achieved RCB 0-1. The objective response rate (ORR) and disease control rate (DCR) were 93.8% (95% CI, 84.8%-98.3%) and 98.4% (95% CI, 91.6%-100%), respectively. Subgroup analyses revealed pCR rates of 64.8% (35/54) in patients with stage II disease and 60.0% (6/10) in those with stage III disease. The pCR rate was 64.9% (24/37) in node-negative patients and 63.0% (17/27) in node-positive patients. Treatment-emergent adverse events (TEAEs) of any grade occurred in all 64 patients, with grade ≥3 TEAEs reported in 24 patients (37.5%). The most common grade ≥3 TEAEs were alopecia (20.3%), anemia (14.1%), neutropenia (10.9%), and leukopenia (10.9%). **Conclusions:** The NeoTAPPL trial demonstrates that an anthracycline-free neoadjuvant regimen is an effective and tolerable treatment strategy for patients with TNBC. The regimen achieved a high pCR rate, which remained consistent across key prognostic subgroups, including disease stage and nodal status. The safety profile was manageable, with no new safety signals identified. Clinical trial information: ChiCTR2300071925. Research Sponsor: National Science and Technology Major Project (2025ZD0543900); Development Center for Medical Science & Technology National Health Commission of the People's Republic of China WKZX2023CX010002.

Outcomes after recurrence on neoadjuvant chemo-immunotherapy (NCIT) in patients (pts) with high-risk early-stage triple-negative breast cancer (eTNBC).

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Background: NCIT improves survival in high-risk eTNBC; however, trial-based data show that most relapses after NCIT are early. Real-world data are lacking. **Methods:** This retrospective study included pts from the DFCI Multicenter TNBC registry with eTNBC or estrogen receptor (ER)-low ($\leq 10\%$), HER2-negative breast cancer (BC) treated with NCIT who underwent surgery before 7/1/2025. Aims were to evaluate (1) patterns of relapse; (2) BC-specific event-free survival (BC-EFS) from the first NCIT dose to relapse, contralateral BC, or death; (3) first-line (1L) metastatic systemic treatment patterns, and (4) time to progression (TTP). **Results:** 220 pts were identified, with median age of 50.1 yrs (IQR: 40.5–60.8). Median follow-up (FU) was 32.7 months (mo) (IQR, 30.4–34.4). At last FU, 29 pts (13.2%) had relapsed (locoregional, n=2; distant, n=27). Among these, 86.2% had not experienced pathologic complete response. Among relapsed pts with PD-L1 assessment (n=16), 43.8% (n=7) had a Combined Positive Score (CPS) < 10 ; 56.2% (n=9) had a CPS ≥ 10 . BC-EFS is shown in the Table. 1L therapy consisted of antibody-drug conjugate (ADC) in 51.7% (n=15), Poly ADP-ribose Polymerase inhibitor (PARPi) in 13.8% (n=4), chemotherapy in 13.8% (n=4), ADC+PARPi in 3.4% (n=1), CIT in 3.4% (n=1), and HER2-directed in 3.4% (n=1); 10.3% (n=3) died before 1L therapy. Median (m)TTP in 1L (n=26) was 7.7 mo (95% CI, 6.0–13.0) and detailed in the Table. Among pts with disease-free interval (DFI) ≤ 6 mo (n=8), mTTP was 5.1 mos (2.7–NR), with TTP rates of 50.0% (25.0–100.0) at 6 mo and 16.7% (2.9–95.3) at 12 mo. In those with DFI 6–12 mo (n=9), mTTP was 9.7 mo (7.4–NR); TTP rates were 88.9% (70.6–100.0) at 6 mo and 25.4% (7.7–83.8) at 12 mo. For DFI > 12 mo (n=9), mTTP was 8.6 mo (5.6–NR), with TTP rates of 71.4% (44.7–100.0) at 6 mo and 28.6% (8.9–92.2) at 12 mo. Among pts treated with 1L ADC (n=16), mTTP was 8.6 mo (7.4–NR); TTP rates were 77.9% (58.4–100.0) at 6 mo and 26.0% (9.9–68.3) at 12 mo. In non-ADC-treated pts (n=10), mTTP was 6.2 mo (3.78–NR), with TTP rates of 60.0% (36.2–99.5) at 6 mo and 20.0% (5.8–69.1) at 12 mo. Median overall survival (from diagnosis) among pts with relapse was 26.3 mo (95% CI, 25.0–NR). **Conclusions:** Relapse after NCIT was predominantly early with poor metastatic outcomes, underscoring an urgent need for new strategies in this population largely excluded from clinical trials. Research Sponsor: Dana-Farber/Harvard Cancer Center; 1P50CA168504; Susan G. Komen; Breast Cancer Alliance; Benderson Family Fund for TNBC Research.

Time from NCIT start (mo)	Any NCIT (n = 216)		KEYNOTE-522 (n = 176)		Time from 1L start (mo)	1L for metastatic TNBC (n = 26)	
	BC-EFS % (95% CI)	Event N	BC-EFS % (95% CI)	Event N		TTP survival % (95% CI)	Event N
6	100.0 (100.0, 100.0)	0	100.0 (100.0, 100.0)	0	6	70.8 (54.6, 91.7)	7
12	95.4 (92.5, 98.4)	9	95.0 (91.7, 98.4)	8	12	23.6 (11.0, 50.5)	17
18	89.4 (84.9, 94.0)	19	89.7 (84.9, 94.8)	15	18	14.2 (5.0, 40.3)	19
24	86.4 (81.3, 91.8)	23	86.0 (80.3, 92.2)	19	24	9.4 (2.5, 35.2)	20
36	79.9 (72.2, 88.3)	27	82.2 (74.8, 90.3)	21			

Predicting chemotherapy benefit in premenopausal women with intermediate genomic scores using deep learning.

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Background: The TAILORx trial demonstrated that adjuvant chemotherapy can be safely omitted in postmenopausal women with node-negative HR+/HER2- breast cancer and a 21-gene Recurrence Score (RS) of 11–25. However, chemotherapy benefit could not be excluded for pre/peri-menopausal women with RS 16–25, creating a clinical dilemma that may lead to overtreatment. Using TAILORx data, we have shown that deep learning (DL) applied to hematoxylin and eosin (H&E) can accurately identify women with low or high RS (Shamaï et al., *Lancet Oncol*, 2026). We hypothesized that DL applied to H&E could be used to predict chemotherapy benefit in pre/peri-menopausal women with RS 16–25, thereby facilitating precise treatment de-escalation. **Methods:** We trained a DL model using H&E slides of both post- and pre/peri-menopausal women from TAILORx, with low (RS<16) and high (RS>25) genomic scores (N=5811), to predict distant recurrence-free interval (DRFI), while excluding patients with RS 16–25 from the training process. The test cohort consisted of women from TAILORx with RS 16–25. Within TAILORx, this test group was originally randomized to either endocrine therapy alone or chemo-endocrine therapy, enabling a direct evaluation of the model's ability to predict chemotherapy benefit. For comparison, RSCLIN was also computed. **Results:** When testing on pre/peri-menopausal women with RS 16–25 (N=1234), the model classified 942 (76%) and 292 (24%) as low and high risk. For patients receiving no chemotherapy, the model demonstrated high prognostic performance for DRFI (C-index=0.75; 95% CI: 0.67–0.82), and strong risk stratification (HR=5.43; 95% CI: 2.87–10.29, $p<0.001$). In the low-risk group, no benefit from chemotherapy was observed (HR=1.07, 95% CI: 0.54–2.15, $p=0.84$). In the high-risk group, chemotherapy was associated with a significant improvement in DRFI (HR=3.57, 95% CI: 1.54–8.30, $p=0.003$). A significant interaction between treatment and risk group was observed ($p=0.024$). The model outperformed RSCLIN (p -interaction=0.314). When testing on postmenopausal patients with RS 16–25 (N=2249), the model could not predict chemotherapy benefit (p -interaction=0.926). **Conclusions:** This digital pathology signature provides prognostic information for distant recurrence and predictive information for chemotherapy benefit in pre/peri-menopausal women with HR+/HER2-, node-negative early breast cancer with RS 16–25. These findings support the potential use of histopathology-based DL to guide chemotherapy de-escalation in this clinically challenging subgroup. The inability of the model to predict chemotherapy benefit in postmenopausal women suggests that the deep learning signature may be identifying tumors sensitive to chemotherapy-induced ovarian suppression, highlighting a subset who could benefit from OFS as an alternative to chemotherapy. Research Sponsor: Israel Innovation Authority; Zimin Institute for Artificial Intelligence Solutions in Healthcare; Israel Precision Medicine Partnership.

EA1181: Accuracy of pre-surgery MRI to predict pathologic complete response after taxane, trastuzumab, and pertuzumab (THP) in HER2-positive breast cancer.

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Background: Accurate prediction of pathologic complete response (pCR) after preoperative therapy for HER2-positive (HER2+) breast cancer can help triage patients to immediate surgery vs additional preoperative therapy. Pre-surgery (i.e., after neoadjuvant therapy) imaging studies may help estimate the likelihood of pCR. In EA1181, patients (pts) with stage II-III A HER2+ breast cancer received four cycles of preoperative taxane, trastuzumab, and pertuzumab (THP×4). Pre-surgery imaging was required, though the specific imaging modality was not mandated. Here, we report the accuracy of pre-surgery breast MRI to predict pCR (ypT0/Tis, ypN0). **Methods:** Among 2,141 pts treated with THP×4, 1,378 had pre-surgery breast MRI and were representative of the overall cohort, although T3 tumors were more common (16% vs 9%). MRI reports were available for 1,351 pts; all reports were centrally reviewed and classified as radiologic complete response (rCR; no residual tumor enhancement and normalization of lymph nodes, if applicable) or radiologic residual disease (rRD). Reports with indeterminate radiologic response were independently reviewed by two study radiologists blinded to pathology outcomes. Among pts with rCR who had pathologic residual disease (pRD), we also assessed the extent of residual disease by residual cancer burden (RCB) score. Among pts with rRD who had a pCR, we determined the proportion who only had residual ductal carcinoma in situ (DCIS). **Results:** See Table. **Conclusions:** After neoadjuvant therapy, preoperative MRI accurately predicted pCR in 86% of patients with HER2+/ER- disease and may help identify patients who can proceed directly to surgery. MRI is insufficient to predict pCR for pts with HER2+/ER+ disease, as only 55% with complete response on MRI had a pCR at surgery. A pre-surgery MRI that indicated residual disease was accurate in 80% of pts with HER2+/ER+ disease, but in only 45% of pts with HER2+/ER- cancer. Accurately predicting residual disease after THP×4 allows for consideration of additional therapy that may increase the chance of pCR. Combining imaging like MRI with other biomarkers, such as tissue-based markers or circulating tumor DNA, may improve prediction of pCR and facilitate personalization of treatment decisions in HER2+ breast cancer. Research Sponsor: National Cancer Institute; Breast Cancer Research Foundation; Susan G. Komen.

All pts with pre-surgery MRI (n=1351)
pCR rate overall in this cohort = 47%

MRI result	pCR	Pathology	pRD
rCR	70.6% (341/483)		29.4% (142/483)
rRD	34% (295/868)		78% had RCB1
ER- (n=589)*	21% of 295 had DCIS only		66.01% (573/868)
Overall pCR rate in ER- subset = 68%			
MRI result	pCR	Pathology	pRD
rCR	86.1% (205/238)		13.9% (33/238)
rRD	55.3% (194/351)		85% had RCB1
ER+ (n= 762)*	19% of 194 had only DCIS		44.7% (157/351)
Overall pCR rate in ER+ subset = 31%			
MRI result	pCR	Pathology	pRD
rCR	55.5% (136/245)		44.5% (109/245)
rRD	19.5% (101/517)		76% had RCB1
	26% of 101 had only DCIS		80.5% (416/517)

Biological subtype discordance after neoadjuvant therapy in early breast cancer: Findings from a 1,500-patient cohort with residual disease.

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Background: Although biomarker reassessment is standard in recurrent breast cancer, its role in early breast cancer with residual disease (RD) after neoadjuvant therapy (NAT) remains not well established, despite potential implications for adjuvant treatment decisions in the post-NAT setting. **Methods:** We retrospectively analyzed patients with early breast cancer who underwent surgery after NAT and had RD between January 2019 and May 2025. Only patients with estrogen receptor (ER), progesterone receptor (PR), and HER2 status assessed on both pretreatment biopsy and matched surgical specimens were included. Biological subtype discordance was analyzed across luminal, HER2-positive, and triple-negative breast cancer (TNBC). Multivariable logistic regression was used to identify clinicopathological factors associated with subtype change. **Results:** Among 1,504 eligible patients with residual disease, biomarker discordance involving ER, PR, and/or HER2 was observed in 502 cases (33.4%). A change in biological subtype occurred in 221 patients (14.7%). Subtype discordance was most frequent in tumors initially classified as HER2-positive (39.3%), compared with TNBC (10.6%) and luminal disease (6.2%) ($p < 0.001$). Accordingly, patients with HER2-positive breast cancer at diagnosis were significantly more likely to experience subtype discordance after NAT compared with luminal tumors (absolute difference 33.1%, $p < 0.001$) and TNBC (absolute difference 28.7%, $p < 0.001$), with a smaller but statistically significant difference also observed between TNBC and luminal disease (absolute difference 4.4%, $p = 0.023$). HER2-positive and TNBC tumors predominantly shifted toward a luminal phenotype, whereas luminal tumors more commonly converted to HER2-positive or TNBC subtypes, indicating substantial post-treatment biological heterogeneity. On multivariable analysis, baseline biological subtype remained the strongest independent predictor of subtype change, with higher odds for HER2-positive (OR = 9.14, $p < 0.001$) and TNBC tumors (OR = 1.71, $p = 0.029$) compared with luminal disease. Lobular histology was associated with a significantly lower likelihood of subtype discordance (OR = 0.50, $p = 0.040$), whereas type of NAT, tumor grade, and Ki-67 were not associated with subtype change. **Conclusions:** In this large cohort of patients with residual disease after NAT, approximately one in seven experienced a change in biological subtype, with the highest discordance observed in initially HER2-positive tumors. These findings support routine biomarker reassessment in early breast cancer with residual disease to better inform adjuvant treatment decisions and to account for post-treatment biological heterogeneity. Research Sponsor: None.

Treatment patterns and oncologic outcomes in patients with triple-negative (TN) lobular breast cancer.

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Background: Triple-negative breast cancer (TNBC) with invasive lobular carcinoma (ILC) histology represents an exceedingly rare (<1% of breast cancers) and aggressive disease subtype with poorly described outcomes. In an effort to better understand treatment patterns and prognosis for these patients, we conducted an analysis using the National Cancer Database to assess treatments and outcomes in this high-risk, understudied population. **Methods:** We identified patients ≥ 18 years with stage I–III TNBC diagnosed between 2017–2022 who underwent mastectomy or lumpectomy with ILC or invasive ductal histology (IDC) (n=80,589). Of these patients, 69,940 were treated with chemo- or immunotherapy (CTx/IO). Subgroup analysis included patients treated with neoadjuvant chemotherapy (NACT) $\pm$ IO (n=47,822). Among this subgroup, trends in NACT $\pm$ IO and pathologic complete response (pCR) rates by histology were assessed using the Cochran–Armitage test. Associations between histology and NACT use or pCR were evaluated with multivariable logistic regression. Impact of pCR on overall survival (OS) was examined via Kaplan–Meier estimates and multivariable Cox models with propensity score weighting and matching (1:1 by stage and NACT type). **Results:** Among 80,589 patients with TNBC (median age 58 years), 79,645 (98.8%) had IDC and 944 (1.2%) had ILC. Patients with ILC were older (66 vs 58 years) and less likely to receive CTx/IO compared to those with IDC (75.5% vs 86.9%). Among 69,940 patients treated with CTx/IO, those with ILC were older (median age 65 vs 56 years), had higher clinical tumor stage, and were less likely to receive NACT compared to those with IDC (61.9% vs 68.4%; $p < 0.001$). Among 47,822 patients who received NACT $\pm$ IO, patients with ILC had significantly lower pCR rates (16.1% vs 40.2%; aOR=0.44, 95% CI 0.34–0.57). The addition of IO showed a trend toward improved pCR rates in ILC (aOR=1.69, 95%CI 0.95–3.01, $p=0.07$). In 29,330 matched patients, pCR was associated with improved 5-year OS (94% vs 78%, $p < 0.001$). However, in 108 matched ILC patients, no survival difference was observed by pCR status (5-year OS: 66% with pCR vs 69% without pCR, $p=0.54$). In a multivariable Cox model with inverse probability weighting among patients who received NACT $\pm$ IO, ILC was associated with increased mortality risk (aHR=1.34, 95%CI 1.05–1.70, $p=0.02$), after adjustment for pCR, IO, age, race, tumor size, and insurance status, among other factors. **Conclusions:** Patients with TN-ILC who received NACT had lower pCR rates and worse OS compared to those with TN-IDC. Although limited by small sample size, this is the largest analysis of its type in the current NACT and IO era. These data suggest that pCR in TN-ILC may lack the prognostic significance it has in TN-IDC. These findings highlight the need for larger studies and novel therapeutic approaches tailored to the distinct biology of this rare subtype. Research Sponsor: Breast Cancer Research Foundation; Susan G Komen Breast Cancer Foundation.

Early results of neoadjuvant therapy with pyrotinib, subcutaneous trastuzumab, and capecitabine for HER2-positive early breast cancer from a prospective, single-arm, multicenter trial.

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Background: Neoadjuvant therapy has become a standard approach for HER2-positive early breast cancer, improving outcomes, pCR, and survival. Prior studies show pyrotinib combined with trastuzumab and chemo is effective and safe, but mainly via intravenous routes, impacting quality of life. This trial is the first to assess a fully oral regimen—pyrotinib, SC trastuzumab, and capecitabine—in low- to intermediate-risk patients, focusing on efficacy and safety. **Methods:** This single-arm, multicenter phase II trial (NCT06483386) will enroll 109 treatment-naïve adults with stage I-II, T1c-2N0-1 HER2-positive EBC (IHC 3+ or IHC 2+/FISH+). From May 2024 to June 2026, patients will receive 6 cycles of neoadjuvant pyrotinib (400mg daily), SC trastuzumab (600mg q3w), and capecitabine (1000mg/m² BID, days 1-14 followed by a 7-day break). The primary endpoint is pathological complete response (pCR) rate, as defined by RECIST 1.1. Secondary endpoints include event-free survival (EFS), objective response rate (ORR), breast-conserving rate (BCR) and safety. **Results:** A total of 47 patients were enrolled from May 2024 to December 2025, of whom 43 underwent surgery and 43 had pathologic assessment available. The median age was 51 years (range 33-65), and 97.9% had an ECOG PS of 0. The majority of patients had stage II disease (89.4%), with T2 tumors (91.5%); 57.4% were clinically node-positive. The pCR rate among pts with evaluable pathology was 48.8% (21/43), and ORR was over 90%. The BCR was 65.1% (25/48). In biomarker-defined subgroups, total pathological complete response (tpCR) was achieved in 53.6% (15/28) of ER negative, HER2 positive patients, and in 40.0% (6/15) of ER positive, HER2 positive patients. The most common AEs were diarrhea, nausea, anorexia, and gastrointestinal dysfunction. The incidence of grade 3 diarrhea is 19.1%, and all cases are controllable with medication, confirming good safety profile. **Conclusions:** The fully non-intravenous neoadjuvant regimen combining pyrotinib, SC trastuzumab, and capecitabine is an efficacious and safe regimen for patients with low- to intermediate-risk HER2-positive early breast cancer. This regimen offers a more convenient and less burdensome treatment for this patient population, potentially improving quality of life and treatment adherence. Clinical trial information: NCT06483386. Research Sponsor: None.

Health-related quality of life with low-dose pembrolizumab plus chemotherapy in early triple-negative breast cancer: Findings from the PLANeT trial.

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Background: The PLANeT trial randomized stage II–III TNBC patients to neoadjuvant chemotherapy with or without low-dose pembrolizumab. Primary efficacy end point results were presented at ESMO Congress 2025. QoL was assessed at baseline, mid-treatment, and end-treatment using the EORTC QLQ-C30 across seven domains. Longitudinal changes were analyzed using mixed-effects models with LS-mean estimates and change from baseline at each timepoint. **Methods:** Stage II–III TNBC patients were randomized in a 1:1 ratio to receive standard NACT with or without pembrolizumab (50 mg Q6W $\times$ 3 cycles) prior to surgery. QoL was assessed at baseline, mid-NACT (after 4 cycles), and at the end of NACT (after 8 cycles) using the EORTC QLQ-C30 questionnaire. Seven key QoL domains were analyzed: global health status/QoL (GHS), physical, role, emotional, cognitive, social functioning, and pain. Longitudinal QoL changes were compared between arms using mixed-effects models (MMRM) adjusted for nodal status. Least-squares (LS) mean scores and changes from baseline were estimated for each timepoint. **Results:** Among 157 patients (median age 49), baseline QoL was high and comparable between arms. QoL declined during neoadjuvant therapy in both groups, with the greatest burden mid-treatment and partial recovery by cycle 8. LS-mean global QoL fell by 14 points in each arm, with no meaningful separation between treatments across any functioning domain. Pain increased in both groups, and financial difficulty peaked mid-treatment before improving by cycle 8. Overall, low-dose pembrolizumab did not compromise QoL compared with chemotherapy alone. **Conclusions:** Adding low-dose pembrolizumab to neoadjuvant chemotherapy in TNBC did not worsen patient quality of life. The trajectory of functioning and symptom scores was nearly identical to chemotherapy alone, indicating that incorporating reduced-dose immunotherapy does not add to the treatment burden from the patient's perspective. Clinical trial information: CTRI/2024/01/062088. Research Sponsor: Indian council of medical research; grant numbers Development; Research/Small/5411/2023–2024, EM/Dev/SG/170/1232/2023/JJC].

Least-squares mean (LS-mean) scores at cycle 8 and changes from baseline for all EORTC QLQ-C30 domains, comparing pembrolizumab + chemotherapy vs chemotherapy alone in the PLANeT trial.

Domain	Pembro + Chemo (C8 LS-mean)	Change	Chemo Alone (C8 LS-mean)	Change	Between-Arm Δ (Change)
Global QoL	39.61	–14.19	41.27	–13.61	–0.58
Physical Functioning	73.09	–19.92	74.49	–18.14	–1.78
Role Functioning	85.68	–10.90	85.65	–12.66	+1.76
Emotional Functioning	78.31	–11.11	77.00	–10.34	–0.77
Cognitive Functioning	88.03	–5.99	83.97	–8.44	+2.45
Social Functioning	83.33	–13.04	82.07	–12.87	–0.17
Pain	67.31	+20.73	52.11	+12.45	+8.28

Taxane and platinum combination as a predictor of pathologic complete response in I-SPY2 by gene expression breast cancer signatures.

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Background: Carboplatin is part of NCCN-preferred neoadjuvant chemotherapy (NAC) for stage II-III triple negative (TN) early-stage breast cancer (eBC) as addition to taxane-containing standard-of-care, and significantly improves pathologic complete response (pCR) rates in multiple trials. In hormone receptor (HR)+/HER2- disease, platinum addition has been explored in investigational settings but is not standard. In I-SPY2 (NCT01042379), high-risk eBC pts were randomized to standard taxane-anthracycline (T-AC) with or without investigational agents. One arm evaluated carboplatin plus the PARP inhibitor veliparib added to T-AC (VC arm; 32 HR+/HER2- and 39 TN pts, n = 71). Two gene signatures, a 205-gene Platin Drug Response Predictor (Platin-DRP) and a 113-gene taxane response predictor, have been validated for association with response to platinum agents and taxane-based regimens, respectively. This study evaluated their combined association with pCR in the I-SPY2 VC arm and their potential to inform platinum benefit in taxane-based NAC. **Methods:** Agilent gene expression data (GSE194040) from 987 high-risk eBC tumors were analyzed, focusing on 71 VC-arm pts and 179 HER2- T-AC pts. Samples were scored using each gene signature on a percentile scale (0–100). Associations between a 50-point increase in score and pCR were assessed using logistic regression with one-sided tests and 90% confidence interval (CI) lower bound (LB), unless otherwise specified. **Results:** The pCR rate in the VC arm was 38% (27/71), compared with 17.3% (31/179) in the control arm. In the VC arm, both the Platin-DRP (OR = 3.4, p = 0.016, 90% CI LB = 1.36) and the taxane predictor (OR = 3.88, p = 0.01, 90% CI LB = 1.54) were associated with pCR after adjustment for HR status and retained independent predictive value after adjustment for MammaPrint risk. The platinum and taxane scores were moderately correlated (r = 0.53). In a bivariable model, inclusion of the Platin-DRP trended toward improved fit beyond the taxane score alone (two-sided (2s) p = 0.082). Dichotomization at 50 showed highest pCR in double-high pts (55%, 16/29), intermediate rates in discordant pts (33%, 7/21), and lowest rates in double-low pts (19%, 4/21). Quartile stratification further separated outcomes, with 78% pCR (7/9) in the high-high quartile and 0% (0/8) in the low-low quartile. The taxane score showed no evidence of arm-specific effects (control vs VC; 2s p = 0.97), whereas the Platin-DRP showed directionally stronger associations in the VC arm (2s p = 0.12). **Conclusions:** Taxane and platinum gene expression signatures showed complementary associations with pCR in the I-SPY2 veliparib-carboplatin arm. Joint modeling and stratification identified subgroups with distinct responses, supporting the potential utility of combining drug-specific biomarkers to refine patient selection for platinum addition in taxane-based NAC. Research Sponsor: None.

Delayed serplulimab combined with nab-paclitaxel and epirubicin in high-risk, early HR+/HER2– breast cancer (HELEN-B 018): A multicenter, single-arm, phase 2 trial.

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Background: Novel treatment options are needed to improve long-term outcome of high-risk early HR+/HER2– breast cancer. Evidence shows a programmed death 1 inhibitor combined with chemotherapy increases pCR rates in this subtype. We aimed to evaluate the efficacy and safety of serplulimab combined with nab-paclitaxel and epirubicin in high-risk, early HR+/HER2– breast cancer. **Methods:** This multicentre, single-arm, phase 2 trial was conducted in China at 6 hospitals. Patients were eligible if they were 18 years or older, with previously untreated early HR+/HER2– breast cancer, and Ki-67 greater than or equal to 20%, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Participants were allocated to intravenous nab-paclitaxel (260 mg/m²) and intravenous epirubicin (75 mg/m²) on the first day and intravenous serplulimab (4.5mg/kg) on the third day of the treatment cycle. 6 cycles of neoadjuvant treatment were administered. The primary outcome was pCR (defined as ypNo or ypTo/is), assessed in the full analysis set, which included all patients who had started the trial treatment. We estimated that with enrollment of 109 participants, this trial would have 80% power to detect a true difference in the percentage of patients with a pCR of 10% at a one-sided alpha level of 0.025, with a dropout rate of 10%. This study is registered with ClinicalTrials.gov (NCT06394661). **Results:** Between Apr 28, 2024, and May 24, 2025, 136 patients were assessed for eligibility; 27 were ineligible and 109 participants were enrolled in this study, of whom 101 participants started trial treatment. Median age of the participants was 49 [range, 30 to 72] years at the time of enrolment, and 45 (44.6%) were PD-L1 positive (CPS ≥1). pCR was achieved in 23 patients (22.8%, 95%CI 15.3%–32.4%). PCR rate was numerically higher in patients with PD-L1 positive tumors (44.4%, 95%CI 30.0%–59.9%). During the neoadjuvant phase, 30 (29.7%) patients experienced grade 3 or higher treatment-related adverse events. The most common grade 3–4 adverse events were increased alanine aminotransferase (ALT; six [5.9%]), increased aspartate aminotransferase (AST; five [5.0%]), and diarrhea (four [4.0%]). There were no treatment-related deaths. **Conclusions:** Delayed serplulimab combined with nab-paclitaxel and epirubicin showed promising anti-tumour activity and manageable safety in patients with HR+/HER2– breast cancer; the pCR rate was higher in PD-L1 expression tumor. These findings support further evaluation of this regimen in randomized controlled trials. Clinical trial information: NCT06394661. Research Sponsor: None.

Impact of pembrolizumab infusion timing on outcomes in early-stage triple-negative breast cancer: A real-world exploratory analysis (Neo-Real).

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Background: Neoadjuvant pembrolizumab combined with chemotherapy is the standard of care for early-stage triple-negative breast cancer (TNBC) based on KEYNOTE-522, improving pathologic complete response (pCR) and event-free survival (EFS). Emerging data suggest that immunotherapy timing may influence oncologic outcomes; however, evidence in early-stage TNBC and in combination regimens is limited. We conducted an exploratory real-world analysis to evaluate the association between infusion timing and clinical outcomes. **Methods:** Neo-Real/GBECAM-0123 is a multicenter real-world cohort including patients with early-stage TNBC treated with neoadjuvant pembrolizumab-based chemotherapy in Brazil and Argentina. In this analysis, patients treated between 2019 and 2024 with available infusion timing data were included. Infusion timing was classified as Early ($\leq 20\%$ of pembrolizumab infusions initiated at or after 14:00) or Late ($> 20\%$ initiated at or after 14:00). The primary endpoint was pCR (ypT0/Tis ypN0). Secondary endpoints included EFS, defined according to KEYNOTE-522 criteria. Sensitivity analyses using timing definitions were performed. **Results:** Among 419 patients with available infusion timing data (Early: n=265; Late: n=154); 385 underwent surgery and were evaluable for pCR. Baseline clinicopathologic characteristics were largely balanced between groups, although stage III disease was numerically more frequent in the Early group (30.9% vs 23.6%, p=0.134). Treatment features, including use of dose-dense chemotherapy and number of neoadjuvant pembrolizumab cycles (median 8 in both groups), were similar. pCR rates did not differ according to infusion timing (Early: 62.5% vs Late: 64.1%; p=0.827). Late infusion timing was associated with improved EFS, with a 2-year EFS of 90.7% versus 82.7% (p=0.013). In multivariable Cox regression adjusting for age, clinical stage, pathologic response, tumor grade, histology, and number of neoadjuvant pembrolizumab cycles, Late infusion timing remained associated with improved EFS (HR 0.34; 95% CI 0.15–0.80; p=0.013). Sensitivity and subgroup analyses, including evaluation of the timing of the first pembrolizumab infusion using an earlier cut-off (11:00), as well as analyses by histology, clinical stage, and pathologic response, yielded consistent results. **Conclusions:** In this exploratory real-world analysis of patients with early-stage TNBC treated with neoadjuvant pembrolizumab-based chemotherapy, infusion timing was not associated with pCR. However, later infusion timing was associated with improved EFS. These findings contrast with observations reported in other tumor types and underscore the need for further studies to clarify the impact of immune checkpoint inhibitor infusion timing on clinical outcomes in TNBC. Research Sponsor: None.

DCE-MRI for assessment of pathologic complete response after completion of neoadjuvant therapy in triple-negative breast cancer patients.

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Background: Triple-negative breast cancer (TNBC) is an aggressive molecular subtype that accounts for approximately 15%–20% of all breast cancer diagnoses. We aimed to investigate the utility of presurgical DCE breast MRI as a predictive marker for pathologic complete response (pCR) after neoadjuvant treatment (NAT) in TNBC patients and to compare the predictive value of early versus delayed enhancement for residual tumor detection. **Methods:** A total of 308 Stage I–III TNBC patients who underwent preoperative DCE-MRI after completion of NAT followed by surgery were enrolled in an IRB-approved prospective clinical trial (NCT02276433). Tumor size was measured using three-dimensional measurements of the index lesion during both the early (1 min) and delayed (6 min) phases of DCE-MRI. Treatment response at surgery (pCR vs. non-pCR) and the pathologic size of residual disease were documented. Correlation between pCR and residual enhancement on DCE-MRI was assessed using McNemar's test. Spearman's rank correlation coefficient was used to assess concordance between the longest diameter on MRI and pathology. Differences between longest diameter on DCE-MRI and pathology were compared using the Wilcoxon signed-rank test. **Results:** Among the 308 TNBC patients, 47% (145/308) achieved pCR following treatment. Residual disease detection on the early phase of DCE-MRI demonstrated higher sensitivity for predicting pCR compared to the delayed phase (79% vs. 69%, $p < 0.001$); however, it had lower specificity (78% vs. 84%, $p = 0.008$). Absence of enhancement in both early and delayed phase DCE-MRI predicted pCR with positive predictive values (PPV) of 80% and 83%, respectively. Residual enhancement in both phases predicted non-pCR with negative predictive values (NPV) of 77% and 71%, respectively. Both early and delayed DCE-MRI phases demonstrated a similar moderate positive correlation with pathology ($r = 0.64$ vs. 0.62). There was no significant difference between the longest diameter measured on early phase DCE-MRI and pathology ($p = 0.706$), whereas a significant difference was observed for the delayed phase ($p < 0.001$), which overestimated residual disease. **Conclusions:** Presurgical DCE-MRI demonstrated strong performance in predicting pCR among TNBC patients following NAT. The early and delayed phases of DCE-MRI may each capture different aspects of tumor characteristics, potentially providing complementary information for prediction. Clinical trial information: NCT02276433. Research Sponsor: National Cancer Institute.

Development of a multivariable prognostic model for pathological response using anatomical and pathological variables in early triple-negative breast cancer treated with neoadjuvant chemo-immunotherapy: Initial results.

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Background: The combination of chemotherapy and immune checkpoint inhibitors is the standard of care for most patients with early triple negative breast cancer (eTNBC). Higher residual cancer burden (RCB) after receiving neoadjuvant chemo-immunotherapy (NCI) is associated with worse outcomes; however, reliable tools to predict pathological response remain limited. **Methods:** We conducted a multicenter prospective cohort study including patients with eTNBC treated with NCI. Anatomical and pathological variables were collected. Multivariable logistic regression was used to develop a prognostic model for pathological response. RCB 0–1 was the primary outcome. $p < 0.1$ was used for the selection of candidate parameters, and $p < 0.05$ for the final assessment of the multivariate model. ROC curves and the Hosmer–Lemeshow tests were applied to assess the model performance. **Results:** A total of 109 patients with eTNBC with NCI from six centers in Argentina were included, with tumor samples centrally collected and reviewed for centralized pathological assessment. Regarding the immune microenvironment, qualitative tumor-infiltrating lymphocytes (TILs) were categorized according to the International Immuno-Oncology Biomarker Working Group classification as low (score 1) in 44.4% and intermediate-to-high (scores 2–3) in 55.6% of patients. Pathologic complete response (pCR) was achieved in 64.8% of patients. Histological grade (Grade 3 vs. 2: OR 3.2; 95% CI 0.95–11), TIL categories (TILs score 2: OR 3.4; 95% CI 0.84–14 and score 3: OR 6.3; 95% CI 1.1–37) and axillary node involvement (present vs. absent: OR 0.28; 95% CI 0.083–0.95) were selected for the final multivariate model. The final model showed good discrimination (AUC = 0.82) with adequate calibration, confirmed by a non-significant Hosmer–Lemeshow test ($\chi^2 = 3.28$, $p = 0.35$). **Conclusions:** The model enabled stratification of patients into distinct risk groups with significantly different probabilities of achieving RCB scores of 0 or 1. This approach may provide additional information for risk stratification and prognosis, improving our understanding of which patients are more likely to achieve pathological response. Further studies will assess the external validation of the model. Research Sponsor: Conquer Cancer, the ASCO Foundation.

Efficacy and safety of the pertuzumab biosimilar BCD-178 versus the originator pertuzumab in patients with HER2-positive locally advanced breast cancer: Results from the international, double-blind, randomized, phase III PREFER trial.

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Background: Pertuzumab, a HER2-targeting monoclonal antibody, significantly improves outcomes for patients with HER2-positive breast cancer (HER2+ BC) in different settings in combination with another HER2-agents with/without chemotherapy. BCD-178 is a biosimilar of the originator pertuzumab (OP). Preclinical and phase I clinical studies have demonstrated its equivalence to OP. The phase III PREFER trial compared the efficacy and safety of BCD-178 and OP as neoadjuvant and adjuvant therapy in HER2+ BC. **Methods:** The study hypothesized that neoadjuvant therapy containing BCD-178 would yield a pathological complete response (pCR) rate equivalent to that of therapy containing OP in women aged 18–75 years with stage II–III HER2+, hormone receptor-negative invasive BC and a primary tumor > 2 cm. Patients were randomized 1:1 to receive neoadjuvant therapy with either BCD-178 or OP, combined with trastuzumab and chemotherapy (TCHP regimen). The primary endpoint was the pCR rate (ypTo/is, ypNo) assessed by central independent review. Safety was monitored throughout, with adverse events (AEs) graded by CTCAE v5.0. Immunogenicity and pharmacokinetics were also evaluated (NCT05802225). **Results:** Of 398 randomized patients, 201 received BCD-178 and 197 received OP. The median age was 53 years; over one-third of patients in each group had stage IIIB/IIIC disease. pCR rates were 75.0% with BCD-178 and 72.2% with OP (risk ratio [RR] 2.7, 95% CI: -6.0 to 11.6). The 95% CI for the between-group difference in pCR rate fell within the predefined equivalence margins, confirming equivalent efficacy. The safety profiles were comparable. The most common AEs (≥10%) were diarrhea and anemia. Immunogenicity was low and similar between groups: binding antibodies were detected in 1.6% (BCD-178) vs. 1.1% (OP) of patients, and neutralizing antibodies in 1.1% in both groups. The concentration-time profiles and pharmacokinetic profiles (C_{min}, C_{eo}) were also comparable. **Conclusions:** In patients with HER2+, hormone receptor-negative locally advanced breast cancer, the biosimilar BCD-178 demonstrated equivalent efficacy, safety, immunogenicity, and pharmacokinetics to the originator pertuzumab within a neoadjuvant TCHP regimen. Clinical trial information: NCT05802225. Research Sponsor: JSC BIOCAD.

Response to neoadjuvant chemotherapy in both the breast and lymph nodes in patients with inflammatory breast cancer.

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Background: Optimal outcomes in Inflammatory Breast Cancer (IBC) are achieved with tri-modal therapy. We sought to evaluate how differences in response to neoadjuvant chemotherapy (NAC) in the breast and axilla impact locoregional recurrence-free, distant recurrence-free and overall survival in patients with IBC. **Methods:** A retrospective analysis was performed on patients with IBC enrolled in a prospective registry from 2007–2025. All patients underwent NAC followed by modified radical mastectomy. Comparisons between three pathologic response groups—(A) pCR, no residual disease in breast or lymph nodes, (B) complete response in breast but not axillary nodes, and (C) complete response in axillary nodes, but not breast—were performed using Kaplan-Meier and pairwise Cox proportional hazards models. **Results:** 545 patients were included; median age was 50 (IQR:41–58). pCR was identified in 150 (28%) patients, while 34 (6%) were in group B, and 55 (10%) were in group C. Of patients with pCR, 6 (4%) had locoregional recurrence (LRR), compared to 6 (17%) of patients in group B, 5 (9%) of patients in group C, and 79 (25%) in patients without pCR. There was decreased risk of LRR in patients with pCR compared to no pCR, or group B (HR:0.118 CI 0.05–0.27 $P<0.001$; HR:0.18 CI 0.06–0.55 $P=0.017$). A similar decreased risk of LRR was observed in patients with group C compared to no pCR (HR:0.297 CI 0.12–0.73 $P=0.01$). Of patients with pCR, 31 (20%) had distant recurrence, compared to 14 (41%) of patients in group B, 23 (41%) of patients in group C, and 183 (60%) in patients who did not have pCR. There was decreased risk of distant recurrence in patients with pCR compared to no pCR, or patients in group C (HR0.25 CI 0.17–0.37 $P<0.0001$; HR0.43 CI 0.25–0.74 $P=0.007$). There was also a decreased risk of distant recurrence in patients with group C compared to no pCR (HR0.59 CI 0.38–0.91 $P=0.027$). Mean OS was longer in patients with pCR compared to partial response or no pCR (12.4 vs 7.95 years). The risk of death was lower in patients with pCR compared to partial or no pCR, as well as those with group C compared to no pCR. **Conclusions:** In patients with IBC, the lowest risk for recurrence was achieved with pCR. However, even with pCR, there was still a 20% chance of distant recurrence. Partial response through clearance of the lymph node disease provided some reduction in risk of recurrence compared to no pCR. Research Sponsor: None.

Preoperative combination radiotherapy (RT) and immune checkpoint inhibitor (ICI) in early-stage breast cancer: Influence of RT and ICI treatment sequencing (NCT04454528 post-hoc analysis).

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Background: The anti-tumor immune effects of combination radiotherapy (RT) and immune checkpoint inhibitors (ICI) are synergistic. Optimal treatment sequencing, i.e. RT before ICI vs. RT after ICI, remains unclear. Assuming clinical equipoise, we conducted a phase 1b/2 multi-arm adaptive window of opportunity study to evaluate feasibility and treatment response after preoperative (preop) RT before ICI vs. RT after ICI vs. ICI alone. **Methods:** Participants with early-stage breast cancer planning for upfront surgery were eligible to enroll to receive a single preop intravenous dose of pembrolizumab (pembro, an ICI), 200 mg, either alone (Arm 3) or in combination with RT (single fraction, 7 Gy) given before (Arm 1) or after pembro (Arm 2). Primary outcome measures included 1) feasibility of administration of combination RT + pembro in a 21-day preoperative window, and 2) tumor response as measured by % tumor size change post-treatment, including the proportion achieving > 30% tumor reduction (TΔ30). Secondary endpoints included pathologic response as measured by residual cancer burden (RCB). Study sample size was powered for proportion of participants with TΔ30. Assuming 40% of treated participants would achieve TΔ30 compared to untreated participants, 15 subjects would yield 80% power at $\alpha = 0.05$. Comparison of proportions was performed using Chi-squared test. **Results:** Between 1/6/2021 and 1/28/2025, 30 participants enrolled and completed the preop regimen assignment. Median follow-up was 634 days (IQR 256 – 1120 days). All participants proceeded to surgery without delay. There were no adverse events (AEs) $\geq$ grade 3. There was one grade 2 immune-related AE (hypothyroidism). The proportion of participants achieving TΔ30 was 8 of 14 (57.1%), 6 of 11 (54.5%) and 0 of 5 (0%) in Arms 1, 2, and 3 respectively. For TNBC, TΔ30 rate was 6 of 7 (85.7%), 4 of 6 (66.7%) and 0 of 4 (0%) in Arms 1, 2, and 3 respectively. Compared with Arm 3, overall TΔ30 rate was significantly higher for those treated in Arm 1 or 2, $p = 0.0307$ and $p = 0.0433$; and for TNBC, $p = 0.0088$ and 0.0454 , respectively. TΔ30 rate was similar in those treated with RT before (Arm 1) or RT after (Arm 2) ICI. The proportion of participants with major pathologic response (MPR) defined as RCB class 0 or 1 (RCB 0/1) treated in Arms 1, 2, and 3 were 7 of 14 (50%), 1 of 10 (10%), and 0 of 4 (0%) overall and 4 of 7 (57%), 0 of 5 (0%), and 0 of 3 (0%) for TNBC, respectively. The proportion of participants with RCB 0/1 in Arm 1 was numerically and statistically higher than Arm 2 overall and for TNBC, $p = 0.0448$ and $p = 0.0479$, respectively. **Conclusions:** RT given before ICI is more effective than RT given after ICI and resulted in MPR in 57% of participants with TNBC. This chemotherapy-free preop regimen may possibly facilitate chemotherapy omission decision in those achieving MPR in future studies. Clinical trial information: NCT04454528. Research Sponsor: None.

De-escalation of neoadjuvant chemotherapy for HER2-positive breast cancer: A systematic review and meta-analysis.

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Background: The addition of carboplatin to taxane-based dual HER2 blockade (TCbHP) is a standard neoadjuvant regimen for high-risk, HER2-positive breast cancer. However, this combination incurs significant hematological toxicities. Whether omitting carboplatin (THP) preserves efficacy while enabling de-escalation of toxicity remains a critical unanswered question. **Methods:** A comprehensive search of PubMed, Embase, Cochrane CENTRAL, and major oncology conference abstracts was conducted through June 15, 2025, for studies comparing THP with TCbHP. The primary endpoint was pathologic complete response (pCR). Secondary endpoints included grade ≥ 3 hematological toxicities. A non-inferiority margin for pCR was pre-specified at a risk ratio (RR) of 0.85. Data were pooled using a DerSimonian-Laird random-effects model. The study was registered on PROSPERO (CRD420251084035). **Results:** Seven studies (2 RCTs, 5 observational) comprising 2,061 patients (989 THP; 1,072 TCbHP) were included. The pooled pCR rate was 61.9% for THP versus 63.9% for TCbHP (RR 0.92, 95% CI 0.79–1.07). Statistical non-inferiority was not met, as the lower bound of the 95% CI crossed the pre-specified margin. The absolute pCR difference was a modest -2.0%. Although pCR showed substantial heterogeneity ($I^2 = 69\%$), this was largely driven by study design differences (RCTs: RR 1.06 vs. observational: RR 0.80). In stark contrast, the THP regimen demonstrated a profound and remarkably consistent safety advantage, with an 82% reduction in grade ≥ 3 thrombocytopenia (RR 0.18, 95% CI 0.09–0.39), a 69% reduction in anemia (RR 0.31, 95% CI 0.17–0.57), and a 56% reduction in neutropenia (RR 0.44, 95% CI 0.33–0.58). Crucially, all three major hematological toxicity endpoints showed a complete absence of statistical heterogeneity ($I^2 = 0\%$ for all), indicating a robust and generalizable safety benefit. **Conclusions:** While the carboplatin-free THP regimen did not meet the strict criteria for statistical non-inferiority in pCR, the small absolute efficacy decrement is substantially offset by a large, clinically meaningful, and highly consistent reduction in severe hematological toxicities. These findings provide strong evidence to support THP as a reasonable and safer de-escalation strategy for selected patients with HER2-positive breast cancer, particularly those where toxicity is a major concern. Research Sponsor: None.

Structural determinants compared with genetic ancestry and self-reported race in triple-negative breast cancer disparities: A multilevel analysis in an admixed population.

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Background: Triple-negative breast cancer (TNBC) exhibits marked racial disparities in outcomes. However, the contributions of genetic ancestry, self-reported race, and structural determinants remain unclear, particularly in admixed populations. We aimed to disentangle the independent and combined impact of these factors in a Brazilian cohort. **Methods:** We retrospectively studied 156 women with TNBC treated with neoadjuvant chemotherapy at a tertiary center in São Paulo, Brazil (2007–2022). Genetic ancestry was estimated using ancestry-informative markers (AIMs) from an unpublished dataset. Self-reported race followed national census categories. Healthcare system type (public/private) served as a proxy for socioeconomic status. Primary outcomes were pathologic complete response (pCR), overall survival (OS), and disease-free survival (DFS). Multivariable models were adjusted for age, stage, Ki-67, and year of diagnosis. Statistical techniques included multiple imputation, propensity score matching, LASSO regression, and causal mediation analysis. **Results:** The cohort was highly admixed: 27% had $\geq 20\%$ African ancestry (AA). Discordance was observed between genetic and social classifications: 48% of self-identified Black patients had $< 20\%$ AA, while 24% of non-Black patients had $\geq 20\%$ AA. Patients with $\geq 20\%$ AA had higher tumor proliferation (median Ki-67 90% vs 80%) and higher pCR (50.0% vs 41.2%, $p=0.42$) but higher mortality (35.7% vs 25.4%). Black patients more often to use public healthcare (48.4% vs 15.9%, $p<0.001$) present with stage III disease (45.2% vs 35.6%), and receive less dose-dense chemotherapy (41.9% vs 76.1%, $p<0.001$). In adjusted analyses, neither AA nor self-reported race independently predicted pCR, OS, or DFS. Public healthcare use was the strongest independent predictor of worse OS (HR 2.45, 95%CI 1.12–5.36, $p=0.025$) and DFS (HR 2.18, 95%CI 1.08–4.40, $p=0.03$). Clinical stage (OR 0.66, $p=0.022$) and carboplatin use (OR 2.8, $p=0.018$) were the only independent predictors of pCR. Causal mediation analysis showed that 60.1% of the detrimental effect of public healthcare on pCR was mediated by advanced stage at presentation. **Conclusions:** In this pre-immunotherapy Brazilian cohort, TNBC outcome disparities are primarily driven by structural determinants related to healthcare access rather than genetic ancestry or self-reported race. While ancestry and race capture relevant biological and social dimensions, delayed diagnosis and suboptimal treatment delivery were the main mechanisms underlying outcomes. These findings underscore the need to address structural inequities and ensuring equitable access to timely, evidence-based cancer care in admixed populations. Future prospective studies integrating genetic ancestry, socioeconomic factors, and tumor immune profiling are needed. Research Sponsor: National Program for Support of Oncological Care; PRONON - 2500.055.121/2015–12; São Paulo State Research Foundation; FAPESP: 2014/50943–1; 2013/23277–8; National Council for Scientific and Technological Development; CNPq: 465682/2014–6 ; 305464/2013–2.

Predicting treatment effect on distant recurrence free survival from functional tumor volume change during neoadjuvant therapy: A Bayesian hierarchical model of I-SPY 2 MRI and survival data.

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Background: In neoadjuvant cancer trials, early endpoints that predict treatment effect on survival identify promising agents early and support accelerated regulatory approval. However, binary endpoints like pathologic complete response inadequately characterize the full distribution of residual disease in breast cancer, while promising continuous biomarkers like MRI derived functional tumor volume (FTV) are associated with survival outcomes but not widely collected. Using a Bayesian hierarchical model, long-term treatment effects on distant recurrence free survival (DRFS) can be predicted from continuous MRI-derived functional tumor volume (FTV) in the I-SPY 2 platform trial. **Methods:** I-SPY 2 treated 2117 patients from 2010–2022 (12 weeks of paclitaxel $\pm$ experimental agent followed by 4 cycles of doxorubicin + cyclophosphamide), and 1,859 underwent dynamic contrast-enhanced MRI at baseline and after 12 weeks of neoadjuvant therapy. MRI-derived functional tumor volume provided volumetric quantification of dynamic tissue enhancement. Δ FTV was defined as the ratio of 12-week to baseline FTV. A Bayesian joint hierarchical model (brms) fit treatment effects on Δ FTV and DRFS for each treatment regimen by HR/HER2 subtype, controlling for clinical nodal status, clinical T stage, grade, and calendar year. Arms with < 8 subjects are excluded. Performance was assessed using cross-validation, predicting DRFS treatment effects in one held out fold at a time from the learned Δ FTV-DRFS association in the remaining data, then comparing predicted to actual DRFS treatment effect. Sensitivity analyses on priors will be presented. **Results:** Across 1753 patients and 45 treatment–subtype combinations, the estimated treatment effects on Δ FTV and DRFS were highly correlated (posterior correlation -0.91 ; 95% CrI -1.00 to -0.23). Predicted DRFS treatment effect from Δ FTV demonstrated strong concordance with actual DRFS treatment effects (Pearson $r = 0.94$ in TNBC; 0.97 HER2+; 0.80 HR+HER2-). The top 5 treatment–subtype regimens ranked by predicted and actual DRFS were identical. 20 regimens predicted to have $> 70\%$ probability of DRFS benefit over subtype specific controls showed DRFS improvement, yielding 100% specificity and 69% sensitivity at this decision threshold. **Conclusions:** We demonstrate internally validated prediction of neoadjuvant treatment effect on DRFS from MRI-derived change in functional tumor volume in the I-SPY 2 trial of high-risk early breast cancer. This suggests continuous imaging measures capture a range of response to therapy while Bayesian approaches can be effective for predicting treatment effects. This encourages collecting MRI biomarkers in trials to facilitate validation as early endpoints supporting decisions in screening platform trials as well as regulatory accelerated approval. Research Sponsor: None.

Systemic cytokine dynamics during neoadjuvant chemotherapy versus endocrine therapy and CDK4/6 inhibition in high-risk luminal breast cancer: Results from the GEICAM/2019-01-CARABELA trial.

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Background: Chemotherapy (CT) and CDK4/6 inhibitors modulate antitumor immunity primarily within the tumor microenvironment. Whether these effects are reflected systemically during neoadjuvant therapy, differ by treatment, or are associated with response remains unclear. **Methods:** CARABELA is a randomized neoadjuvant trial comparing letrozole (ET) + the CDK4/6 inhibitor abemaciclib vs standard CT in high-risk HR+/HER2- breast cancer. Plasma cytokines were measured at baseline (BL), 2 weeks (wks), 12 wks, and end of treatment (EOT) using multiplex proximity extension assay (Olink Target 96 Immuno-Oncology panel). Analyses included: (1) BL cytokine profiles by menopausal status, Oncotype DX Breast Recurrence Score test result ($RS \leq 25$ vs >25), and Ki67 ($<40\%$ vs $\geq 40\%$); (2) longitudinal cytokine changes (BL to 2 and 12 wks, Δ) by residual cancer burden (RCB 0/I vs II/III), overall and by treatment; (3) EOT cytokine profiles by RCB. Group comparisons were adjusted by false discovery rate (FDR) threshold of 5% controlled by the q-value method. Multivariable logistic regression models were adjusted for menopausal status. Treatment-cytokine interactions were evaluated. **Results:** At BL, 40 cytokines were differentially expressed by menopausal status, with most showing higher levels in postmenopausal patients, including myeloid-associated inflammatory chemokines (CXCL9, CXCL10, MCP-1, MCP-4), angiogenic/matrix-remodeling factors (VEGFA, HGF, MMP7, MMP12), and TNF-related/immune regulatory molecules (TNFRSF12A, TNFRSF9, Galectin-9), indicating chronic systemic inflammation, without enrichment of cytotoxic immune effector programs. No BL cytokine differences met FDR threshold by RCB, RS or Ki67. Early cytokine changes (BL-2 wks) were not associated with RCB. In the ET + abemaciclib arm, no significant changes were observed between BL and 12 wks. In the CT arm, 25 cytokines had a significant increase (BL-12 wks) in patients with RCB II/III with respect to patients with RCB 0/I. These included inflammatory chemokines (IL8, CXCL1, CXCL5, CCL3, CCL4, MCP-3, MCP-4), angiogenic/growth factors (VEGFA, ANGPT1, EGF, PDGF-B), and stress-/TNF-related signaling molecules (CASP-8, TNFSF14, ADA). These cytokines were associated with RCB II/III in multivariable models adjusted for menopausal status. Cytokine-treatment interaction tests did not meet FDR threshold. **Conclusions:** Postmenopausal women display a distinct cytokine profile consistent with chronic systemic inflammation. Neoadjuvant CT induces pronounced systemic cytokine changes, while ET + CDK4/6 inhibition does not. Increased inflammatory and angiogenic cytokines during CT are associated with residual disease, supporting longitudinal systemic immune profiling as a marker of treatment resistance in high-risk luminal breast cancer. Clinical trial information: NCT04293393. Research Sponsor: GEICAM Spanish Breast Cancer Group.

Neoadjuvant mitomycin C plus carboplatin followed by paclitaxel vs. standard doxorubicin–cyclophosphamide followed by paclitaxel–carboplatin in BRCA1/2-associated breast cancer.

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Background: Triple-negative breast cancer (TNBC) associated with BRCA1/2 mutations is an aggressive disease subtype characterized by high sensitivity to chemotherapy. Accumulating evidence suggests the efficacy of mitomycin C, both as monotherapy and in combination with platinum agents, in BRCA1/2-driven tumors. This clinical study aimed to compare mitomycin C-based chemotherapy regimens with standard neoadjuvant chemotherapy in patients with BRCA1/2-associated TNBC. **Methods:** A total of 52 patients with BRCA1/2 pathogenic variants and TNBC stage T1–3N0–3M0 were enrolled. Patients were randomized to an experimental arm (n=26) receiving mitomycin C (10 mg/m²) plus carboplatin (AUC 5) (MCbP) for four cycles followed by weekly paclitaxel (80 mg/m²) for 12 cycles (MCbP-T), or to a control arm (n=26) receiving doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) (AC) for four cycles followed by weekly paclitaxel (80 mg/m²) plus carboplatin (AUC2) for 12 cycles (AC-TCbP). Treatment efficacy was assessed according to RECIST criteria and the rate of pathological complete response (pCR) after surgery. **Results:** After four cycles of MCbP/AC, clinical complete response (cCR) was observed more frequently in the MCbP group compared with the AC group (58% vs 7.7%; p = 0.0002). Upon completion of neoadjuvant chemotherapy, cCR remained significantly higher in the experimental arm (65.4% vs 42%; p = 0.037). The pCR rate was 81% versus 62% (p = 0.12), while Miller–Payne grade V pathological response was achieved in 77% and 65% of patients, respectively (p = 0.084). During a 26-month follow-up, adverse events occurred in 3.8% of patients in the experimental group and 12% in the control group; one death was reported only in the AC-TCbP arm (p = 0.6). Grade III leukopenia and neutropenia were more frequent in the AC-TCbP group (42% and 46%) compared with MCbP-T (4% and 8%; p = 0.002 and p = 0.003, respectively). Thrombocytopenia of any grade occurred more frequently in the MCbP-T group (36% vs 0%; p < 0.001). Grade II alopecia was observed in all patients in the control group and in none of the MCbP-T patients (p < 0.001). **Conclusions:** In BRCA1/2-associated TNBC, the MCbP-T regimen demonstrates efficacy comparable to standard anthracycline-based chemotherapy with platinum agents, while providing a more favorable safety profile and a lower incidence of adverse events. Research Sponsor: ГРАНТ; 21-75-30015.

Integration of molecular subtyping and immune profiling to predict pathologic complete response in HER2+ breast cancer treated with neoadjuvant dual HER2 therapy.

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Background: Neoadjuvant outcomes are variable in human epidermal growth factor receptor 2-positive (HER2+) early breast cancer (EBC), highlighting the unmet need for predictive biomarkers. The Blueprint (BP) assay classifies tumors by molecular intrinsic subtype, whereas the ImPrint hormone receptor-positive (HR+) and ImPrint triple-negative genomic signatures predicted immune sensitivity in the ISPY2 trial. Because HER2+ EBCs are genomically heterogeneous, and because anti-HER2 has an immunologic mechanism of action, we hypothesized that BP and ImPrint could be used to predict outcomes (pathologic complete response, pCR) following neoadjuvant chemotherapy + anti-HER2 (trastuzumab + pertuzumab, HP). **Methods:** We evaluated n=252 HER2+ EBCs receiving neoadjuvant chemotherapy + HP in the prospective, observational FLEX study. Tumors were classified by BP subtype (HER2, Luminal A/B, or Basal) and ImPrint (+ or -). Fisher's exact test was used to compare pCR rates across BP/ImPrint results. Multivariable logistic regression was used to evaluate independent associations with pCR, adjusting for nodal status and tumor size. **Results:** 72% of HER2+ EBCs were HR+ and 28% were HR-. In HR+/HER2+ EBC, 52% were classified by BP as non-HER2 (Luminal A 6%, Luminal B 44%, Basal 2%), whereas in HR-/HER2+ EBC, 14% were classified genomically as non-HER2, all of which were Basal. In the HR+/HER2+ subgroup, pCR rates differed significantly by BP subtype and ImPrint, with the highest pCR observed in BP-HER2/ImPrint+ tumors (Table). Similar significant differences were observed in HR-/HER2+ EBC. In a multivariable model of the HR+/HER2+ subgroup, BP and ImPrint independently predicted pCR after controlling for node status and tumor size (BP-HER2 odds ratio/OR: 8.23 [95% CI: 3.47–21.44]; p<0.001; ImPrint+ OR: 4.48 [95% CI: 1.48–14.89]; p<0.05). **Conclusions:** An integrated genomic approach that combines BP and ImPrint maximizes prediction of pCR outcome in this dataset, particularly for the HR+/HER2+ subgroup. Further evaluation is warranted, as these data could be useful for guiding clinical decision-making, including selection of chemotherapy backbone and adjuvant therapy. Importantly, this approach may help identify patients who are overtreated or undertreated with current strategies, including those with exceptional treatment sensitivity who may be candidates for chemotherapy de-escalation. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

pCR rates by genomic subtypes within HR+/HER2- EBC (Fisher's exact test).				
Biomarker	Subtype*	N	pCR rate (%)	p-value
Blueprint	HER2	87	55	< 0.001
	Luminal B	80	20	
ImPrint	Positive	30	60	0.006
	Negative	151	32	
Blueprint + ImPrint	HER2, ImPrint+	14	79	< 0.001
	HER2, ImPrint-	73	51	
	Luminal B, ImPrint+	14	43	
	Luminal B, ImPrint-	66	15	

*Excluded Luminal A and Basal due to small N.

Event-free survival from the randomized phase 2 neoHIP trial evaluating neo-adjuvant taxane, HER2-targeted therapy, +/- pembrolizumab in early-stage HER2-positive breast cancer.

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Background: In early-stage HER2-positive breast cancer, achieving a pathological complete response (pCR) after neoadjuvant therapy is strongly associated with improved event-free survival (EFS); however, a substantial proportion patients (pts) fail to achieve pCR, requiring subsequent adjuvant systemic therapy and remaining at higher risk for recurrence. Pembrolizumab (pembro) is well-tolerated, invigorates anti-tumor immunity, and may enhance response of chemotherapy and/or anti-HER2. We previously reported the positive primary outcome of the randomized phase 2 neoHIP trial, showing an improvement in pCR with the addition of pembro to neoadjuvant paclitaxel, trastuzumab, and pertuzumab (4 cycles, THP-pembro, pCR: 67% v. THP: 48%, $p=.026$). With long-term follow-up now mature, we now report EFS outcomes. **Methods:** Pts aged ≥ 18 years with stage II–III HER2-positive breast cancer were randomized, stratified by hormone receptor status and nodal status, to receive neoadjuvant THP or THP-pembro. EFS was defined as the time from randomization to progression of disease precluding surgery, local or distant recurrence, or death from any cause. EFS was estimated using the Kaplan–Meier (KM) method and compared between arms using a two-sided stratified log-rank test. Data were analyzed with a cutoff date of January 23, 2026. **Results:** Among 116 pts (58 per arm) randomized to THP +/- pembro, median follow-up was 37 months (range, 33–43). The 36-month EFS rate was 95% (95% CI, 89–100) for THP and 100% (95% CI, 100–100) for THP-pembro, with a trend towards significance ($p=.099$). Three EFS events were observed, all occurring in the THP arm, with one death related to recurrence and $n=2/3$ events occurring in patients with non-pCR. **Conclusions:** THP + pembro was associated with 100% EFS after a median follow-up of 37 months, whereas recurrences were observed in the THP arm, consistent with historical EFS expectations for neoadjuvant chemotherapy + dual HER2-targeted therapy. Although not powered for EFS, these findings support definitive evaluation of THP +/- pembro in a phase III trial. Clinical trial information: NCT03747120. Research Sponsor: Merck Sharp & Dohme; Breast Cancer Research Foundation.

Neoadjuvant DAN-222 plus niraparib in high-risk HER2-negative breast cancer: Results from the I-SPY 2 adaptive platform trial.

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Background: I-SPY 2 is a multicenter phase II adaptive platform trial evaluating novel agents for stage II–III high-risk breast cancer using response-predictive subtypes (RPS) and a sequential neoadjuvant treatment design of up to three blocks (A/B/C). Investigational regimens are given in Block A, followed by response-guided escalation to standard-of-care (SOC) therapy (tx) in subsequent blocks or early surgery for responders. Topoisomerase I (TOPO1) inhibition plus PARP inhibition may enhance DNA damage and tumor response. DAN-222 is a tumor-targeted polymeric camptothecin conjugate designed to improve the therapeutic index of TOPO1 inhibition. Based on favorable phase 1 safety and preliminary activity in metastatic breast cancer, DAN-222 plus niraparib was evaluated as Block A tx in HER2– disease. Notably, the neoadjuvant regimen used a higher dose of niraparib (200 mg daily) than the prior phase 1 metastatic study. **Methods:** Patients (pts) with HER2– breast cancer were randomized to DAN-222 plus niraparib for up to 12 weeks in Block A. Response was assessed by serial MRI and biopsy. Inadequate responders escalated early to SOC tx in Blocks B/C. Primary endpoint was pathologic complete response (pCR). Secondary endpoints included residual cancer burden, safety, early discontinuation, and treatment-strategy performance versus subtype-specific SOC tx controls. Given established PARPi sensitivity in *BRCA*mut disease, the key objective was to assess clinically meaningful activity of DAN-222 plus niraparib in *BRCA*wt pts. Accordingly, a prespecified Bayesian interim futility analysis focused on *BRCA*wt and tested the probability of the true pCR rate after Block A alone exceeded 15% after 50 pts. **Results:** Fifty pts enrolled from Sep to Dec 2024. In *BRCA*wt (n=47), estimated Block A pCR was 3%, with posterior probability of 0.02 that that true pCR exceeded 15%, meeting futility criteria and prompting arm closure. Across all blocks, pCR rate was 57% (8/14) for HR–HER2–; 11% (4/36) for HR+ HER2–, largely after SOC tx. 2/3 *BRCA*mut pts achieved pCR. Treatment strategies initiating with DAN-222 plus niraparib underperformed subtype-specific controls. 68% discontinued Block A early, mainly due to toxicity. Grade ≥3 cytopenias were common: neutropenia (n=25; 50%), anemia (24%), and thrombocytopenia (18%). Cystitis occurred in 36% (1 grade ≥3). **Conclusions:** Neoadjuvant DAN-222 plus niraparib showed insufficient activity and no treatment-strategy benefit in *BRCA*wt HER2– breast cancer, underscoring challenges for TOPO1–PARP inhibitor combinations. Although not supported for further development in this setting, these results highlight the strength of I-SPY 2 in rapidly enrolling patients and quickly distinguishing ineffective from promising therapeutic strategies to accelerate progress toward improved outcomes for patients with curable breast cancer. Clinical trial information: NCT01042379. Research Sponsor: None.

Maternal and neonatal complications associated with breast cancer systemic treatments: A VigiBase disproportionality analysis study.

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Background: Pregnancy-associated breast cancer (PrBC) presents unique diagnostic and therapeutic challenges, with rising incidence due to delayed childbearing. Understanding maternal-fetal safety of systemic anticancer therapies during pregnancy is critical for informed treatment planning. **Methods:** We performed a case/non-case disproportionality analysis using VigiBase, the WHO global pharmacovigilance database up to January 2024, to evaluate maternal and fetal/neonatal outcomes associated with breast cancer (BC) systemic treatments. We included reports involving pregnancy, antineoplastic treatment during pregnancy, and cancer. The exposure group consisted of reports mentioning a BC treatment at any time during pregnancy. The primary outcome was the reporting odds ratio (ROR) of maternal-fetal complications in the BC treatment group involving at least one of the four main BC treatments: doxorubicin, epirubicin, docetaxel, paclitaxel, compared to other anticancer treatments. Secondary analyses assessed outcomes with all BC treatments and trimester-specific risks of the four main treatments. **Results:** Of 3,310 pregnancy-related reports, 1,789 involved BC treatments. Median maternal age was 27.4 years (standard deviation SD 13.8) in the BC treatment group versus 29.3 years (SD 11.7) in the other anticancer treatment group. Adverse pregnancy or neonatal outcomes were reported in 998 (55.8%) BC treatment reports versus 470 (30.9%) in other anticancer treatments. Anthracyclines were associated with neonatal immunodeficiency (ROR=11.0, 95%CI 3.2–40), hematologic disorders (ROR=1.7, 95%CI 1.1–2.5), infections (ROR=2.3, 95%CI 1.4–3.8), and pregnancy complications including IUGR (ROR=2.1, 95%CI 1.7–2.7) and hypertension/pre-eclampsia (ROR=1.9, 95%CI 1.2–2.9). Epirubicin was linked to craniofacial (ROR=7.6, 95%CI 2.5–23.5) and genitourinary malformations (ROR=6.3, 95%CI 2.1–18.9). Taxanes were associated with IUGR (paclitaxel ROR=2.8; docetaxel ROR=2.8), with paclitaxel linked to sensory defects (ROR=5.2, 95%CI 2.2–12.3) and hyperbilirubinemia (ROR=4.1, 95%CI 2.0–8.4), and docetaxel to neonatal neurologic disorders (ROR=3.6, 95%CI 1.4–9.3). First-trimester exposure (n=26) markedly increased risks of congenital malformations, i.e. face (ROR=13, 95%CI 2–79) and musculoskeletal malformation (ROR=8, 95%CI 1.1–60). **Conclusions:** BC treatments during pregnancy are associated with increased specific maternal and neonatal risks, with distinct drug- and trimester-specific variations. These findings highlight the need for individualized treatment planning and targeted fetal surveillance. Research Sponsor: “Contrats ED: Programme blanc Institut Curie PSL” during this study; “SHS INCa”, and is part of a research project on young women funded by Monoprix*; France 2030 Grant for the Women's Cancers Institute, referenced ANR-23-IAHU-0006.

Optimal timing of endocrine therapy interruption for pregnancy in young women with hormone receptor–positive early breast cancer.

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Background: The POSITIVE trial showed that temporary interruption of adjuvant endocrine therapy (ET) after 18–30 months to attempt pregnancy did not increase short-term recurrence risk in young women with hormone receptor–positive (HR+) breast cancer (BC). However, whether this effect varies by baseline recurrence risk and the timing of interruption remains uncertain. **Methods:** Using the French National Health Data System (SNDS), we emulated two target trials among women aged ≤ 42 years with early-stage HR+ BC diagnosed between 2011 and 2020. Trial 1 emulated the POSITIVE design, comparing ET interruption at 18–30 months with uninterrupted ET for ≥ 24 months. Trial 2 compared nine ET-interruption windows (6-month intervals) with uninterrupted ET for ≥ 24 or ≥ 60 months. The primary endpoint was the 5-year risk of BC events. Analyses used a clone-censor-weight approach with marginal structural models. **Results:** In Trial 1 ($n = 10,835$), ET interruption at 18–30 months was associated with a 5-year BC event risk of 17.2%, compared with 16.0% for uninterrupted ET ≥ 24 months (risk difference, 1.2 percentage points; 95% CI, -0.7 to 3.1). Risk varied by baseline recurrence risk: interruption had minimal impact in low- or intermediate-risk women (risk difference, -0.6 percentage points; 95% CI, -2.7 to 1.6) but increased risk in high-risk women (risk difference, 5.8 percentage points; 95% CI, 1.8 to 10.0). In Trial 2 ($n = 22,916$), earlier ET interruption was associated with higher 5-year BC risk, which decreased with longer prior ET duration. Compared with uninterrupted ET ≥ 24 months, interruption at 6–12 months increased risk by 8.3 percentage points, whereas interruption at 24–30 months increased risk by 2.7 percentage points. Low- or intermediate-risk women showed comparable risk when interruption occurred at 24–30 months, whereas high-risk women required ≥ 36 –42 months of ET to achieve similar safety. Among pregnancy-seeking women, 64% conceived, and 47% resumed ET. **Conclusions:** The oncologic impact of temporary ET interruption depends on baseline recurrence risk and prior ET duration. Interruption after 24 months appears safe for low- or intermediate-risk women, whereas high-risk patients may benefit from delaying interruption to at least 36 months. These findings support a risk-adapted approach to fertility counseling. Research Sponsor: None.

GLP-1 RA for primary prevention of post-mastectomy lymphedema in breast cancer patients: A multicenter real-world analysis.

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Background: Post-mastectomy lymphedema (PML) remains a significant morbidity for breast cancer (BC) survivors, particularly following axillary lymph node dissection (ALND). Complications, including recurrent cellulitis, lymphangitis, and chronic pain, significantly impair quality of life. While weight optimization is a cornerstone of PML management, the specific role of Glucagon-like Peptide-1 Receptor Agonists for the primary prevention of PML is poorly characterized. Data is limited to single-center retrospective studies (1) and case reports. This is the first, large-scale, multi-center, real-world analysis to evaluate the efficacy of GLP-1 RA for the primary prevention of PML in BC patients. **Methods:** Utilizing the TriNetX Global Collaborative Network, a retrospective cohort study was conducted on a population of 150 million patients across 108 healthcare organizations (Jan 2000 – Jan 2025). We evaluated the impact of GLP-1 RAs on the incidence of PML in BC patients. Patients were stratified into two cohorts: those who underwent mastectomy and received GLP-1 RAs, and a control group of mastectomy patients without GLP-1 RA exposure. 1:1 Propensity Score Matching (PSM) was used to balance cohorts for demographics, BMI, comorbidities, concurrent medications, and laboratory values. Following a median 650-day follow-up, hazard ratios (HR) and 95% Confidence Intervals (CI) were calculated using Kaplan-Meier survival analysis and Cox proportional hazards models to assess PML risk. **Results:** After 1:1 propensity score matching, 61,630 patients were included (n = 30,815 per cohort). The GLP-1 RA cohort had a mean age of 62.1 ± 10.8 years and was mainly female (99.2%). Racial distribution was 71.0% White, 18.0% Black or African American, and 2.9% Asian. Standardized mean differences for all matched covariates were <0.1 , indicating excellent balance within the cohort. Kaplan-Meier survival analysis demonstrated a 63% significant reduction in incident PML among GLP-1 RA users compared to the control group (HR 0.373; 95% CI, 0.324–0.429; $p < 0.0001$). The absolute incidence of PML was 0.88% (258/29,259) in the GLP-1 RA cohort vs 2.58% (779/30,237) in the control group, yielding an absolute risk reduction of 1.7% and a number needed to treat (NNT) of 59. **Conclusions:** In this large-scale, real-world analysis, GLP-1 RA use was associated with a profound 63% reduction in the risk of PML. These findings suggest that GLP-1 RAs may serve as a potent primary preventive role in BC survivorship, potentially through mechanisms beyond weight loss, including systemic anti-inflammatory effects and a disease-modifying role in the lymphatic microenvironment. With a NNT of 59, incorporating GLP-1 RAs into the supportive care of high-risk BC patients could significantly reduce the burden of chronic lymphedema. Prospective randomized controlled trials are warranted to validate these results. Research Sponsor: None.

Real-world treatment patterns and mortality associated with GLP1-RAs in breast cancer patients.

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Background: GLP1 Receptor Agonists (GLP1) are widely used for type 2 diabetes (DM2) and obesity in adults. However, data on modern utilization and associated health outcomes, including all-cause mortality, in breast cancer (BC) patients is limited. We evaluated these endpoints in a BC population from a large US national healthcare database. **Methods:** Using Truven MarketScan, a commercial insurance claims database which includes over 270 million patients, we extracted eligible invasive BC patients diagnosed between 2014 and 2023 who were ≥ 18 years old, completed definitive BC surgery (index date), received GLP1 for at least 3 continuous months, and had available mortality data. Overall survival (OS) was defined as the time from BC surgery to death from any cause; patients alive at the time of analysis or lost to follow-up were censored at last contact date. Propensity score matching (1:1 ratio) was used to match patients who received GLP1 with those who did not, based on clinical prognostic factors (age; sex; deyo comorbidity index (CI); receipt of immunotherapy, chemotherapy, adjuvant endocrine therapy; DM2; weight category; stroke; myocardial infarction (MI)/coronary artery disease (CAD); heart failure); Kaplan-Meier estimates and log-rank tests were used to compare OS between groups and hazard ratios (HR) were estimated using multivariable Cox proportional hazards models. **Results:** In 137,493 BC patients, 7,249 (5.3%) received a GLP1 and over half ($n=4,019$; 55.4%) initiated it after BC surgery. The median follow up time in GLP1 users was 32 (IQR 15–57) months. In GLP1 users the median age was 59 (IQR 53–64) years; 5,860 (80.8%) had DM2 and 1,825 (25.2%) had a CI ≥ 3 ; in those with weight data available ($n=4,687$), 4,609 (98.3%) were in the overweight or obese category. A total of 3,828 (52.8%) received GLP1 concurrent with anti-cancer systemic therapy (chemotherapy, immunotherapy, or adjuvant endocrine therapy). The median duration of GLP1 use was 2.1 (IQR 0.8–6.1) years. GLP1 use increased over time (3.2% in 2014, 5.2% in 2018, 7.2% in 2023). Semaglutide was the most common agent prescribed across all years (35.8%) and exhibited the greatest annual increase in use after 2018. In the propensity score matched cohort, OS was significantly higher in GLP1 users vs non-users ($n=7,248$ per group): 5 year OS 95.8% GLP1 vs. 89.5% non-users (adjusted HR 0.41, 95% CI: 0.34–0.49, $p<0.001$). **Conclusions:** We describe one of the largest observational studies on real-world GLP1 prescription patterns and associated mortality in a BC cohort. Use of these agents is increasing over time in BC patients. Our research supports other emerging epidemiologic data suggesting a potential all-cause mortality benefit with these incretin mimetics in this population. Prospective studies are warranted to clarify the biological mechanisms underlying this association, including metabolic health implications and effects on BC tumor biology. Research Sponsor: None.

Real-world cumulative exposure of various endocrine-disrupting chemicals and association with breast cancer risk via common carcinogenic pathway.

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Background: Convergent evidence suggests carcinogenicity of endocrine disrupting chemicals (EDCs). But there is a lack of large-scale epidemiological evidence concerning real-world EDCs mixture exposure and breast cancer (BC). A dataset of emerging knowledge of toxic pathways provides a valuable toolkit to infer the carcinogenicity of chemicals, but current studies of this thus filed are rare. We test whether real-world EDCs exposure, independently or in mixture, increases BC risk in the population, through carcinogenic toxic pathways. **Methods:** A total of 234,273 women from the UK Biobank cohort were followed for a median of 13.85 years. The annual monitoring record from UK Water Quality Sampling Harmonised was used to estimate the exposure to 13 EDCs (e.g., lead and chlorpyrifos-methyl) for each woman by Kriging interpolation model. The association between EDCs and breast cancer was analyzed by Cox proportional hazard model (for single EDC) and weighted quantile sum (WQS) regression (for mixture). The EDCs were also added to the modified Gail model to test their additional contribution. Twenty-seven Olink proteins were selected via EDC-BC toxic pathway dataset and BC genetic propensity score model to examine their correlation with EDCs. Interaction between EDCs and these proteins and SNPs within their sequence were analyzed by multiplicative model. **Results:** During the follow-up period, 9,282 women developed BC, 984 of whom died. All the 13 EDCs showed association with increased BC risk. Each unit increase of the 13-EDC mixture was associated with 2.15 fold (95% CI, 2.01-2.31) of BC risk and 4.18 fold of BC-related mortality (95% CI, 3.39-5.17), and 34.38 % of total morbidity and 59.6% of BC-related mortality in the population were attributable to EDC mixture. The risk of hormone receptor-positive BC was higher than that of hormone receptor-negative BC (HR: 2.87 vs HR: 2.03, $p = 0.002$). The EDCs provided 2.1 % improvement to the modified Gail model of BC prediction. For the 27 Olink proteins referring to BC toxic pathway and genetic propensity score, 26 (96.3%) correlated with at least one EDC (average number ≥ 8), among which NACC1 protein mediated up to 98.8% (chlorpyrifos-methyl) of the individual EDC's effect on BC. The EDC mixture showed interaction with multiple proteins, including NACC1 and estrogen receptor 1, on BC-related mortality. **Conclusions:** Various EDCs in the real world may increase BC morbidity and mortality via common carcinogenic pathways. Future policies of novel EDC emission and safety evaluations must consider the cumulative EDC stressor in the environment because they may act as a whole. Research Sponsor: National Health Commission of China; Grant No. 2024ZD0525600.

Impact of fertility concerns on endocrine therapy.

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Background: Adolescent and young adult (AYA) women with breast cancer who have not completed their desired childbearing pre-diagnosis may be more likely to decline adjuvant endocrine therapy (ET) and/or to temporarily or permanently stop ET to pursue pregnancy. Fertility counseling and use of fertility preservation strategies (e.g., oocyte/embryo cryopreservation) might impact these decisions. **Methods:** In the Valuing Opinions and Insights from Cancer Experiences (VOICE) Study, we investigated whether use of fertility preservation strategies were associated with ET initiation and early discontinuation amongst AYAs with fertility concerns. Eligible females were diagnosed with stage 1–3 estrogen–receptor positive breast cancer at age 15–39 during 2013–2022 and responded to a survey in 2023–2024. Those who reported that they had not completed their desired family size or had been unsure about having completed their desired family size at the time of their cancer diagnosis were categorized as having had fertility concerns. ET initiation was defined as 2+ ET prescription fills within 18 months after diagnosis. Among ET initiators, we assessed early discontinuation (defined as lack of ET prescription fill over any 180 day period until 5 years after their first ET fill date). Due to inadequate power, we did not model the relationship between oocyte/embryo cryopreservation and ET initiation. However, we did have power to assess the association between oocyte/embryo cryopreservation and ET discontinuation using multivariable Cox regression to calculate Hazard Ratios (HR) and 95% Confidence Intervals (CI). HRs for discontinuation were adjusted for age at diagnosis, stage, study site, diagnosis year, income, and children before diagnosis (yes/no). **Results:** Among 518 AYA breast cancer survivors, 56% (N = 290) had fertility concerns at diagnosis. Of these 290, 41% had 1+ child before diagnosis, 90% received fertility counseling, 27% froze eggs or embryos, and 10% had 1+ child after diagnosis. The majority (89%) initiated ET. Among the 32 who did not initiate ET, 7 (22%) reported that fertility concerns impacted that decision. Oocyte/embryo cryopreservation was used by 26% of ET initiators and 34% of ET non–initiators. Among the 258 ET initiators, 89 (35%) discontinued ET early. Compared to those who did not use fertility preservation strategies, patients who froze oocytes/embryos were more likely to discontinue ET (HR 1.89; 95% CI 1.18–3.05). Among those who discontinued ET, 19% had 1+ child after diagnosis (compared to 2% among those who did not discontinue ET). **Conclusions:** This study confirmed prior studies showing that many AYAs with breast cancer have fertility concerns, and these concerns may impact decisions about ET. In our analysis, those who cryopreserved oocytes/embryos were more likely to discontinue ET early, and a higher proportion who discontinued ET had 1+ live birth after breast cancer. Research Sponsor: National Cancer Institute; P01CA 233432.

Long-term safety outcomes of pregnancy among young breast cancer survivors: Results from a prospective, multicenter cohort study.

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Background: Prospective data on the risk of breast cancer (BC) recurrence among young BC survivors who have a subsequent pregnancy are limited. We sought to evaluate the long-term impact of pregnancy and live birth on BC outcomes in the Young Women's Breast Cancer Study (NCT01468246), a prospective multicenter study of women aged ≤ 40 years at BC diagnosis.

Methods: Women with stage 0–III BC without prior hysterectomy were included. The primary endpoint was breast cancer-free interval (BCFI) between patients with and without a (a) pregnancy and (b) live birth after BC. Secondary endpoints were distant recurrence-free interval (DRFI) and overall survival (OS). A time-varying Cox proportional hazards model was performed by estrogen receptor (ER) status, controlling for age at diagnosis, tumor stage, HER2 status, tumor grade, parity at diagnosis, and germline pathogenic variant status. **Results:** Among 1,016 BC survivors at a median follow-up of 12 (range, 0.5–18.5) years, 198 reported ≥ 1 pregnancy and 165 reported ≥ 1 live birth post-diagnosis. Among survivors who reported a post-diagnosis pregnancy, median age at diagnosis was 32 (range, 17–40) years; most had stage I (35%) or II (40%) BC, with 72% hormone receptor (HR)–positive and 25% HER2+; 42% were nulligravid and 60% were nulliparous at diagnosis. Among BC survivors who did not become pregnant post-diagnosis, median age at diagnosis was 37 (range, 21–40) years; most had stage I (35%) or II (43%) BC, with 75% HR–positive and 28% HER2+; 25% were nulligravid and 29% were nulliparous at diagnosis. Among BC survivors with ER–positive tumors ($n = 737$), pregnancy after BC was not associated with a difference in BCFI (adjusted hazard ratio [HR] 0.60, 95% CI 0.31–1.16, $P = 0.130$), DRFI (HR 0.73, 95% CI 0.35–1.55, $P = 0.416$), or OS (HR 0.58, 95% CI 0.24–1.40, $P = 0.227$). Similarly, live birth after BC did not impact BCFI (HR 0.83, 95% CI 0.45–1.55, $P = 0.560$), DRFI (HR 1.04, 95% CI 0.52–2.06, $P = 0.923$), or OS (HR 0.77, 95% CI 0.34–1.76, $P = 0.541$). Outcomes among BC survivors with ER–negative tumors ($n = 278$) were also not affected by post-diagnosis pregnancy (BCFI [HR 1.48, 95% CI 0.70–3.14, $P = 0.304$], DRFI [HR 1.59, 95% CI 0.68–3.75, $P = 0.287$], OS [HR 0.99, 95% CI 0.39–2.49, $P = 0.975$]) or live birth (BCFI [HR 1.02, 95% CI 0.41–2.53, $P = 0.974$], DRFI [HR 0.80, 95% CI 0.24–2.69, $P = 0.722$], OS [HR 0.39, 95% CI 0.09–1.69, $P = 0.208$]). **Conclusions:** In this multicenter, prospective study with 12 years of median follow-up, pregnancy and live birth after BC did not impact BC events or overall survival, irrespective of ER status. These long-term data from a modern cohort provide reassurance for young BC patients interested in future fertility. Clinical trial information: NCT01468246. Research Sponsor: None.

Impact of an artificial intelligence–based management model on psychological and behavioral outcomes in breast cancer patients undergoing home CDK4/6 inhibitor therapy: A multicenter randomized controlled trial.

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Background: Patients receiving CDK4/6 inhibitors (CDK4/6i) often face significant psychological and physical challenges. This study evaluated the multi-dimensional impact of an AI-based management model (Group A), a customized active follow-up model (Group B), and conventional care (Group C) on the psychological status, quality of life (QoL), and biological indicators of patients with HR+/HER2- breast cancer and their primary caregivers. **Methods:** In this randomized controlled trial (2024–2025), 140 patient-caregiver dyads were enrolled and randomized into Group A (n=47), Group B (n=45), or Group C (n=48). Longitudinal assessments were conducted using the Self-Rating Anxiety/Depression Scales (SAS/SDS), EORTC QLQ-C30, and PRO-CTCAE. Statistical analyses included mixed-design ANOVA for longitudinal changes, multiple correspondence analysis (MCA) for caregiver coping patterns, and Pearson correlation for psychological and serological indicators. **Results:** Baseline characteristics were balanced across groups ($P > 0.05$). Mixed-design ANOVA revealed significant time-by-group interaction effects for anxiety ($F=5.961$, $P < 0.001$) and depression ($F=4.931$, $P < 0.001$). During follow-up, Groups A and B showed significantly better psychological stability and depression relief compared to Group C; Group C's psychological status deteriorated over treatment cycles, peaking at T3 (16 weeks), while Groups A and B remained stable or improved ($P < 0.001$). Regarding QoL, Groups A and B significantly outperformed Group C in cognitive, emotional, social functioning, and global health ($P < 0.05$), with Group A showing superior cognitive function scores. MCA identified a strong clustering between the AI-based model and "positive coping strategies" among caregivers, whereas Group C was associated with "severe psychological stress". Pearson analysis showed SAS/SDS scores positively correlated with ALT ($r=0.178$, $P < 0.05$) and glucose ($r=0.221$, $P < 0.05$). Furthermore, Group A achieved a higher capture rate of adverse events via AI monitoring, effectively mitigating high-grade toxicity risks. **Conclusions:** AI-based management and customized follow-up significantly improve psychological outcomes and QoL in breast cancer patients on CDK4/6i. The correlation between psychological stress and physiological markers (ALT, Glucose) highlights the necessity of a "bio-psycho-social" approach in oncology management. These findings support integrating AI models into precision survivorship care. Research Sponsor: None.

Temporal trends in adherence to adjuvant endocrine therapy across age groups in hormone receptor–positive breast cancer.

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Background: Adjuvant endocrine therapy (ET) reduces recurrence and mortality in hormone receptor–positive breast cancer, yet adherence remains suboptimal. Adherence varies by age, with younger patients at higher risk for non-adherence. Whether increased awareness has improved adherence over time is unclear. We evaluated temporal trends in ET adherence.

Methods: We conducted a retrospective cohort study using the MarketScan claims database. Eligible patients were 18–100 years old with non-metastatic breast cancer (2009–2022), treated with surgery within 6 months of diagnosis, and began adjuvant ET (aromatase inhibitor [AI] or tamoxifen) within 1 year of diagnosis. The analysis included patients insured 1 year prior to and 1 year following ET initiation. ET was assessed using proportion of days covered (PDC) and defined as adherent (PDC ≥ 0.80) vs non-adherent for the year after ET initiation. Trends in adherence were evaluated using the Cochran–Armitage trend test and logistic regression with an age–calendar year interaction. Age was categorized as <50 vs ≥ 50 years. Multivariable logistic regression was used to identify factors associated with ET adherence, reported as adjusted odds ratios (ORs). **Results:** Among 88,994 patients receiving ET (57,002 AI, 31,992 tamoxifen) from 2010–2022, the average adherence rate was 77.7% (79.3% AI, 74.9% tamoxifen). Adherence was lower in patients <50 vs ≥ 50 years (74.1% vs 78.8%; OR 0.85, 95% CI 0.81–0.89). In patients <50 on an AI, adherence increased over time from 66.6% in 2010 to 76.8% in 2022 (OR per year 1.07, 95% CI 1.05–1.09, $p < 0.001$), whereas no increase in adherence over time was seen in young patients on tamoxifen or in any patients aged ≥ 50 years. In a multivariable analysis of the entire cohort (Table), younger age and polypharmacy (>10 concurrent medications) were associated with lower odds of adherence, while receipt of 90-day prescription supplies, chemotherapy (neoadjuvant/adjuvant), and CDK4/6 inhibitors were associated with higher odds of adherence. **Conclusions:** Young women remain at high risk for ET non-adherence. While tamoxifen adherence did not improve over time, AI adherence increased over time in younger patients. This likely reflects heightened awareness, better supportive care, and clinician–patient discussions emphasizing AI adherence in young, high-risk populations. In contrast, despite similar increases in awareness, AI adherence has not improved in postmenopausal patients. These results highlight a persistent gap in ET adherence and the need for targeted interventions across age groups. Research Sponsor: None.

Factors associated with adherence to adjuvant endocrine therapy.

Covariate	Adjusted OR	95% CI
Age <50 vs ≥ 50 years	0.85	0.81–0.89
Polypharmacy	0.80	0.78–0.84
90-day prescription supply	2.80	2.71–2.89
Neoadjuvant chemotherapy	1.30	1.19–1.43
Adjuvant chemotherapy	1.29	1.23–1.34
CDK4/6 inhibitor use	1.55	1.15–2.08

Patient-reported outcomes from the adjuvant ado-trastuzumab emtansine (T-DM1) for older patients with HER2+ breast cancer (ATOP) trial.

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Background: Prospective data on efficacy, quality of life, and treatment-related toxicities in older adults with breast cancer are limited. The ATOP trial (NCT03587740) evaluated T-DM1 in older adults and demonstrated favorable 5-year invasive disease-free survival. Here, we report patient-reported adverse events (AEs) and health-related quality of life (HRQOL) findings from ATOP. **Methods:** ATOP was a single-arm, phase II, multicenter study of adjuvant T-DM1 for those aged 60 with stage I-III HER2+ breast cancer. Protocol therapy included postoperative administration of T-DM1 (3.6 mg/kg) every 21 days for one year (17 cycles). PRO-CTCAE (assessing specific symptoms) and EQ-5D (a measure of HRQOL) surveys were administered electronically or on paper at baseline (pre-treatment), on Day 1 of each treatment cycle, and at a single 6–12-month post-treatment time point. Participants who responded to the baseline and at least one follow-up survey were included in the PRO analysis. EQ-5D changes from baseline were assessed using general linear mixed models. Summary statistics were used to assess PRO-CTCAE scores to evaluate which symptoms developed between baseline and 1 subsequent survey(s) and their severity. **Results:** Among the 111 patients enrolled on ATOP (median age=71, range 60–88 years), 98 responded to the baseline survey and 1 subsequent survey(s). 1435 surveys were returned that included at least one PRO-CTCAE response, and 1661 surveys were returned that included EQ-5D. The Table displays the % of participants who reported PRO-CTCAE symptoms that worsened from baseline to any severity level (scores >0) or to a severe level (scores ≥3). More than 60% of survey respondents reported new or increased dry mouth, fatigue, muscle aches, decreased appetite, nausea, pain, and/or numbness/tingling at some point during or after treatment, but these were usually not severe. EQ-5D scores did not change significantly from baseline at any time point. **Conclusions:** In this adjuvant trial for patients aged >60, participation rates for PRO data collection were high. Reassuringly, global HRQOL was not impacted by T-DM1, and though frequently reported, the vast majority of patient-reported symptoms were mild. Future analyses of this trial will focus on duration and predictors (clinical and biomarker-based) of severe AEs, agreement between patient-reported and clinician-reported AEs, and whether sharing PRO reports with clinicians impacted clinician-reported AE grades. Clinical trial information: NCT03587740. Research Sponsor: Genetech; Gateway for Cancer Research; Gloria Spivak Advancement Fund; Susan G Komen for the Cure; Bakes for Breast Cancer.

Most common new or worsening symptoms reported via PRO-CTCAE in ATOP (n=95).

Symptom	% with score >0	n (%) with score 3+
Dry mouth	79%	26%
Fatigue	71%	29%
Muscle aches	69%	20%
Decreased appetite	69%	12%
Nausea	67%	6%
Pain	66%	21%
Numbness/tingling	65%	9%
Blurry vision	60%	4%
Mouth or throat sores	60%	5%

Breast cancer—specific mortality in invasive lobular versus ductal carcinoma over 30 years.

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Background: Invasive lobular carcinoma (ILC) differs biologically from invasive ductal carcinoma (IDC) and has been associated with delayed recurrence. However, long-term patterns of breast cancer-specific mortality (BCSM) following ILC remain incompletely described. We aimed to characterize temporal patterns of BCSM associated with ILC vs IDC over extended follow-up. **Methods:** We conducted a population-based study using the SEER program. Women diagnosed with stage I–III IDC or ILC from 1990 to 2012 were included. BCSM was the primary endpoint, with death from other causes treated as a competing event. Unadjusted cumulative incidence functions estimated BCSM by histology. Fine-Gray competing risks models were used to compare histologies overall and within hormone receptor (HR)-defined subgroups, with all models adjusted for age at diagnosis, year (y) of diagnosis, HR status (where applicable), tumor size, nodal status, tumor grade, surgery, radiation, and chemotherapy. Non-proportional effects were identified visually and modeled using time-varying coefficients. Landmark competing risks analyses assessed late BCSM among long-term survivors. **Results:** Among 423,479 women included, 41,027 (9.7%) had ILC and 382,452 (90.3%) had IDC; median follow-up was 16.7 y (range 0.1–33 y). During follow-up, 77,926 breast cancer deaths and 111,814 deaths from other causes occurred. In unadjusted analyses of the overall population, BCSM was lower for ILC than IDC at 5 and 10 years and higher for ILC at 20 and 30 years (Table). In adjusted Fine-Gray models, lobular histology demonstrated a significant time-varying association with BCSM ($p < 0.001$). Associations between histology and BCSM differed by HR status (p for interaction = 0.0029). In time-varying models restricted to HR+ disease, the adjusted subdistribution hazard ratio (sHR) for ILC versus IDC increased over time, reaching 1.19 (95% CI 1.15–1.23) at 10 y, 1.34 (1.28–1.41) at 20 y, and 1.44 (1.36–1.54) at 30 y. In landmark analyses among HR+ survivors, ILC remained associated with higher late BCSM beyond 10 y (sHR 1.36, 95% CI 1.29–1.43) and beyond 15 y (sHR 1.32, 95% CI 1.20–1.45). **Conclusions:** ILC is associated with a distinct temporal pattern of BCSM compared with IDC. Although unadjusted early BCSM is lower for ILC, adjusted risk increases over time and exceeds that of IDC in the late post-diagnosis period, particularly among HR+ disease. These findings highlight the importance of long-term risk assessment and survivorship strategies tailored to lobular histology. Research Sponsor: None.

Unadjusted cumulative incidence of BCSM by histology (%; 95% CI).

Y since diagnosis	Overall population		HR+	
	IDC	ILC	IDC	ILC
5	9.8 (9.7–9.9)	7.3 (7.0–7.5)	6.5 (6.4–6.6)	6.4 (6.1–6.6)
10	15.0 (14.9–15.2)	14.3 (13.9–14.6)	11.9 (11.8–12.0)	13.4 (13.1–13.8)
20	19.6 (19.5–19.8)	21.6 (21.2–22.1)	17.2 (17.0–17.4)	21.0 (20.5–21.4)
30	22.0 (21.8–22.2)	24.5 (23.9–25.2)	19.8 (19.5–20.0)	23.9 (23.1–24.6)

From treatment to survivorship: The CORE randomized study of a supervised exercise intervention in early-stage breast cancer.

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Background: Physical exercise is recommended by international guidelines to mitigate treatment-related toxicity and improve quality of life in patients with breast cancer (BC). However, adherence to physical activity recommendations remains low, and evidence from randomized studies conducted in real-world clinical settings is limited. The CORE study evaluated the impact of a structured, supervised exercise program on fatigue and health-related quality of life (HRQOL) in patients with early-stage BC. **Methods:** CORE is a single-center, randomized controlled trial enrolling patients with early-stage BC undergoing or recently completing curative treatment. Seventy patients were randomized 1:1 to usual care (control, n = 45) or a 3-month supervised exercise intervention (exercise, n = 45). Primary endpoints were physical fatigue (EORTC QLQ-BR45), cardiorespiratory fitness and muscle strength, and HRQOL (EORTC QLQ-C30 summary score). Secondary analyses explored changes in additional symptom and functional scales, as well as health status assessed by the EQ-5D questionnaire. Between-group differences in change from baseline to 3 months were analyzed with adjustment for multiple comparisons. **Results:** At 3 months, patients assigned to the exercise intervention experienced a statistically significant reduction in physical fatigue compared with usual care (mean difference -5.3; 95% CI -10.0 to -0.6; adjusted P = 0.027). HRQOL significantly improved in the exercise group (mean difference 4.8; 95% CI 2.2-7.4; adjusted P = 0.0003). In addition, within the exercise group, significant pre-post improvements were observed across several EORTC QLQ-C30 symptom and function scales, including fatigue, pain, dyspnea, nausea/vomiting, physical functioning, and role functioning, indicating a broad positive impact of the supervised strength training program on overall health status and daily functioning. Consistently, pre-post analyses in the exercise group using the EQ-5D demonstrated significant improvements in mobility, daily activities, and pain/discomfort dimensions. **Conclusions:** A 3-month supervised exercise program significantly reduced physical fatigue and improved HRQOL in patients with early-stage breast cancer. These findings reinforce the role of structured, supervised exercise as a key component of survivorship and supportive care, offering a scalable and effective strategy to reduce symptom burden, enhance functional capacity, and promote overall patient well-being. Research Sponsor: Spanish Society of Medical Oncology; AYUDAS A PROYECTOS DE INVESTIGACION.

Impact of GLP1 receptor agonists on survival of breast cancer patients.

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Background: Large cohort studies have shown a survival benefit with the use of GLP1 receptor agonists (GLP1 RA) in cancer patients. The impact of GLP1 RA usage in breast cancer (BC) and the different subtypes is unknown. To investigate the potential influence of GLP1 RA usage on BC survival, a study was conducted on a large institutional database. **Methods:** A de-identified institutional database identified newly diagnosed Stage I, II, and III BC patients from 2005 to present and use of GLP1 RA. The study compared survival rates for BC patients with and without GLP1 RA and further stratified by BC subtype [ER+HER2-, HER2+, ER-PR-HER2-(triple negative BC (TNBC))], BMI, and age. Kaplan-Meier survival curves were used to estimate overall survival. This study analyzed de-identified data accessed through Mayo Clinic Platform Discover. Per 45 CFR 46.102, this activity did not require IRB review. Data was extracted using an established privacy-preserving protocol and de-identified via expert determination under the HIPAA Privacy Rule. Raw EHR data and other unreported data cannot be shared due to de-identification parameters. **Results:** 88015 BC patients were identified, of which 3919 (4.5%) received GLP1 RA. The 5-year survival rate was 98.5% with vs 85.5% without GLP1 RA (p-value <0.0001). The survival benefit persisted for different BMI's and ages: BMI >30 (98.4% vs 85.1%), >25 (98.4% vs 85.4%), and age <50 (99.5% vs 89.3%) and >50 (98.1% vs 84.8%) [all p<0.0001]. 21770 patients with ER+ disease were identified, of which 1412 (6.5%) received GLP1 RA. The 5-year survival rate was 99.0% vs 87.7% (p-value <0.0001). The survival benefit persisted by BMI and age: BMI >30 (99.0% vs 86.2%), >25 (98.9% vs 87.1%) and age <50 (99.6% vs 90.5%) and >50 (98.7% vs 87.2%) [all p<0.0001]. 3599 patients with HER2+ disease were identified, of which 202 (5.6%) received GLP1 RA. The 5-year survival rate was 99.3% vs 80.1% (p-value <0.0001). The survival benefit persisted by stratification: BMI >30 (100.0% vs 80.0%, p-value <0.0004), and <25 (97.7% vs 76.2%, p-value <0.019), and age <50 (100% vs 87.0%, p-value <0.043) and >50 (99.0% vs 77.2%, p-value <0.0002). 8389 patients with TNBC disease were identified, of which 360 (4.3%) received GLP1 RA. The 5-year survival rate was 91.0% vs 71.9% (p-value <0.0001). The survival benefit persisted by stratification: BMI >30 (96.4% vs 72.9%, p-value <0.0001), >25 (93.2% vs 71.8%, p-value <0.0001), and age <50 (96.0% vs 73.0%, p-value <0.0028) and >50 (88.9% vs 71.8%, p-value <0.0001). For those TNBC patients who received GLP1 RA, having a BMI >30 conferred a protective effect with a 5-year survival rate was 97.9 vs 89.8% (p-value <0.0014). **Conclusions:** The study suggests that GLP1-RA improves 5-year survival rates of patients with BC and this applies to all subtypes of BC. These results suggest that further study of the impact of GLP1-RA on BC patients is warranted. Research Sponsor: None.

Lymphopenia in breast cancer and association with clinical outcomes: An analysis from over 30,000 patients.

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Background: Lymphopenia is an independent prognostic factor for overall survival in patients with solid tumors. Low circulating lymphocytes represents impaired adaptive immunity, which can compromise antitumor immune responses and increase the risk of treatment-related toxicity. Despite having an ICD-10 code (D72.810), lymphopenia as a diagnosis might be often underrecognized and overlooked. We aimed to analyze the prevalence and concordance of lab-defined lymphopenia with the clinical diagnosis and the association of lab-defined lymphopenia with clinical outcomes in a large cohort of patients with breast cancer. **Methods:** We identified patients with breast cancer between 1/1/2011–12/31/2024 in a single institution using ICD-10 codes. Stage and subtype was determined using ICD codes, with recurrence defined by any ICD code for metastatic disease at least 6 months after initial diagnosis. Lab-defined lymphopenia was defined by absolute lymphocyte count (ALC) <1000 cells/ μ L. Baseline and on-treatment lymphopenia using ICD codes was compared to lab-defined baseline and on-treatment lymphopenia using Cohen's κ concordance statistic (0–1). Univariate logistic regression was performed to evaluate the association of lab-defined lymphopenia with recurrence. Overall mortality was analyzed using Cox proportional hazards regression. **Results:** 36,496 patients with breast cancer were included in the analysis. Most (89.7%) patients had early-stage breast cancer and estrogen receptor (ER)-positive disease (50.5%). At breast cancer diagnosis, 2,368 (6.5%) patients had lab-defined lymphopenia and 56 (0.02%) had lymphopenia diagnoses, demonstrating significantly low concordance by ICD codes ($\kappa = 0.0268$). Similarly, on-treatment lymphopenia was also discordant by ICD codes, with lab-defined on-treatment lymphopenia occurring in 5,564 (15.2%) of patients and 257 (0.7%) by ICD codes ($\kappa = 0.0459$). In early-stage breast cancer, baseline lab-defined lymphopenia was associated with increased risk of recurrence (OR 1.74; 95% CI 1.42–2.06; $p < 0.001$) and increased risk of mortality (HR 2.13; 95% CI 1.92–2.37; $p < 0.001$). In the metastatic setting, baseline lab-defined lymphopenia was associated with increased risk of mortality (HR 1.50; 95% CI 1.32–1.69; $p < 0.001$). Multivariable analysis demonstrated that lab-defined lymphopenia at diagnosis was associated with increased mortality (HR 2.47; 95% CI 2.01–3.02, $p < 0.001$), after adjusting for ER status, stage, and type of treatment. **Conclusions:** Lymphopenia is significantly underdiagnosed during breast cancer treatment, and is independently associated with increased risk of recurrence and death. These findings highlight the need for improved recognition of lymphopenia as a prognostic factor and tailored strategies to augment systemic immunity and potentially improve long-term outcomes for patients. Research Sponsor: None.

Impact of social marginalization on stage at presentation and survival for invasive lobular versus ductal breast carcinoma.

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Background: We aim to determine how indices of social marginalization impact stage at diagnosis, health services use, and overall survival comparing invasive ductal (IDC), pure (pILC) and mixed lobular (mILC) breast carcinoma (ILC) between 2005 and 2025 in the province of Ontario, Canada. **Methods:** Using population-based administrative healthcare datasets at Institute of Clinical Evaluative Sciences (ICES) Ontario, we identified all cases of IDC, pILC and mILC in Ontario, Canada between 2005 and 2025 using ICD-O-3 codes. We compared prior healthcare utilization between groups. We further compared clinical and healthcare utilization measures between four Ontario Marginalization (ON-MARG) indices: household and dwellings (includes % living alone, housing density), material resources (includes unemployment and education level), age and labour force (includes % seniors and not participating in the work force), and racialized and newcomer populations (includes % of recent immigrants). Using a multivariable Cox proportional hazards regression analysis incorporating sociodemographic, tumour and treatment factors, we assessed the impact of social marginalization indices on survival for the overall cohort and for ILC cases. Statistical analysis was performed using SAS and P values < 0.05 were significant. **Results:** We identified 16,122 (9%) pILC, 7,284 (4%) mILC and 156,870 (87%) IDC cases. At diagnosis, increasing marginalization for household and dwellings, material resources, and age and labour force correlated with less likelihood to having had a mammogram within 1 and 5 years prior to diagnosis ($P < .0001$). Increasing marginalization in these three quintiles correlated with worse clinical stage at diagnosis for both IDC and ILC ($P < .001$). Patients diagnosed with pure ILC breast cancer had 1.14 times (95%CI: 1.11 - 1.18) the likelihood of mortality in the follow-up relative to females diagnosed with IDC breast cancer. Increasing marginalization in the ON-MARG indices had a worse mortality for the overall cohort and for ILC cases, except for the racialized and newcomer populations quintile ($P < .0001$). **Conclusions:** In Ontario, Canada, the indices of social marginalization found to be associated with worse survival after a breast cancer diagnosis were household and dwellings, material resources, age and labour force but not racialized and newcomer populations. These findings highlight personalized risk factors for worse stage at presentation and survival for both IDC and ILC, independent of clinical and treatment factors. Research Sponsor: Conquer Cancer, the ASCO Foundation.

HIGHLIGHT 1: A randomized, placebo-controlled, double-blind, phase 3 clinical study to investigate the efficacy and safety of fezolinetant for treatment of moderate to severe vasomotor symptoms (hot flashes) in women with stage 0 to 3 hormone receptor–positive breast cancer who are receiving adjuvant endocrine therapy.

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Background: Breast cancer is the most common cause of death due to malignant neoplasms in women globally. Adjuvant endocrine therapy, e.g., tamoxifen and aromatase inhibitors, can lead to premature menopause and vasomotor symptoms (VMS). Fezolinetant is a non-hormonal neurokinin 3 receptor antagonist that is an approved treatment option for moderate to severe VMS due to menopause in multiple regions worldwide, including North America, Europe, Asia, and Australia, at a dose of 45 mg once daily. The pathophysiology of VMS in women undergoing cancer treatment is not fully elucidated but is hypothesized to have similar etiology to VMS associated with menopause, i.e., rapid decline of estrogen. **Methods:** This global, double-blind, placebo-controlled phase 3 study (HIGHLIGHT 1 [NCT06440967]) was designed to assess efficacy and safety of fezolinetant 45 mg once daily in moderate to severe VMS associated with tamoxifen or aromatase inhibitors for hormone receptor–positive breast cancer from stage 0 (cancer cells have not spread to nearby tissue) to stage 3+ (cancer has spread from breast to lymph nodes near the breast or the chest wall). HIGHLIGHT 1 comprises screening (28 days), treatment (52 weeks), follow-up (3 weeks after final treatment), and extension follow-up (until week 104). Eligible participants will be randomized 1:1 to fezolinetant 45 mg or placebo and stratified by adjuvant endocrine therapy and prior chemotherapy. Participants will record their VMS daily on an electronic diary. The study is currently recruiting. Participants are women (target enrollment n = 540; 382 enrolled as of 24 Nov) ≥ 18 years with ≥ 7 moderate to severe VMS episodes/day receiving hormone therapy for stage 0–3 hormone receptor–positive breast cancer. Key exclusions: history/current malignancy other than hormone receptor–positive breast cancer (stage 0 to 3) or basal cell carcinoma. Co-primary endpoints: mean change from baseline to week 4 and 12 in frequency and severity of moderate to severe VMS. Key secondary endpoints: mean change from baseline to week 12 in MENQOL VMS domain score and PROMIS Total Score Sleep Disturbance–Short Form 8b. Co-primary endpoints and key secondary endpoints will be analyzed using mixed models for repeated measures. Treatment-emergent adverse events (TEAEs) assess fezolinetant safety and tolerability. The DMC last reviewed the study in November 2025 and suggested that the study continue as planned. Clinical trial information: NCT06440967. Research Sponsor: Astellas Pharma Inc.

Precision DC: Personalized neoantigen dendritic cell vaccine pilot trial for high-risk triple-negative breast cancer after neoadjuvant therapy.

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Background: Treatment for stage II–III triple negative breast cancer (TNBC) uses neoadjuvant chemoimmunotherapy (NCT) with the goal of achieving pathologic complete responses. TNBC patients with significant residual cancer burdens (RCB II/III) after NCT have a high risk of early relapse/death despite use of adjuvant therapies like capecitabine. Moffitt Cancer Center's breast program uses a highly immunogenic dendritic cell vaccine platform (DC1) against HER2 overexpressing tumors in previous studies demonstrating anti-tumor efficacy (Han, JAMA Onc 2025). TNBC often has multiple somatic mutations leading to expression of altered immunogenic proteins known as neoantigens. We hypothesize that the residual primary TNBC after NCT can be sequenced to identify the most immunogenic neoantigens and include them as targets in an adjuvant DC1 vaccine to stimulate cytotoxic T cell responses that eliminate residual micrometastatic disease. The PRECISION DC trial was initiated to study the feasibility of adjuvant neoantigen DC1 vaccines for high risk TNBC. Correlatives include immune response to neoantigens using ELISPOT and immuno-peptidomics to study processing of peptides by the dendritic cells (NCT06435351). **Methods:** PRECISION DC is a single-arm pilot study open at the Moffitt Cancer Center enrolling stage II–III TNBC patients with RCB II/III disease and who are within 18 months of their last dose of KEYNOTE-522 chemotherapy without known metastatic disease. Eligible patients will have their residual tumor tissue whole exome sequenced, and mutated 25 mer long peptides are analyzed using a modified NetMHCII pipeline to rank these mutations based on a combined score representing multiple factors including expression, predicted MHC binding, and antigenicity. The top ten scoring peptides that also pass a peptide synthesis screen for excessive hydrophobicity are selected for inclusion in each patient's personalized DC1 vaccine. The relevant peptides for each patient are used to stimulate pheresed autologous dendritic cells ex-vivo. Moffitt's GMP cell therapy facility creates cryopreserved aliquots of 50 million cells to create DC1 vaccine doses. Patients get three intranodal DC1 inguinal injections q2weeks under ultrasound guidance in the priming phase and then two booster shots at 6 and 12 months either before or after adjuvant capecitabine (if given) per treating physician guidance. PRECISION DC opened 10/2024 and accrual to date is 22/26 planned patients with 4 remaining patients already identified. Primary endpoint is feasibility (% pts with successful vaccine administration w/ goal > 60%); secondary endpoints include safety, immune responses, and 5-year disease-free outcomes. If successful, PRECISION DC will set the stage for a prospective randomized trial of personalized autologous DC1 neoantigen vaccines to prevent recurrence of residual TNBC following NCT. Clinical trial information: NCT06435351. Research Sponsor: None.

ASPRIA: A single-arm phase 2 trial of atezolizumab with sacituzumab govitecan to prevent recurrence in triple-negative breast cancer.

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Background: Despite marked improvements in neoadjuvant chemoimmunotherapy (NACT) and adjuvant treatment for patients with early-stage triple negative breast cancer (TNBC), over 30% of patients with residual disease after NACT experience disease recurrence or death within 36 months. Understanding which patients are at greatest risk of relapse and designing effective interventions to prevent disease recurrence are major unmet needs. Circulating tumor DNA (ctDNA) can detect molecular residual disease (MRD) in TNBC and has demonstrated prognostic and predictive ability in the neoadjuvant setting; ctDNA thus represents a promising biomarker to select at-risk patients. Sacituzumab govitecan is a Trop-2 targeted antibody-drug conjugate leveraging a topoisomerase 1 payload that is approved for metastatic HR+ breast cancer and TNBC. Atezolizumab is an immune checkpoint inhibitor that interferes with the binding of PD-L1 to PD-1. The ASPRIA trial hypothesizes that ctDNA can identify patients with TNBC and residual disease after NACT at greatest risk for relapse, and that the combination of sacituzumab govitecan and atezolizumab may effectively treat MRD through cytotoxicity and anti-tumor immunity, leading to ctDNA clearance and improved clinical outcomes. **Methods:** The ASPRIA trial is an open-label, single-arm phase II trial evaluating sacituzumab govitecan in combination with atezolizumab in patients with early-stage TNBC. Eligible patients have residual invasive disease in the breast and/or lymph nodes following curative-intent therapy and detectable ctDNA, as assessed by a personalized, tumor-informed assay (Signatera, Natera, Inc.). The study includes a screening phase, with ctDNA presence assessed for the first 60 individuals to ensure feasibility, with a minimum prevalence threshold of approximately 15%. Patients with detectable ctDNA will undergo restaging imaging, and those without evidence of metastatic disease proceed to treatment. Up to 32 ctDNA-positive patients will receive atezolizumab 1200 mg IV on day 1 plus sacituzumab govitecan 10 mg/kg IV on days 1 and 8 of a 21-day cycle for 6 cycles. On-treatment ctDNA assessments will occur at weeks 3, 9, and at end of therapy. Participants will be followed for recurrence and survival every 6 months for 3 years. The primary objective is to determine the rate of ctDNA clearance after 6 cycles of therapy. Secondary objectives include estimating the ctDNA prevalence, assessing clearance after 1 and 3 cycles, evaluating recurrence risk and survival outcomes (iDFS, RFI, DMFS), and characterizing safety (per CTCAE v5). Correlative studies will examine predictors of ctDNA positivity, associations between treatment response and Trop-2 or PD-L1 expression in primary and residual tumors, temporal ctDNA dynamics in relation to relapse, and patient perspectives on ctDNA testing. Clinical trial information: NCT04434040. Research Sponsor: Stand Up to Cancer (SU2C); Natera, Inc.

NoLEEta: No chemotherapy in intermediate-risk HR+ HER2– early breast cancer treated with ribociclib in the adjuvant setting—A non-inferiority phase III trial.

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Background: Historically, the treatment paradigm for hormone receptor-positive, HER2–negative early breast cancer (HR+ HER2– eBC) has relied on endocrine therapy (ET) and adjuvant chemotherapy. However, the absolute benefit of adjuvant chemotherapy is closely tied to baseline risk, being notably modest in intermediate risk eBC, while associated with significant short- and long-term toxicities. The phase III NATALEE trial demonstrated the efficacy of an adjuvant three-year treatment with ribociclib and ET in prolonging invasive disease-free survival (iDFS) in patients with high-risk HR+ HER– eBC. Contrarily to similar studies of CDK4/6 inhibitors in this setting, NATALEE included a group of patients with intermediate clinical risk (pT1–2 pN1, pT3–4 pN0 or pT2 pN0 with histological grade 3 or grade 2 with Ki67 $\geq$ 20%). These patients are usually treated with adjuvant chemotherapy based on the tumor clinicopathological characteristics or the results of a genomic signature. Nevertheless, the absolute benefit of adjuvant chemotherapy in these patients is uncertain (and likely reduced) in the context of an adjuvant treatment strategy that includes a CDK4/6 inhibitor. The NoLEEta trial aims at demonstrating that patients with intermediate-risk HR+ HER2– eBC treated with ribociclib and ET could be spared chemotherapy side effects while ensuring similar survival outcomes. **Methods:** NoLEEta is an international, randomized, open-label, non-inferiority phase III trial. Main inclusion criteria are: HR+ HER2– eBC after curative surgery, at intermediate risk of relapse (pT0–2 pN1, pT3–4 pN0, pT2 pN0 G3 or pT2 pN0 G2 with Ki67 $\geq$ 20%), eligible for adjuvant chemotherapy (per investigator decision, based on clinicopathological parameters or using a genomic signature). Eligible patients are randomized (1:1) to either receive ribociclib and ET (investigational arm without chemotherapy) or chemotherapy followed by ribociclib and ET (control arm). Primary endpoint is invasive breast cancer-free survival (iBCFS), defined in accordance with the STEEP system as the interval between randomization and the earliest occurrence of ipsilateral invasive breast tumor recurrence, local–regional invasive recurrence, distant recurrence, invasive contralateral breast cancer, or death from any cause. Secondary endpoints include invasive disease-free survival, distant disease-free survival, overall survival, interval and type of iBCFS events, incidence and severity of adverse events, and health-related quality of life. Enrollment in NoLEEta started in December 2025, with a target objective of 3902 randomized patients across 8 countries. One interim analysis is planned. Clinical trial information: NCT07237256. Research Sponsor: Novartis; Menarini Silicon Biosystems; Women's Cancer Institute of Institut Curie.

Interception of molecular relapse in breast cancer: The SURVIVE HERoes study (NCT06643585).

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Background: Current research on circulating tumor DNA (ctDNA) in the adjuvant setting of early breast cancer (eBC) demonstrates its strong prognostic significance. Patients who are ctDNA-positive in the absence of radiological evidence of disease recurrence (i.e., molecular relapse) have significantly reduced disease-free and overall survival. Secondary adjuvant intervention trials employing highly potent therapeutic agents represent an innovative and promising strategy to intercept disease recurrence at the molecular stage. **Methods:** SURVIVE HERoes is a phase III, randomized clinical trial comparing the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) with standard of care (SoC) in patients with molecular residual or recurrent disease. Eligible patients must have a positive circulating tumor DNA (ctDNA) result detected using a tumor-informed assay (RaDaR), while staging examinations show no evidence of residual or recurrent disease. Participants must have HER2-positive, HER2-low, or—following an approved study amendment—HER2-ultralow early breast cancer (eBC), irrespective of hormone receptor (HR) status, and must have completed primary therapy, including surgery with R0 resection, with or without chemotherapy and/or radiotherapy. 180 participants are randomized in a 2:1 ratio to receive T-DXd (+ endocrine therapy for HR positive patients) or standard of care for 48 weeks, followed by a 48-week follow-up phase. Stratification factors include hormonal receptor status (positive versus negative) and HER2-status (positive versus low versus ultralow). Staging examinations and ctDNA assessments will be performed every 12 weeks during the 2-year study phase per patient. The study is accompanied by a comprehensive translational research program. The primary endpoint is the ctDNA clearance rate after 48 weeks, comparing participants in the experimental arm (receiving T-DXd) with those in the control arm (receiving standard of care), irrespective of ctDNA test results at other time points. Secondary endpoints include invasive disease-free survival, overall survival, ctDNA clearance at other time points, safety, and quality of life (QoL), as assessed by EORTC QLQ-C30 and PA-F12. Recruitment: Recruitment began in Q2/2025 and is anticipated to continue until 2030. Fifty sites across Germany are planned for participation. Discussion: Treating ctDNA-positive patients without radiographic evidence of recurrence is a novel therapeutic strategy. If SURVIVE HERoes and similar studies targeting molecular relapse yield positive results, they could pave the way for a new molecularly driven personalized surveillance and treatment approach. Clinical trial information: NCT06643585. Research Sponsor: Astra Zeenca; NeoGenomics; tosoh Bioscience; Menarini Silicon Biosystems.

PREDICT-RD: Postoperative molecular residual disease by ctDNA surveillance in TNBC with residual disease (TBCRC-071).

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Background: Patients with residual triple-negative breast cancer (TNBC) post-neoadjuvant therapy, particularly those with higher residual cancer burden (RCB II/III), remain at high risk of recurrence despite standard adjuvant therapy. Current post-treatment surveillance relies primarily on clinical follow-up and imaging, which have limited sensitivity to detect disease at a subclinical stage and rarely enable early therapeutic intervention. Circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) assessment allows detection of tumor-derived DNA in the absence of radiographic disease and offers a framework to identify patients at high risk of recurrence, who may be candidates for early, biomarker-informed treatment escalation prior to overt metastatic recurrence. PREDICT-RD is designed to evaluate the clinical implications of post-surgical ctDNA surveillance in patients with high-risk, early-stage TNBC. We hypothesize that longitudinal monitoring with a tumor-informed, high sensitivity ctDNA assay will identify an MRD-only state in at least 10% of patients, defined by ctDNA positivity in the absence of clinical or radiographic recurrence. A secondary objective is to assess outcomes among patients with ctDNA-detected molecular relapse who undergo adjuvant treatment escalation with datopotamab deruxtecan (Dato-DXd). Dato-DXd is an antibody-drug conjugate composed of a monoclonal antibody targeting TROP2 linked to a topoisomerase I inhibitor payload. In TNBC, Dato-DXd has demonstrated a manageable safety profile and promising efficacy, including an improvement in median PFS of 5.3 months over SoC chemotherapy in the first line setting for patients who are not candidates to receive immunotherapy (TROPION-Breast02). **Methods:** PREDICT-RD (TBCRC-071) is a prospective phase II, interventional, open-label, single-arm, multi-center study. The trial will enroll 78 patients with Stage II or III TNBC with residual disease (RCB II/III) following neoadjuvant chemo-immunotherapy and surgery. Patients will undergo serial blood sampling for ctDNA assessments using a clinically available tumor-informed personalized assay (Signatera Genome, Natera, Inc.) at predefined intervals during adjuvant therapy and subsequent surveillance. ctDNA test results will be disclosed to both the treating provider and the patient. A positive ctDNA result will prompt consideration of imaging for distant disease. The primary endpoint is the prevalence of MRD-only relapse. Patients meeting these criteria will be considered for treatment escalation with Dato-DXd (up to eight cycles), with ctDNA clearance as a secondary endpoint. Patient-reported fear of recurrence and quality of life will be serially evaluated. Post-treatment surveillance will continue for up to three years following initial consent. Recruitment is anticipated to begin in early 2026 (NCT07069595). Clinical trial information: NCT07069595. Research Sponsor: Gateway for Cancer Research; G-24-800; Daiichi Sankyo; Conquer Cancer, the ASCO Foundation; Natera; Daiichi Sankyo.

SIGNAL-ER-101: Signatera-guided CDK4/6 inhibitor therapy in breast cancer.

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Background: The monarchE and NATALEE trials showed that the addition of a CDK4/6 inhibitor (CDK4/6i; abemaciclib or ribociclib) to adjuvant endocrine therapy (ET) improves invasive disease-free survival (iDFS) in patients with ER+/HER2- high-risk and high-intermediate risk early breast cancer (eBC), including those with node-positive disease and select high-risk node negative tumors. However, the absolute benefit was modest (monarchE: 6.4% at 4 years; NATALEE: 3.3% at 3 years) suggesting that while a subset of patients derive benefit, many high-risk patients will not recur following ET alone. Improved strategies are needed to more precisely identify patients most likely to benefit from adjuvant CDK4/6i. Circulating tumor DNA (ctDNA) is an established biomarker of molecular residual disease (MRD) in eBC; its detection is associated with a significant risk of recurrence, and lack of detection with highly sensitive assays is associated with excellent prognosis. The SIGNAL-ER-101 trial evaluates whether tumor informed ctDNA detection during post-surgical adjuvant therapy can identify ER+/HER2- patients at highest risk of recurrence who are most likely to benefit from the addition of a CDK4/6i to standard-of-care (SOC) adjuvant ET and avoid overtreatment in patients who are likely to benefit with ET alone. **Methods:** SIGNAL-ER-101 is a Natera-sponsored prospective, open-label, single-arm, multicenter phase II treat-on-MRD study that aims to enroll 725 patients with intermediate-risk, stage II ER+/HER2- eBC who have undergone surgical resection and have no prior exposure to a CDK4/6i. Patients will be enrolled before receipt of any planned chemotherapy and/or radiation and within 6 months of initiating ET. Personalized, tumor-informed ctDNA testing will be performed using the Signatera Genome assay (Natera, Inc.), developed from archived tumor tissue and matched normal DNA to detect tumor-specific variants in plasma. Patients who are ctDNA-positive at baseline will be initiated on adjuvant CDK4/6i (ribociclib or abemaciclib) plus ET for a minimum of two years. Patients who are ctDNA-negative will receive ET alone and undergo MRD surveillance with ctDNA testing every three months. Upon detection of ctDNA during surveillance, patients will undergo staging scans to exclude distant metastatic disease prior to the addition of CDK4/6i therapy to ET. Selection of the specific CDK4/6i and ET will be at the discretion of the treating physician based on available SOC adjuvant therapy options. Patients will be followed for up to nine years to assess outcomes, including the study primary endpoint (iDFS) and key secondary endpoints (e.g., overall survival). The primary endpoint will be met if 4-year iDFS is non-inferior to that from NATALEE (3% non-inferiority margin: 93.9% vs 90.9%), aiming to evaluate whether ctDNA-guided treatment preserves efficacy while reducing over-treatment. Recruitment is expected to begin in March 2026. Clinical trial information: NCT07214532. Research Sponsor: Natera Inc.

GEMINI-BREAST: Evaluating minimal residual disease (MRD) through longitudinal circulating tumor DNA (ctDNA) profiling in breast malignancies.

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Background: While advancements in early-stage breast cancer (ESBC) treatment have improved survival, disease recurrence and therapeutic resistance remain significant challenges. Current biomarkers guide initial treatment, yet novel diagnostics are required to improve risk stratification and recurrence prediction. Circulating tumor DNA (ctDNA) offers a non-invasive method for detecting minimal residual disease (MRD), potentially enabling the identification of molecular relapse before radiographic progression. However, deeper validation of ctDNA kinetics across the treatment continuum is needed to inform precision oncology strategies in ESBC. Additionally, the logistical complexity of tissue-dependent assays presents a barrier to scalability. In order to address these gaps, the purpose of the GEMINI-BREAST study is to evaluate a methylation-based, tissue-free ctDNA assay (Tempus xM) and integrate this with comprehensive clinical and multi-omic data to determine prognostic utility for invasive disease-free survival (iDFS) and long term outcomes in patients with ESBC. **Methods:** GEMINI-BREAST (NCT07211178) is a prospective, non-interventional, multi-center study enrolling up to 900 participants with ESBC treated with curative intent. Eligible patients enroll into one of three analytical cohorts (n ~ 300 each): Cohort 1 enrolls pre-neoadjuvant therapy (high-risk HR+/HER2- [Stage II-III], HER2+ [Stage II-III], or TNBC [Stage I-III]); Cohort 2 enrolls post-surgery/pre-adjuvant therapy (same subtypes, no evidence of disease); and Cohort 3 enrolls long-term survivors (high-risk HR+/HER2- [Stage II-III], ≥ 5 years since diagnosis). Longitudinal blood samples for ctDNA analysis and archival tissue for NGS are collected at standard-of-care intervals, including, as applicable: pre-neoadjuvant, neoadjuvant on-treatment (weeks 3, 6, 12) and post-treatment, post-surgical/pre-adjuvant, adjuvant on-treatment (every 3 months), end of definitive therapy, surveillance for up to 5 years (every 3-6 months for Cohorts 1/2; every 6-12 months for Cohort 3), and at progression/recurrence. The primary objective is to evaluate the association between ctDNA dynamics (Cohort 1) or MRD status (Cohort 2/3) and iDFS, with secondary endpoints assessing overall survival, lead time to recurrence, and the predictive value of ctDNA clearance for pathological complete response. Recruitment is currently ongoing at U.S. sites. Clinical trial information: NCT07211178. Research Sponsor: Tempus AI.

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

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Background: The TAILORx and RxPONDER trials showed that recurrence score (RS) identifies many postmenopausal pts who do not benefit from addition of ACT to endocrine therapy (ET); however, RS also identifies subsets who do benefit (node-neg/high clinical risk/RS 16–20, node-neg/RS 21–25, and node-pos/RS ≤ 25). Most premenopausal pts in these trials did not receive ovarian function suppression (OFS) as part of their ET regimen. Given the observed benefit from OFS in high-risk premenopausal pts with HR+/HER2– BC in SOFT/TEXT, we question whether the ACT benefit in TAILORx/RxPONDER was due to chemotherapy-induced OFS. To address this, we developed OFSET, a phase III clinical trial comparing OFS+ET to ACT+OFS+ET. **Methods:** We hypothesize that addition of ACT to OFS+ET is superior to OFS+ET in improving invasive breast cancer-free survival (IBCFS) among premenopausal pts with early-stage HR+/HER2– tumors, and a 21-gene RS between 16–25 (for pN0 pts) and 0–25 (for pN1 pts). Secondary objectives include invasive disease-free survival, overall survival, distant recurrence-free interval, breast cancer-free interval, and health-related quality of life (HRQOL). Pts must be node-neg with RS 16–20 (plus high clinical risk), RS 21–25, or have 1–3 positive nodes with RS ≤ 25 . Stratification is by nodal status/RS status (pN0 RS 16–25; pN1 RS 0–15; pN1 RS 16–25), intent to receive CDK4/6 inhibitor (yes; no), and age (18–39; ≥ 40). Pts are randomized after surgery to either OFS+ET or ACT+OFS+ET. ET is an aromatase inhibitor (AI) per physician discretion; or tamoxifen if AI is not tolerated or if OFS is incomplete. Radiotherapy will be administered per protocol guidelines. An HRQOL sub-study will assess severe menopausal symptoms (measured by FACT ESS-19) and pain severity (PROMIS) between arms. Blood and tumor specimens will be collected for future research. We anticipate accrual of 3,960 pts in 7 yrs, 7 mos. Per NSABP B-28/RxPONDER data, 5-yr IBCFS of pN1 pts on the ACT+OFS+ET arm is estimated at 92.3%. Per TAILORx data, 5-yr IBCFS of pN0 pts on the ACT arm is ~95%. Assuming 56% of pts to be pN0 and 44% pN1, and a 0.5% annual loss-to-follow-up rate, the definitive analyses to detect a hazard ratio: 0.75 with ACT+OFS+ET v OFS+ET, with 1-sided α of 0.025 and 80% power, will require 380 IBCFS events, expected to occur ~11 yrs after study initiation. Accrual is 496/3,960 (from 8/2023 to 1/2026). NCT #: NCT05879926. Clinical trial information: NCT05879926. Research Sponsor: U.S. National Institutes of Health; U10 CA180868; U.S. National Institutes of Health; U10 CA180822; U.S. National Institutes of Health; UG1 CA189867; U.S. National Institutes of Health; U24 CA196067.

A randomized trial of sentinel node biopsy omission after neoadjuvant systemic therapy in clinically node-negative or selected node-positive breast cancer.

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Background: Omission of axillary surgery has been established as a safe option in selected patients with early-stage breast cancer undergoing upfront surgery. In the neoadjuvant systemic therapy (NST) setting, however, axillary surgery remains standard practice. Ongoing trials, including EUBREAST-01, ASICS, and ASLAN, are evaluating the safety of omitting sentinel lymph node biopsy (SLNB) after NST, but these studies have largely been limited to single-arm designs and to patients with confirmed breast pathologic complete response (pCR). Retrospective studies suggest that axillary nodal clearance after NST may be predicted using tumor subtype, treatment response, and post-NST imaging, independent of breast pCR. The NeoNAUTILUS trial was designed to prospectively evaluate the safety of omitting SLNB after NST in patients predicted to have no residual axillary disease, using axillary response-based selection rather than breast pCR. **Methods:** NeoNAUTILUS is a prospective, multicenter, randomized, controlled, non-inferiority trial being conducted at 23 centers in Korea. Eligible participants are women aged ≥ 20 years with clinical T1–T3 invasive breast cancer who have completed NST and are candidates for breast-conserving surgery (BCS). Patients with clinical No disease of any subtype are eligible. Selected patients with clinical N1 disease are eligible if they have HER2-positive, triple-negative, or estrogen receptor-low-positive tumors and demonstrate a $>30\%$ reduction in primary tumor size on post-NST magnetic resonance imaging. All participants must have no suspicious lymph nodes on post-NST axillary ultrasound. Participants are randomized 1:1 to BCS with SLNB or BCS without axillary surgery, stratified by clinical nodal status (cNo vs cN1) and tumor subtype. Patients remain blinded to treatment allocation until surgery. Whole-breast irradiation is planned for all patients, with protocol-defined axillary radiation fields in the no-SLNB group according to initial nodal status. The primary endpoint is 5-year invasive disease-free survival. Secondary endpoints include overall survival, distant metastasis-free survival, ipsilateral axillary recurrence, locoregional recurrence, and patient-reported quality of life. A total of 464 patients are planned for enrollment over 3 years with a minimum follow-up of 5 years. Enrollment began in May 2025 and is ongoing. Clinical trial registration: NCT06704945; KCT0010174. Clinical trial information: NCT06704945. Research Sponsor: None.

MELODY: A prospective non-interventional multicenter cohort study to evaluate different imaging-guided methods for localization of malignant breast lesions (EUBREAST-4/iBRA-NET/AGO-B-062; NCT05559411).

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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% (in DCIS up to 30%). Other techniques (radioactive seed or radio-occult lesion localization, intraoperative ultrasound, magnetic, radiofrequency, and radar localization) have been developed with the aim of overcoming these disadvantages. However, comparative data on the rates of successful lesion removal, negative margins, and re-operations are limited. In most studies, the patient perspective, addressing e.g. discomfort and pain, has not been evaluated. The aim of MELODY (MEthods for LOcalization of Different types of breast lesions) is to evaluate different imaging-guided localization methods with regard to oncological safety, patient-reported outcomes, surgeon and radiologist satisfaction and economic impact. **Methods:** The EUBREAST and the iBRA-NET have initiated the MELODY study to assess breast localization techniques and devices from several perspectives (NCT05559411, <http://eubreast.org/melody>). MELODY is a prospective intergroup cohort study which enrolls female and male patients planned for breast-conserving surgery with imaging-guided localization for invasive breast cancer or DCIS. Multiple or bilateral lesions and neoadjuvant chemotherapy are allowed. Primary outcomes are: 1) Intended target lesion and/or marker removal, independent of margin status on final histopathology, and 2) Negative resection margin rates at first surgery. Secondary outcomes are, among others: rates of second surgery and secondary mastectomy, Resection Ratio (defined as actual resection volume divided by the calculated optimum specimen volume), duration of surgery, marker dislocation rates, rates of marker placement or localization failure, patient-reported outcomes, rates of “lost markers”, radiologist and surgeon satisfaction, and health economic evaluation of the different techniques. Enrollment started in January 2023. Up to 26 January 2025, 9727 patients from 27 countries were enrolled in the study. The study is expected to complete patient enrollment in year 2026. The study will be conducted in 30 countries and is supported by the Oncoplastic Breast Consortium (OPBC), AWOGyn, AGO-B, SENATURK, the American Society of Breast Surgeons (ASBS) and the Korean Breast Cancer Study Group (KBCSG). Clinical trial information: NCT05559411. Research Sponsor: None.

A molecular subtype–guided, chemotherapy-free neoadjuvant strategy using SHR-A1811 plus pertuzumab for hormone receptor–positive/HER2-positive breast cancer: A phase II trial in progress.

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Background: Hormone receptor–negative/HER2–positive breast cancer achieves high pathological complete response (pCR) rates with chemotherapy–based HER2–targeted therapy, whereas hormone receptor–positive (HR+)/HER2–positive disease consistently demonstrates lower pCR rates and substantial chemotherapy–related toxicity, representing an unmet clinical need. Antibody–drug conjugates (ADCs) may address this gap by enhancing HER2–directed cytotoxic delivery while potentially avoiding conventional chemotherapy. SHR-A1811 (ruikang–trastuzumab) is a next–generation HER2–directed ADC conjugated to a topoisomerase I inhibitor with a high drug–to–antibody ratio (≈ 6) and has demonstrated superior preclinical activity compared with trastuzumab emtansine. HER2–directed ADCs may be particularly advantageous in HR–positive/HER2–positive tumors, including those with HER2 immunohistochemistry (IHC) 2+ and in situ hybridization (ISH)–positive status, through bystander killing effects that may overcome heterogeneous or lower–level HER2 expression. Emerging evidence suggests that ADC activity is retained in HR–positive/HER2–positive breast cancer and may be enhanced when combined with pertuzumab, providing the rationale for evaluating neoadjuvant SHR-A1811 plus pertuzumab in this population. **Methods:** This prospective, open–label, single–arm phase II trial enrolls women aged > 18 and < 70 years with previously untreated stage II–III HR–positive/HER2–positive breast cancer. All patients receive neoadjuvant SHR-A1811 (4.8 mg/kg intravenously every 3 weeks) plus pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks) for four cycles. Baseline Blueprint profiling classifies tumors as luminal or non–luminal. Treatment is adaptively tailored based on molecular subtype and RECIST v1.1 response after four cycles. Patients with luminal subtype and stable disease switch to a chemotherapy–free regimen of trastuzumab, pyrotinib (a HER2–directed tyrosine kinase inhibitor), dalpiciclib (a CDK4/6 inhibitor), and an aromatase inhibitor, while patients with luminal subtype achieving partial or complete response and all non–luminal tumors continue SHR-A1811 plus pertuzumab for two to four additional cycles before surgery. Circulating tumor DNA (ctDNA) is assessed at baseline, after four cycles, and preoperatively. The primary endpoint is pCR (ypT0/is ypN0); secondary endpoints include event–free survival, objective response rate, and safety, with exploratory analyses evaluating associations among molecular subtype, ctDNA dynamics, and treatment response. Clinical trial information: NCT07307287. Research Sponsor: None.

NOGA: Neoadjuvant treatment optimization via MRI-guided de-escalation in stage II–III TNBC—A phase 2 study.

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Background: Pembrolizumab combined with neoadjuvant chemotherapy improves pathological complete response (pCR) rates and survival in stage II–III triple-negative breast cancer (TNBC), establishing the KEYNOTE-522 regimen as the standard of care. This regimen consists of two phases: four cycles of paclitaxel/carboplatin with pembrolizumab (TCa+P), followed by four cycles of adriamycin/cyclophosphamide with pembrolizumab (AC+P). However, anthracycline-containing chemotherapy contributes substantial short- and long-term toxicity. A subset of patients may achieve pCR after the initial TCa+P phase, raising the possibility that treatment intensity may be reduced in selected responders. Breast MRI demonstrates high concordance with pCR in hormone receptor-negative breast cancer and represents a promising, noninvasive biomarker to guide response-adapted de-escalation strategies. **Methods:** This is a prospective, investigator-initiated, multicenter, single-arm phase II trial evaluating MRI-guided de-escalation of neoadjuvant chemotherapy plus immunotherapy in patients with early TNBC. Eligible patients have Stage II–III (T2–T3N0 or T1–T3N1) TNBC and are candidates for the KEYNOTE-522 regimen. All patients receive four cycles (12 weeks) of TCa+P, followed by mid-treatment breast MRI. Patients achieving radiologic complete response (MRI-CR) proceed directly to surgery, omitting anthracycline-containing chemotherapy. Patients with radiologic residual disease (MRI-RD) complete the full neoadjuvant regimen including AC+P. The primary endpoint is pCR rate among patients with MRI-CR undergoing early surgery. Key secondary endpoints include recurrence-free survival, overall survival, toxicity, and patient-reported outcomes. Exploratory analyses include longitudinal circulating tumor DNA (ctDNA) dynamics to assess early molecular response, minimal residual disease, and correlates with MRI-CR, pCR, and long-term outcomes. The expected pCR rate among patients achieving MRI-CR is $\geq 87\%$, compared with a benchmark rate of 65%. The study uses a Simon's optimal two-stage design (one-sided $\alpha=0.05$, 80% power). In stage 1, 10 MRI-CR patients proceeding directly to surgery will be evaluated, with early stopping for futility if the efficacy threshold is not met. If successful, stage 2 will enroll an additional 17 MRI-CR patients, for a total of 27 evaluable patients. Assuming an MRI-CR rate of $\sim 50\%$, 54 patients will be enrolled overall. The study is open for recruitment at two tertiary academic hospitals in Israel, and 9 of the planned 54 patients have been enrolled. The NOGA trial represents a novel precision oncology approach in early TNBC, with the potential to minimize toxicity without compromising efficacy in selected responders. Clinical trial information: NCT07327021. Research Sponsor: None.

A phase 2 clinical trial in progress of (Z)-endoxifen plus goserelin as neoadjuvant therapy in premenopausal women with ER+/HER2– breast cancer (EVANGELINE).

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Background: Early (14–28 day) on-treatment suppression of tumor proliferation during neo-adjuvant endocrine therapy (NET) is strongly associated with favorable long-term outcomes in estrogen receptor–positive (ER+) HER2– breast cancer. In premenopausal women, tamoxifen with or without ovarian function suppression (OFS) results in suboptimal Ki-67 suppression compared with aromatase inhibitor + OFS. (Z)–endoxifen (ENDX), the active metabolite of tamoxifen, dually inhibits ER signaling and PKC β 1-mediated AKT activation, supporting its evaluation as an alternative NET strategy in this population. **Methods:** EVANGELINE (NCT05607004) is an ongoing, multicenter, open-label Phase 2 study evaluating daily 40 mg ENDX plus goserelin administered every 28 days as neoadjuvant therapy in premenopausal women with ER+/HER2–, cT2–3, cN0–1 breast cancer. The primary objective is to determine the proportion of patients with baseline Ki-67 >10% who achieve Ki-67 $\leq$ 10% after 4 weeks of therapy. A Simon two-stage design is used to test whether the Week 4 Ki-67 $\leq$ 10% rate is at least 65%, with 20 patients enrolled into the first stage and, if promising, another 25 patients enrolled into the second stage (cohort A). A parallel cohort of 20 patients with baseline Ki-67 $\leq$ 10% (cohort B) is enrolled to assess objective response rate (ORR) at 24 weeks per RECIST v1.1. Secondary objectives include examining safety and tolerability, residual cancer burden, and PEPI score. Correlative analyses include examining effect of treatment on select tumor and plasma biomarkers. Clinical trial information: NCT05607004. Research Sponsor: Atossa Therapeutics Inc.

ETHAN: A phase II study comparing different endocrine therapies for male breast cancer.

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Background: Male breast cancer is a rare disease, and most cases are hormone receptor-positive (HR+). Due to a lack of clinical trials, male breast cancer has historically been treated based on data extrapolated from women. However, there are substantial knowledge gaps in the comparative efficacy, safety, and patient-reported outcomes of endocrine therapies for men. While tamoxifen is the current standard of care, additional data are warranted for aromatase inhibitors (AI), gonadal suppression, and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors.

Methods: This is an open-label, multicenter, randomized, phase II trial designed to evaluate different endocrine therapies in men with HR+ and human epidermal growth factor receptor 2 (HER2)-negative breast cancer. A total of 60 men will be enrolled across 9 sites within the Translational Breast Cancer Research Consortium (TBCRC). Key eligibility criteria include male sex and stage I, II, or III HR+/HER2- breast cancer before surgical resection of the primary tumor and axillary nodes. Key exclusion criteria include prior anti-cancer therapy within the past 12 months, and inflammatory breast cancer. The trial has two phases. The first phase is a window of opportunity in which newly diagnosed men are randomized 1:1:1 to either tamoxifen (Arm A), anastrozole (Arm B), or anastrozole plus degarelix (Arm C) given for 3 weeks. The primary endpoint for the window phase is Ki-67 reduction from the baseline diagnostic biopsy to the research biopsy at the end of the window phase. The second phase consists of neo-adjuvant treatment, in which the tamoxifen group is randomized 1:1 to tamoxifen (Arm D) vs tamoxifen plus abemaciclib (Arm E), and the anastrozole alone (Arm B) and anastrozole plus degarelix (Arm C) groups are merged and then randomized 1:1 to anastrozole plus degarelix (Arm F) vs anastrozole plus degarelix plus abemaciclib (Arm G). The duration of the neo-adjuvant phase is 4 months, and the primary endpoint of this phase is residual cancer burden (RCB) index at time of surgery. The trial is powered for the RCB endpoint in a 2 x 2 factorial design to detect a 0.6 unit decrease in RCB index with 80% power and alpha = 10%. For the Ki-67 endpoint, we assume an approximately 50% reduction in Arms A and B; Arm C will be of interest if it leads to ≥80% reduction in Ki-67. Secondary endpoints include: change in estradiol and testosterone levels from baseline, preoperative endocrine prognostic index (PEPI) score at surgery, adverse events, and patient-reported outcomes (including quality of life). Tumor tissue will be collected for correlative analyses. The study opened at Dana-Farber in October 2023, and is also open at Mayo Clinic, MD Anderson Cancer Center, Georgetown University, University of North Carolina, University of Pennsylvania, University of Pittsburgh, and Vanderbilt University. One more site will open in 2026. Clinical trial information: NCT05501704. Research Sponsor: TBCRC; BCRF; Eli Lilly; U.S. National Institutes of Health; Male Breast Cancer Global Alliance.

Stereotactic body radiotherapy (SBRT) combined with PD-1 inhibitor and chemotherapy in early-stage treatment-naïve triple-negative breast cancer patients: A multicenter phase III clinical study.

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Background: Early-stage triple-negative breast cancer (TNBC) carries a high risk of locoregional recurrence and distant metastasis. The KEYNOTE-522 trial established that adding an immune checkpoint inhibitor to neoadjuvant chemotherapy in high-risk early-stage TNBC yields a pathologic complete response (pCR) rate of 64.8%. However, nearly 40% of patients still fail to achieve pCR. Radiotherapy not only directly eradicates tumor cells but also can induce systemic immunomodulatory effects, such as promoting tumor antigen release and enhancing T-cell infiltration. Therefore, combining radiotherapy with immune checkpoint inhibitors and chemotherapy represents a promising strategy to improve outcomes in early-stage TNBC. Preliminary data from small-sample, single-arm studies suggest that neoadjuvant stereotactic body radiotherapy (SBRT) combined with an anti-PD-L1 antibody and chemotherapy can increase pCR rate to 90% (Liu C., et al., *Elife*, 2023). However, this therapeutic modality lacks large-scale clinical data to further confirm the radiosensitizing effect of radiotherapy on immune checkpoint inhibitors. This phase III, randomized, controlled, multicenter study aims to evaluate the efficacy and safety of toripalimab (an anti-PD-1 monoclonal antibody) plus chemotherapy with or without SBRT in treatment-naïve TNBC patients. **Methods:** Eligible patients are treatment-naïve, non-metastatic TNBC with clinical stage cT1cN1-2M0 or cT2N0-2M0 (AJCC 8th edition). Patients are randomized 1:1 to receive toripalimab (240 mg, intravenously, every 3 weeks for 8 cycles) plus nab-paclitaxel (260 mg/m², intravenously, every 3 weeks for cycles 1-4) and carboplatin (AUC=5, intravenously every 3 weeks for cycles 1-4) and epirubicin (90-100 mg/m², intravenously, every 3 weeks for cycles 5-8) and cyclophosphamide (600 mg/m², intravenously every 3 weeks for cycles 5-8), with or without SBRT (8 Gy × 3 fractions). All patients undergo surgery 4-8 weeks after completing neoadjuvant therapy. The primary endpoint is investigator-assessed pCR. Secondary endpoints include breast conservation rate, ipsilateral breast recurrence or locoregional recurrence, overall survival (OS), and safety. Sample size was calculated assuming a pCR rate of 64.8% in the control arm (based on KEYNOTE-522) and 80% in the experimental (SBRT) arm. With a one-sided α of 0.025, 80% power, 1:1 allocation, and accounting for a 20% dropout rate, 159 patients per arm (total N=318) are enrolled. The study was initiated in November 2024. Clinical trial information: NCT06627712. Research Sponsor: National Major Science and Technology Projects.

The SURVIVE study: Re-evaluating follow-up in early breast cancer.

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Background: For decades, international guidelines unanimously recommended limiting routine follow-up in early breast cancer (EBC) to clinical exams and breast imaging, to detect potentially curable local relapse early. Additionally, guidelines explicitly advise against screening for distant recurrence in asymptomatic patients, as there remains no survival benefit in patients with earlier detected metastatic disease to date, at the cost of quality of life (1). However, as most of this data was published over 30 years ago, a re-evaluation of EBC follow-up strategies is urgently needed, considering numerous novel treatment options for both EBC and metastatic breast cancer patients. **Methods:** Study Design: The SURVIVE study is a prospective, multicenter, randomized controlled trial investigating a liquid-biopsy based follow-up in intermediate- to high-risk EBC patients. 3,500 EBC patients after completion of primary therapy (surgery, chemo- or radiotherapy) are randomized 1:1 to either standard or liquid-biopsy guided (intensified) follow-up. All patients receive guideline-based follow-up procedures. Additionally, blood samples are taken every 3 months (years 1–3), later every 6 months (years 4–5). While samples from patients in the standard-arm are biobanked, samples from the interventional arm are analyzed longitudinally for tumor markers (CA 27.29, CEA, CA 125, Tosoh Bioscience), CTCs (CellSearch, Menarini), and ctDNA (RaDaR, Neogenomics). The detection of abnormalities via liquid biopsy leads to staging examinations. For patients with confirmed recurrence, treatment hereafter follows national guidelines. The detection of true molecular relapse (positive liquid biopsy without clinical evidence of recurrence) leads to further monitoring within the SURVIVE protocol and creates the unique opportunity for treatment-intervention studies, such as SURVIVE HERoes (NCT06643585). **Endpoints:** The two co-primary endpoints are overall survival (OS) and the lead time, measured as the time from positive biomarker to positive imaging in the interventional arm. Secondary endpoints include breast cancer-specific survival, quality of life, and biomarker performance. **Recruitment:** As of January 2026, recruitment is active in 98 study centers in Germany. Currently, nearly 2,400 patients have been randomized since December 2022. **Conclusion:** The SURVIVE study is a long-anticipated study assessing whether intensified follow-up, guided by liquid biopsy, leads to earlier detection of recurrence and improved overall survival in EBC. NCT05658172. **Funding:** German Federal Ministry of Education and Research (BMBF), NeoGenomics, Menarini Silicon Biosystems, Tosoh Bioscience. **Bibliography:** Moschetti I, Cinquini M, Lambertini M, Levaggi A, Liberati A. Follow-up strategies for women treated for early breast cancer. *Cochrane Database Syst Rev.* 2016;CD001768. **Clinical trial information:** NCT05658172. **Research Sponsor:** German Federal Ministry of Research, Technology and Space; NeoGenomics Inc.; Menarini Silicon Biosystems; Tosoh Biotech.

Pre-operative chemotherapy versus surgery first with peri-operative interventions in early triple-negative and HER2-positive breast cancer: An open-label, phase 3, randomized controlled trial (PRaCTiSE).

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Background: Surgery is a mainstay of treatment of breast cancer. Neoadjuvant chemotherapy (NACT) has not proven to be more effective in improving long-term outcomes when compared with adjuvant (EBCTCG, Lancet Oncol, 2018). Although pathological complete response (pCR) is surrogate at the individual patient level, it has not translated into improved outcomes across trials (BMJ, 2021). Triple-negative (TN) and HER2-positive breast cancer patients with non-pCR are treated with risk-adapted maintenance regimens (NEJM, 2025; NEJM, 2017). We previously proved efficacy of pre-operative progesterone and intra-operative peri-tumoural lignocaine in improving disease-free and overall survival (JCO, 2011; JCO, 2023). We are currently testing the effectiveness of a “Surgery first” versus “Pre-operative ChemoTherapy” approach in patients with early TN and HER2-positive tumours. **Methods:** This is a prospective, open-label randomized trial. Patients with cT1c/2, cN0/1, histologically proven, TN or HER2-positive breast cancer are screened. The study is approved by Institutional Ethics and has been registered on CTRI (CTRI/2024/02/063118). Eligible patients fit for surgery and NACT are randomized after consenting. Stratification criteria are menopausal status (pre-peri/post), cN stage (N0/N1), and TN/HER2+. “Surgery first” arm receives intramuscular progesterone injection 4–14 days before surgery and peri-tumoral 0.5% lignocaine infiltration intra-operatively. All patients are treated with standard adjuvant chemotherapy and targeted therapy and radiotherapy protocols. “Pre-operative ChemoTherapy” arm receives standard NACT. Chemotherapy backbone is anthracycline, cyclophosphamide, and paclitaxel in all patients, with addition of carboplatin and pembrolizumab in NACT for TN and anti-HER2 targeted therapy (dual if node positive) in HER2+ setting. Response assessment is done clinically after each cycle and with imaging after every 3–4 cycles. Maintenance pembrolizumab/capecitabine for TN and anti-HER2 targeted therapy/t-DM1 for HER2+ tumours as per response is offered for standard duration. Surgery in both arms is breast conservation surgery with or without oncoplasty or mastectomy with or without reconstruction, depending on imaging findings, response, and patient choice. All primary tumors are clipped in NACT arm. Axillary staging procedure is carried out and, if positive macro-metastatic nodes on frozen section, level I–III axillary dissection is done. A total sample size of 1350 (1500 accounting for loss-to-follow-up) split equally between two groups, or 257 events, achieves 80% power to detect hazard rate of 0.70173 when the proportions surviving in each group are 0.78 and 0.84 at a significance level (alpha) of 0.05 using a two-sided log rank test. An interim is planned at 50% DFS events. Clinical trial information: CTRI/2024/02/063118. Research Sponsor: None.

Anbenitamab plus albumin-bound docetaxel (nab-docetaxel) ± carboplatin (Cb) versus trastuzumab and pertuzumab plus docetaxel (THP) ± Cb as neoadjuvant therapy for HER2-positive early or locally advanced breast cancer: A randomized, open-label, multicenter, phase 3 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, 2026, issue of the *Journal of Clinical Oncology*.