ASCO 2026: Highlights in Breast Cancer Research

Authors: Pooja P. Advani,[1] *Roberto A. Leon-Ferre[1]

1. Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA
*Correspondence to LeonFerre.Roberto@mayo.edu

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The American Society of Clinical Oncology (ASCO) 2026 Annual Meeting delivered a broad and scientifically rigorous breast cancer program spanning metastatic and early disease settings. In metastatic triple-negative breast cancer (TNBC), updated antibody-drug conjugate (ADC) data from ASCENT-03/04, TROPION-Breast02, and the novel bispecific ADC iza-bren in PANKU-Breast02 consolidated and expanded treatment options. In hormone receptor (HR)-positive disease, SERENA-6, persevERA, and VIKTORIA-1 illustrated that benefit from next-generation endocrine and PI3K-pathway agents is context-dependent. In early TNBC, KEYNOTE-522 confirmed durable survival benefit with perioperative pembrolizumab and chemotherapy, while OPTIMA and SENOMAC advanced the de-escalation agenda across chemotherapy and axillary surgery, and lidERA established the first Phase III evidence for an oral selective estrogen receptor degrader (SERD) in the adjuvant setting.

METASTATIC BREAST CANCER

SG as 1L Treatment for mTNBC: PFS2 Data from ASCENT-03 and ASCENT-04

Key takeaway: Despite high rates of crossover, updated PFS2 d ata from ASCENT-03 and ASCENT-04 suggest a benefit of using SG in the first-line mTNBC setting.

Sacituzumab govitecan (SG) was established as a second-line (2L) or later treatment option for metastatic TNBC (mTNBC) based on the results of the ASCENT trial, which showed significant improvements in PFS and overall survival (OS) compared to chemotherapy (OS improvement from 6.9 to 11.8 months). Subsequently, two trials[1,2] have evaluated SG as a first-line (1L) therapy option: ASCENT-04 compared SG+pembrolizumab versus chemotherapy+pembrolizumab for programmed death-ligand 1 (PD-L1) positive mTNBC (median PFS: 11.2 versus 7.8 months; HR: 0.65); and ASCENT-03 compared SG monotherapy versus chemotherapy for PD-L1(-) or immunotherapy ineligible mTNBC (median PFS: 9.7 versus 6.9 months; HR: 0.62). Both trials incorporated crossover to SG at progression for those randomized to the control arm, with nearly 80% of patients in the control arm receiving SG as 2L treatment in each trial. At ASCO 2026, progression-free survival 2 (PFS2) data presented showed that the median PFS2 was superior in the SG arm in both trials: in ASCENT-04, median PFS2 was not reached with SG+pembrolizumab versus 21 months with the control regimen (HR: 0.67); and in ASCENT-03, median PFS2 was 18.2 versus 14.0 months (HR: 0.70). These results suggest that the benefit of 1L SG persists even though most control patients eventually received SG, suggesting that there may be a benefit from earlier exposure. However, open questions remain, as: (1) PFS2 is a contested endpoint, with variable definitions and no standardization of restaging imaging timing once patients cross to 2L; and (2) OS remains immature in both trials.

> **“The benefit of 1L SG persists even though most patients in the control arm eventually received SG”**

Dato-DXd as 1L Treatment for PD-L1(-) or Immunotherapy-Ineligible mTNBC: Additional Efficacy Endpoints from TROPION-Breast02

Key takeaway: Additional efficacy endpoints from TROPION-Breast02 suggest that the benefit pf 1L Dato-DXd extends beyond first progression.

The TROPION-Breast02 trial[3] demonstrated superior median PFS and OS with 1L datopotamab deruxtecan (Dato-DXd) compared to chemotherapy for PD-L1(-) or immunotherapy-ineligible mTNBC (median PFS: 10.8 versus 5.6 months; HR: 0.57; median OS: 23.7 versus 18.7 months; HR: 0.79), establishing it as a robust 1L treatment option for this population. New efficacy analyses presented at ASCO 2026 showed that additional efficacy endpoints all favored Dato-DXd over chemotherapy, including time to first subsequent therapy (10.9 versus

5.6 months; HR: 0.49), PFS2 (15.6 versus 11.8 months; HR: 0.61), and time to second subsequent therapy (16.7 versus 12.6 months; HR: 0.67). Like in the ASCENT-03 and ASCENT-04 trials, these results reinforce that the benefit of 1L Dato-DXd may persist beyond the first progression event, as suggested previously by the demonstrated improvement in OS. However, unlike the ASCENT-03 and ASCENT-04 trials, TROPION-Breast02 did not include crossover, and less than half of patients in the control arm have received an antibody drug conjugate (ADC) as subsequent therapy, which may play a role in the observed OS benefit.

Iza-bren, a First-in-Class Bispecific ADC for Previously Treated mTNBC (PANKU-Breast02)

Key takeaway: Iza-bren, a novel first-in-class bispecific ADC targeting EGFRxHER3, significantly improved PFS and OS compared to chemotherapy in previously treated mTNBC.

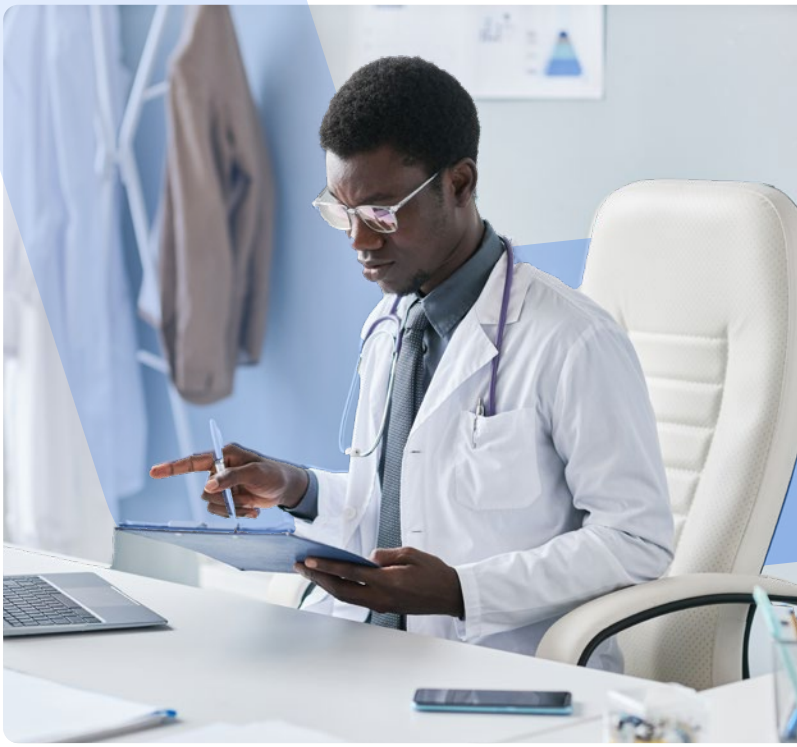
The Phase III randomized PANKU-Breast02[4] trial evaluated the first-in-class EGFRxHER3 bispecific ADC delivering a topoisomerase I inhibitor payload in 418 patients with mTNBC who had received 1–2 prior lines of therapy. Patients were randomized to izalontamab brengitecan (Iza-bren) versus investigator's choice chemotherapy, and demonstrated superior median PFS (8.5 versus 3.1 months; HR: 0.29) and median OS (15.9 versus 12.5 months; HR: 0.60), with an objective response rate of 52% versus 21%. The frequency of Grade 3 or higher adverse events (AE) was 89% with Iza-bren compared to 63% with chemotherapy, with similar rates of AEs leading to treatment discontinuation between arms, but more frequent dose reductions and interruptions in the Iza-bren arm. The main adverse events were hematologic, with the rates of Grade ≥3 anemia, leukopenia, neutropenia, and thrombocytopenia being 47%, 56%, 58%, and 53%, respectively, with Iza-bren, compared to 4%, 33%, 47%, and 2%, respectively, with chemotherapy. Despite this, the rate of febrile neutropenia was low (5.3% with Iza-bren versus 0.5% with chemotherapy). Interstitial lung disease was rare (1.4%, all low grade). These results support Iza-bren as a potential new treatment option for patients with mTNBC, and represents a novel

promising ADC that targets different antigens than the currently approved ADCs targeting TROP2 or HER2.

Depth of Response with First-Line T-DXd+P in HER2(+) Metastatic Breast Cancer (DESTINY-Breast09)

Key takeaway: Achievement of complete response or deep partial response with 1L T-DXd+P is associated with more durable disease control.

Trastuzumab deruxtecan plus pertuzumab (T-DXd+P) was established as a new 1L therapy option for metastatic HER2+ breast cancer by the DESTINY-Breast09 trial,[5] which showed a remarkable improvement in the median PFS from 26.9 months with the CLEOPATRA regimen (taxane, trastuzumab, and pertuzumab) to a notable 40.7 months (HR: 0.56) with T-DXd+P. A new analysis presented at ASCO 2026 examined the association of depth of response with long-term outcomes. In the T-DXd+P arm, 15% of patients achieved a complete response (CR), 37% achieved a deep partial response (deep PR, defined as 80–99% tumor reduction), 34% achieved PR (30–79% tumor reduction), and 14% experienced stable/progressive disease. Patients achieving CR or deep PR had higher 24-month PFS rates (85% and 80%, respectively) compared to those with PR and stable/progressive disease (64% and 36%, respectively). The median time to CR or deep PR was 8.4 months and 9.6 months, respectively, with 80% of the intention-to-treat population achieving maximal tumor reduction by 24 months. While these data provide additional reassuring data, the central question on the optimal duration of T-DXd+P in the 1L setting remains: should T-DXd+P be continued until disease progression or prohibitive toxicity (as pursued in DESTINY-Breast09) or could depth of response or other biomarkers be leveraged to de-escalate treatment to a less toxic maintenance strategy (as per previous standard of care based on CLEOPATRA, and supported by PATINA and HER2CLIMB-05)? Studies such as DEMETHER and DB-GUIDE evaluating



T-DXd induction followed by maintenance are designed to address this question.

Next-Generation Endocrine and PI3K-Pathway Targeting in ER-Positive/HER2-Negative Metastatic Breast Cancer (SERENA-6, persevERA, and VIKTORIA-1)

Key takeaway: Three trials in ER-positive/HER2-negative metastatic breast cancer collectively demonstrate that the benefit of next-generation endocrine and PI3K-pathway targeting is highly context-dependent: camizestrant improves outcomes in ESR1-mutated disease detected by liquid biopsy, giredestrant fails to add to CDK4/6 inhibition in unselected first-line disease while succeeding in post-CDK4/6 settings, and gedatolisib offers a clinically meaningful and better-tolerated alternative to alpelisib in PIK3CA-mutant disease.

Three trials demonstrate that the benefit of next-generation endocrine and PI3K-pathway targeting is highly context-dependent. SERENA-6[6] evaluated proactive switching to camizestrant upon liquid biopsy detection of an emergent *ESR1* mutation in patients on 1L AI plus CDK4/6 inhibition, without awaiting

radiographic progression. Updated data (at a median follow up of 23.5 months) showed a near-doubling of median PFS (16.8 versus 9.2 months; HR: 0.45) with consistent benefit in *PIK3CA*- and *TP53*–co-mutated disease and single versus multiple *ESR1* mutations. Additionally, switch to camizestrant was associated with a 6.6 month PFS2 advantage (HR: 0.63). This was associated with ctDNA clearance with camizestrant plus a CDK4/6 inhibitor that reached 51.0% versus 1.9% with AI plus a CDK4/6 inhibitor. The biology is compelling-*ESR1* mutations confer ligand-independent ER activation and endocrine resistance. However, regulatory acceptance remains uncertain, as the FDA's ODAC voted 6–3 against approval of ctDNA-guided early treatment switching, citing concerns regarding lead-time bias and the lack of validated long-term clinical benefit, with the FDA specifically noting that PFS2 is not an appropriate endpoint to support regulatory approval. OS data will be ultimately decisive.

persevERA[7] asked whether replacing letrozole with giredestrant as CDK4/6 inhibitor partner improves PFS in 1L HR+/HER2-negative metastatic disease setting, and although giredestrant plus palbociclib produced a numerical improvement in PFS of 4.9 months, it did not significantly outperform letrozole plus palbociclib in the 1L treatment setting. Objective response rate and clinical benefit rate was similar in the two groups. Median overall survival is immature. This contrasts with lidERA's adjuvant success (see below), currently suggesting that giredestrant's clinical niche is predominantly in earlier-stage and later-line treatment rather than unselected 1L metastatic disease.

VIKTORIA-1[8] is the most immediately actionable result of this group. Gedatolisib, a pan-PI3K/mTORC inhibitor plus fulvestrant plus palbociclib (triplet) and gedatolisib plus fulvestrant versus alpelisib plus fulvestrant in *PIK3CA*-mutant HR+/HER2-negative advanced breast cancer post-CDK4/6 inhibitor progression showed median PFS of 11.1 and 11.3, respectively, versus 5.6 months (HR: 0.50 with triplet and 0.51 with doublet). The clinically meaningful tolerability advantage over alpelisib, particularly hyperglycemia and diarrhea may enable the real-world uptake that alpelisib never achieved. Unlike oral therapies in this setting, gedatolisib is administered as a weekly intravenous infusion for 3 weeks of

every 4-week cycle, requiring regular clinic visits that may limit treatment accessibility for some patients. The optimal timing of gedatolisib remains uncertain. Whether earlier use after CDK4/6 inhibitor progression or later use following an oral PI3K inhibitor provides greater benefit is unknown. Until prospective data are available, treatment selection will likely be individualized based on efficacy, patient preference, and treatment logistics.

85.1%
77.2%

Treatment benefit with chemotherapy+pembrolizumab versus chemotherapy alone: 7-year OS was 85.1% versus 77.2%

EARLY BREAST CANCER

Perioperative Pembrolizumab in High-Risk Early TNBC: Final Analysis of KEYNOTE-522

Key takeaway: With nearly 8 years of follow-up, the KEYNOTE-522 trial continues to show significant improvements in EFS, distant recurrence-free survival, and OS with the addition of perioperative pembrolizumab to chemotherapy for high-risk early TNBC.

KEYNOTE-522[9] established the incorporation of pembrolizumab to the neoadjuvant and adjuvant treatment strategy for Stage II–III TNBC. The final analysis with a median follow-up of 94 months was presented at ASCO 2026, and confirmed the durability of treatment benefit with chemotherapy+pembrolizumab versus chemotherapy alone: 7-year OS was 85.1% versus 77.2% (HR: 0.64), event-free survival was 78.3% versus 69.8% (HR: 0.68), and distant recurrence-free survival was 82.9% versus 74.2% (HR: 0.64). Subgroup analyses showed that EFS and OS were numerically superior with pembrolizumab, both in patients achieving pathological complete response (pCR) or not. However, the study was not powered for these subgroup analyses. These results further solidify the role of pembrolizumab in high-risk early TNBC, buy the relative contribution of pembrolizumab in the adjuvant versus the neoadjuvant phase of treatment remains an open question. The Optimice-pCR trial will address this question in the subset of patients achieving pCR, by evaluating whether omission of adjuvant pembrolizumab is non-inferior to continuing pembrolizumab in these patients.

Genomically-Guided Chemotherapy Omission in Node-Positive ER-positive/ HER2-Negative Disease (OPTIMA)

Key takeaway: In clinically high-risk ER+/ HER2-negative early breast cancer, PAM50 (Prosigna) risk stratification identifies a subgroup who can safely forgo chemotherapy, extending de-escalation beyond node-negative disease into a population where chemotherapy has long been the reflexive choice.

The OPTIMA[10] Phase III trial enrolled clinically high-risk ER+/HER2-negative early breast cancer, including patients with up to 9 positive nodes or tumor size of at least 30n mm, and used Prosigna (PAM50) testing to guide treatment. The patients were randomly assigned 1:1 to receive standard CET or test-determined CET with an ROR >60 or ET alone with a low ROR score (approximately 68%). The test-directed approach was non-inferior for 5-year invasive breast cancer-free survival (93.6% versus 94.8%), with noninferiority holding across high-risk subgroups, including 4–9 patients who were node-positive and premenopausal women on ovarian suppression. This is clinically significant as OPTIMA provides robust randomized evidence that genomic stratification can help to identify subgroup of women that can safely omit chemotherapy, extending the de-escalation case established in node-negative disease by TAILORx and in 1–3 node-positive patients by RxPONDER. Some of the limitations of this study include: the trial enrolled only patients aged 40+

years, follow-up is a relatively short (4 years), the population was predominantly White, and the design was powered for noninferiority rather than superiority. In premenopausal patients, part of chemotherapy's benefit comes from inducing ovarian suppression rather than direct cytotoxicity; the favorable result in this subgroup therefore likely depends on endocrine regimens that include deliberate ovarian suppression, rather than endocrine monotherapy alone. Overall, the trial supports avoiding chemotherapy in roughly two-thirds of tested patients, a meaningful reduction in treatment burden for a substantial proportion of high-risk disease.

Omission of Completion Axillary Dissection: SENOMAC

Key takeaway: Long-term follow-up from SENOMAC confirms that omission of completion axillary lymph node dissection (ALND) in sentinel node-positive patients undergoing breast-conserving surgery or mastectomy does not compromise locoregional control or survival, further supporting a de-escalation approach to axillary surgery in appropriately selected patients.

SENOMAC[11] randomized patients with 1–2 sentinel node macrometastases undergoing breast-conserving surgery or mastectomy to completion ALND versus no further axillary surgery. Long-term follow-up at >5 years confirmed equivalent locoregional recurrence, distant recurrence-free survival, and OS, with axillary recurrence <2% in the no-ALND arm. Crucially, SENOMAC extends the ALND omission evidence base, previously established by ACOSOG Z0011 in breast-conserving surgery to mastectomy patients, who have historically undergone completion dissection. The morbidity of lymphedema and shoulder dysfunction is not offset by survival benefit in patients with limited sentinel node disease.

Adjuvant Oral SERD Therapy Across Menopausal Status (lidERA)

Key takeaway: Adjuvant giredestrant significantly reduces invasive disease recurrence in ER+/HER2-negative early breast cancer, with benefit consistent across both premenopausal and postmenopausal patients, establishing the first Phase III evidence for an oral SERD in the adjuvant setting.

lidERA[12] randomized 4,170 patients with Stage I–III ER+/HER2-negative early breast cancer (node-positive, or node-negative with high-risk features) to adjuvant giredestrant or investigator's choice of standard endocrine therapy, with mandatory ovarian function suppression for premenopausal patients and men. At ASCO 2026, subgroup analysis by menopausal status confirmed consistent benefit: in premenopausal patients, 3-year IDFS was 94.0% with giredestrant versus 91.5% with standard therapy (HR: 0.65), while postmenopausal patients showed 91.3% versus 88.3% (HR: 0.74). Distant recurrence-free interval improved similarly in both groups, and giredestrant was associated with fewer treatment discontinuations than aromatase inhibitors. Mandatory ovarian suppression in premenopausal patients ensures the benefit reflects giredestrant's direct effect rather than confounding from differential ovarian function, and the consistency across menopausal strata simplifies clinical decision-making. Overall survival data remain immature.

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