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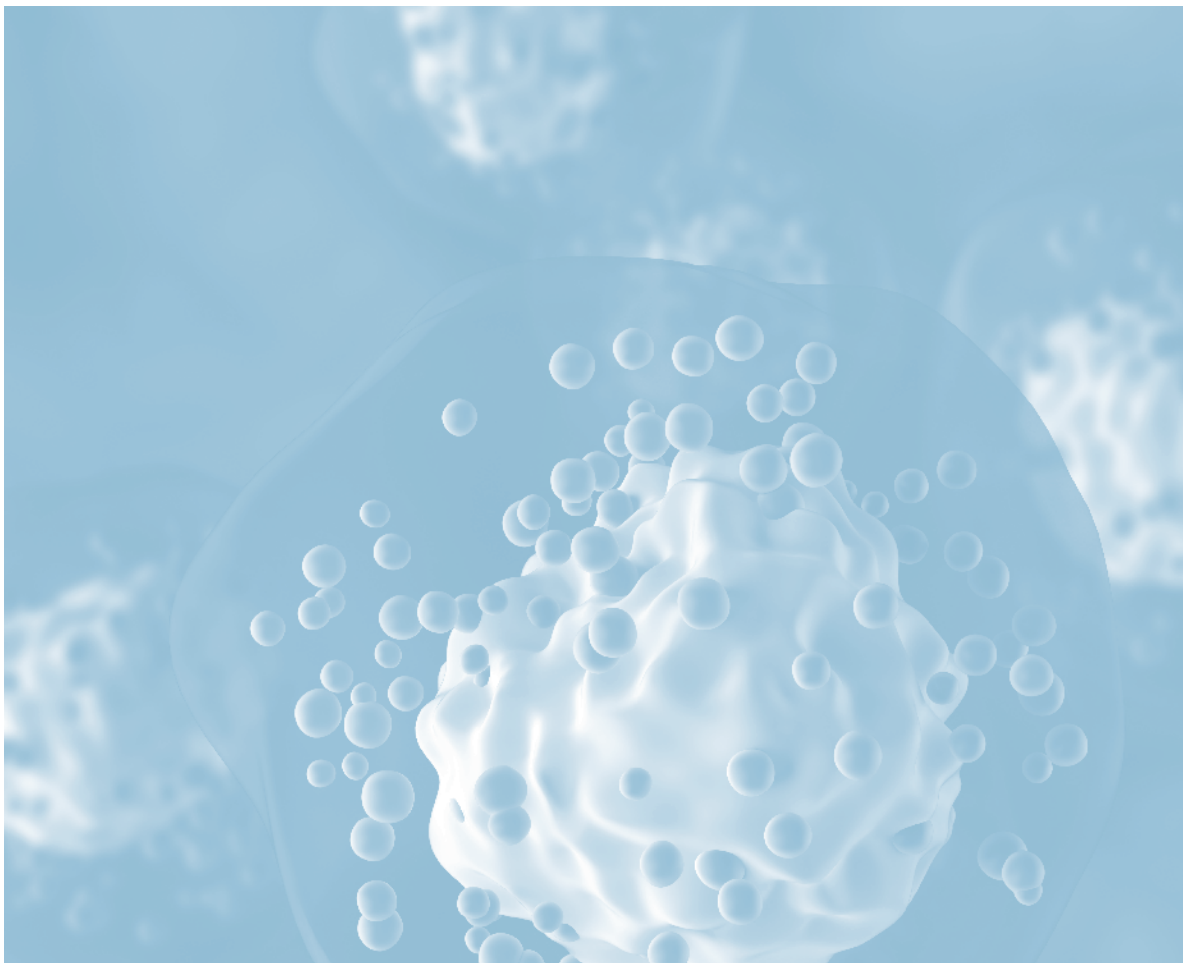
December 2025

Breast Cancer Update

from NEJM Group



- Circulatory Tumor Markers: Promises & Pitfalls
- Evolving Treatment of Metastatic HER2+ Disease
- The Latest in Metastatic Triple-Negative Breast Cancer
- Two Views: Sequencing Antibody–Drug Conjugates



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FROM the Editor

In 2025, we witnessed remarkable progress across the spectrum of breast cancer research and care. This issue of NEJM Group's *Breast Cancer Update* features articles that address evolving challenges and highlight practice-changing data shaping the future of breast cancer diagnosis and treatment.

Dr. Angela DeMichele reviews the emerging role of liquid biopsies in early and metastatic breast cancer, describing how circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) may enable real-time, biology-driven treatment decisions. She highlights the role of ctDNA in metastatic disease in the current clinical practice and discusses the potential role of measurable residual disease (MRD) assays. While enthusiasm is high, definitive evidence of clinical utility is still needed before these assays can be widely incorporated into clinical practice.

Drs. Candace Mainor and Claudine Isaacs examine advances in metastatic HER2-positive disease, highlighting the transformative impact of antibody–drug conjugates (ADCs), such as trastuzumab deruxtecan (T-DXd). Results from the DESTINY-Breast09 trial suggest that T-DXd plus pertuzumab could redefine the standard of care for first-line treatment; however, questions remain regarding sequencing, cost, toxicity, and quality of life.

Drs. Chiara Corti and Ana Garrido-Castro discuss shifting paradigms in metastatic triple-negative breast cancer (mTNBC), where immunotherapy, PARP inhibitors, and ADCs are improving outcomes for biomarker-selected patients. While findings from the ASCENT-04 trial suggest that sacituzumab govitecan in combination with pembrolizumab may soon establish a new standard of care for first-line treatment for selected patients with mTNBC, the impact of this treatment on the selection of subsequent lines of therapy is yet to be established.

Finally, Drs. Paolo Tarantino and Joshua Drago examine sequencing ADCs in metastatic disease, outlining complementary perspectives that underscore both the promise and challenges of this rapidly expanding therapeutic class.

Together, these contributions capture a field in transformation, one defined by accelerating innovation, deeper biologic understanding, and a collective commitment to translating scientific advances into more effective and personalized care for every patient with breast cancer.

Ilana Schlam, MD, MPH

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Topic Update

ctDNA and CTCs in Breast Cancer: Promises and Pitfalls

Angela DeMichele, MD, MSCE, FASCO

During the past 30 years, our understanding of breast cancer biology has greatly expanded and our treatment options have evolved, but our overall treatment paradigm remains largely unchanged. Surgery, radiation, and chemotherapy are often still necessary for patients to avoid recurrence. In metastatic disease, chronic, indefinite therapy continues to be required for control, cure remains elusive, and treatment sequencing still relies on "trial and error," with resistance inevitable. What we need now is a true paradigm shift in how we monitor and treat breast cancer — and genomic analysis of circulating tumor markers offer the best potential for that shift.

Potential Benefits of Assessing Circulatory Tumor Markers

Tumor biopsy and radiologic imaging have traditionally been the primary tools used to assess biology, staging, and treatment response. However, tumor biopsies capture only part of tumor heterogeneity, and scans reveal resistance only after anatomic progression has occurred. Circulatory tumor markers, such as circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs), are unique in that they can be used to detect the presence or absence of disease, define its mutational spectrum, and track response over the course of treatment — all through a blood test. In doing so, these markers could capture the full heterogeneity of disease and open possibilities for biology-driven, personalized therapy.

The use of circulating tumor biomarkers could influence every phase of care, including allowing optimization of neoadjuvant and adjuvant therapy, detecting minimal residual disease after completion of primary therapy, enabling selection of therapy for metastatic disease, and monitoring response to such therapy (Figure). Use of these markers could open up a panoply of new treatment approaches that revolutionize our approach to therapy and improve survival while reducing treatment toxicity across the disease spectrum.

Early efforts to accomplish these goals using CTCs confirmed their tumor origin but were hampered by low sensitivity and the limited genomic information that could be obtained by the cells that were detected (*Clin Chem* 2024; 70:68). ctDNA offers higher sensitivity and specificity than CTCs for profiling tumor mutations and tracking their changes over time (*ESMO Open* 2021; 6:100086). However, integrating ctDNA into the evaluation and treatment paradigm requires rigorous clinical evaluation and evidence generation. Demonstrating clinical utility — that the use of ctDNA to determine treatment improves outcomes — is essential. Although analytic and clinical validity for ctDNA is fairly well established in the early and metastatic settings, clinical utility has not yet been proven.

Clinical Utility of ctDNA in the Metastatic Setting

Targeted therapies are an important treatment modality for metastatic breast cancer, particularly in hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–positive, and *BRCA*-mutated disease. For HR–positive disease, ctDNA panel tests can detect mutations conferring sensitivity (e.g., alterations in the PI3K–AKT–mTOR pathway) or resistance (e.g., *ESR1* mutations, *RB1* loss) without the need for primary tumor tissue. These results guide the use of agents such as the PI3 kinase



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inhibitors alpelisib, capivasertib, and inavolisib. Guidelines from the American Society of Clinical Oncology (ASCO) endorse biomarker testing for treatment selection (*J Clin Oncol* 2022; 40:3205 and 2024; 42:1450), although FDA approval of the tests is based on retrospective analyses rather than prospective clinical trials demonstrating that ctDNA-guided selection improves survival.

The PADA-1 and SERENA-6 trials represent the field's first attempts to demonstrate the utility of ctDNA in estrogen receptor (ER)–positive metastatic breast cancer (*Lancet Oncol* 2022; 23:1367 and *N Engl J Med* 2025; 393:569). In both of these phase 3 trials, researchers tested whether ctDNA-directed therapy, instituted before anatomic progression, improves outcomes. In SERENA-6, patients who had stable disease on first-line aromatase inhibitor (AI) therapy but emergence of an *ESR1* mutation in the blood were randomized to switch early to camizestrant or remain on AI until progression. Those who switched early had longer progression-free survival (PFS, 16 vs. 9.2 months; hazard ratio, 0.44).

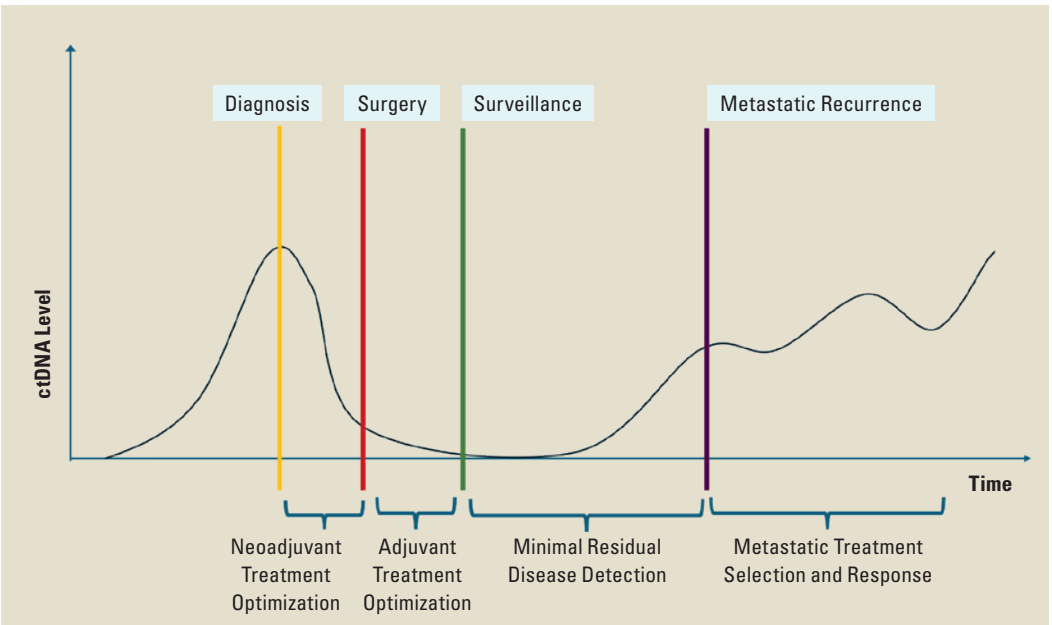
Although this trial met its primary end point, it also raised questions about the clinical utility of ctDNA testing for this indication. Patients continuing AI despite an *ESR1* mutation still derived benefit, suggesting resistance is heterogeneous. Furthermore, whether earlier PFS translates to longer overall survival remains unclear. Finally, assessment of PFS-2 (time from randomization to either progression on the next line therapy or death) was biased by the fact that patients switching early had three prior therapies, while those in the control group had only two; crossover was not permitted, and few of those in the control arm later received a selective estrogen-receptor degrader. Given these aspects of the study design, we do not yet know whether ctDNA-guided early switching improves or shortens survival.

Clinical Utility of ctDNA in the Early-Stage and Surveillance Setting

Clinical utility also remains unproven in early-stage breast cancer. However, studies have shown that ctDNA can be tracked during neoadjuvant therapy and into surveillance, and initial findings are promising:

- Early ctDNA decline predicted pathologic complete response (pCR) in the I-SPY2 trial (*Cancer Cell* 2023; 41:1091).

FIGURE. Circulating Tumor DNA Levels and Their Potential Use Across the Disease Spectrum



- Clearance of ctDNA at completion of neoadjuvant therapy (determined using an ultrasensitive assay) predicted lower recurrence risk in the PREDICT-DNA trial, as reported at the 2025 ASCO annual meeting (*J Clin Oncol* 2025; 43:abstract 1009). Outcomes were similar between patients who cleared ctDNA and those with pCR.
- The presence of detectable ctDNA during adjuvant endocrine therapy predicted imminent relapse in the CHiRP study (*J Clin Oncol* 2022; 40:2408).

The next step in determining clinical utility is to evaluate whether therapeutic interventions that are based on ctDNA findings change the ultimate trajectory of disease. Until this information is available, routine clinical testing for ctDNA is not indicated. The most pressing need at this time is to determine whether a change in ctDNA (reduction or clearance) leads to a change in clinical outcome (delaying or preventing recurrent disease). Demonstrating this link would allow ctDNA clearance to serve as a surrogate end point, enabling shorter trials and eventual regulatory acceptance.

Conclusion

Circulating tumor markers represent a paradigm shift in how breast cancer might be monitored and treated. CTCs first proved that circulating tumor analysis was possible, but ctDNA has surpassed this technology with greater sensitivity, specificity, and dynamic insight into mutational evolution.

Enthusiasm for clinical application of ctDNA testing is understandable but must be tempered by evidence. In metastatic disease, ctDNA is already used to identify mutations and guide therapy eligibility, but prospective proof that ctDNA-directed strategies improve survival is still lacking. The SERENA-6 trial demonstrates feasibility but also highlights pitfalls in trial design and interpretation. In early-stage and surveillance settings, ctDNA shows great potential to predict response and recurrence, potentially enabling tailored escalation or de-escalation of therapy. However, without evidence that ctDNA-guided interventions improve outcomes, testing remains investigational.

The promise of ctDNA is clear: real-time, biology-driven treatment that personalizes therapy, limits ineffective or unnecessary drug exposure, and perhaps prolongs survival. But pitfalls — heterogeneous resistance, trial design challenges, and unproven clinical utility — must be overcome. Only through rigorously designed trials can ctDNA realize its potential to truly change the trajectory of breast cancer care.

Topic Update

Changing Treatment Paradigms in Metastatic Triple-Negative Breast Cancer

Chiara Corti, MD, and Ana C. Garrido-Castro, MD

Triple-negative breast cancer (TNBC), which lacks hormone receptors and overexpression of human epidermal growth factor receptor 2 (HER2), accounts for approximately 15% of breast cancers worldwide (~200,000 cases annually). Nearly one third of patients with TNBC present with de novo metastatic disease, often with visceral involvement (*ESMO Open* 2021; 6:100114). The median overall survival (OS) for patients with metastatic TNBC (mTNBC) remained under 18 months for decades, with recent improvements only in the subset of patients (20%–30%) who are positive for programmed cell death ligand 1 (PD-L1) and therefore eligible for immunotherapy. Chemotherapy was once the standard treatment option for mTNBC but is now joined by immune checkpoint inhibitors, poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors, and antibody–drug conjugates (ADCs), all of which are shifting our treatment paradigms.

Given the biological heterogeneity of TNBC, a biopsy at suspected metastatic recurrence is key, allowing for pathologic confirmation and assessment of both potential subtype discordance and treatment-informing biomarkers.

First-Line Treatment Selection

First-line treatment selection for mTNBC is largely dependent on biomarker assessment — in particular, PD-L1 status and *BRCA1/2* mutation status, which guide the use of immunotherapy and PARP inhibitors, respectively.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors have reshaped the treatment of TNBC, particularly in the PD-L1–positive setting, where they are now considered first-line standard therapy. Support for pembrolizumab in this setting comes from the KEYNOTE-355 trial, in which patients with either de novo mTNBC or a recurrence of TNBC at least 6 months after completing treatment for stage I–III cancer (i.e., a disease-free interval [DFI] ≥6 months) were randomized to receive chemotherapy (paclitaxel, nab-paclitaxel, or carboplatin/gemcitabine) plus either pembrolizumab or placebo (*N Engl J Med* 2022; 387:217). In patients whose tumors expressed PD-L1 (combined positive score [CPS] ≥10), the addition of pembrolizumab was found to significantly improve both median progression-free survival (PFS) and overall survival (OS; 23.0 vs. 16.1 months; hazard ratio [HR], 0.73). These results led to the approval of pembrolizumab in combination with chemotherapy for PD-L1–positive TNBC in 2021 by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Atezolizumab, in contrast, has shown mixed results. In the IMpassion130 trial, conducted among patients with advanced TNBC and DFI ≥12 months, adding atezolizumab to nab-paclitaxel improved



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PFS (7.2 vs. 5.5 months; HR, 0.80) but did not meet the coprimary OS endpoint (*N Engl J Med* 2018; 379:2108). Although a numerical improvement in median OS (25 vs. 18 months) was seen among patients with PD-L1 expression ≥1% in immune cells, statistical significance could not be evaluated because of the prespecified hierarchical nature of statistical testing in the trial (*Lancet Oncol* 2020; 21:44). In IMpassion131, also conducted among patients with advanced TNBC and DFI ≥12 months, adding atezolizumab to paclitaxel offered no benefit to patients with PD-L1–positive tumors (*Ann Oncol* 2021; 32:994). Although the EMA approved atezolizumab plus nab-paclitaxel for patients with PD-L1–positive mTNBC and DFI ≥12 months, approval was withdrawn in the United States.

More recently, immune checkpoint inhibitors have been shown to yield better outcomes when combined with topoisomerase inhibitor–based ADCs than with chemotherapy. In the ASCENT-04/KEYNOTE-D19 trial, reported at the 2025 ASCO Annual Meeting, patients with PD-L1–positive (CPS ≥10) mTNBC (DFI ≥6 months if recurrent disease) who had not received prior therapy for advanced disease were randomized to receive pembrolizumab in combination with either sacituzumab govitecan (a Trop-2-targeted ADC) or chemotherapy (*J Clin Oncol* 2025; 43:LBA109). Those receiving sacituzumab govitecan were found to have longer median PFS (11.2 vs. 7.8 months; HR, 0.65) and longer median duration of response (16.5 vs. 9.2 months); OS data were immature. Of note, less than 5% of patients had received prior immunotherapy, limiting applicability to those with relapse after adjuvant or neoadjuvant pembrolizumab.

Several other phase 3 trials of Trop-2–targeted ADCs in first-line mTNBC are also underway. For example:

- In TROPION-Breast05, involving patients with PD-L1–positive mTNBC, datopotamab deruxtecan (Dato-DXd) with or without durvalumab is being compared against chemoimmunotherapy with pembrolizumab (NCT06103864).
- In immunotherapy-ineligible patients, TROPION-Breast02 is testing Dato-DXd against chemotherapy (NCT05374512), and ASCENT-03 is comparing sacituzumab govitecan to chemotherapy (NCT05382299).
- In TroFuSE-011, involving patients with PD-L1–negative mTNBC, sacituzumab tirumotecan with or without pembrolizumab is being tested against chemotherapy (NCT06841354).

PARP Inhibitors

PARP inhibitors are another option for first-line treatment, with two trials showing benefit in patients with mTNBC and a germline *BRCA1/2* mutation. In the first trial (OlympiAD), olaparib improved PFS compared with non–platinum-based chemotherapy in pretreated patients, showed an exploratory OS advantage in chemotherapy-naive patients, and improved quality of life (*N Engl J Med* 2017; 377:523, *Ann Oncol* 2019; 30:558, *Eur J Cancer* 2023; 184:39, *Ann Oncol* 2017; 28:V96). In the second trial (EMBRACA), talazoparib improved PFS compared with single-agent chemotherapy *(N Engl J Med* 2018; 379:753). Neither trial was powered for OS or compared PARP inhibitors with platinum-based chemotherapy, although both showed activity in platinum-pretreated patients. Olaparib has also demonstrated activity in patients with mTNBC and germline *PALB2* mutations (objective response rate, 75%) and should therefore be considered for this population (*J Clin Oncol* 2024; 42:1021).

Consistent with the synthetic lethality framework, carboplatin also targets DNA repair–deficient tumors and, in g*BRCA1/2*m carriers, was shown to prolong PFS compared with docetaxel, with fewer grade 3/4 adverse events (*Nat Med* 2018; 24:628).

Recommendations for First-Line Treatment

Given the new evidence presented at ASCO 2025 and in the months leading up to it, we seem to be shifting into a new paradigm for the first-line treatment of mTNBC (Figure).

- For patients with PD-L1–positive tumors, sacituzumab govitecan in combination with pembrolizumab may become the new preferred first-line treatment, pending approval by regulatory agencies and endorsement by National Comprehensive Cancer Network/European Society for Medical Oncology guidelines.
- For those with PD-L1–negative tumors and *BRCA1/2* mutations, olaparib or talazoparib is recommended if available; otherwise, platinum-based chemotherapy is preferred.

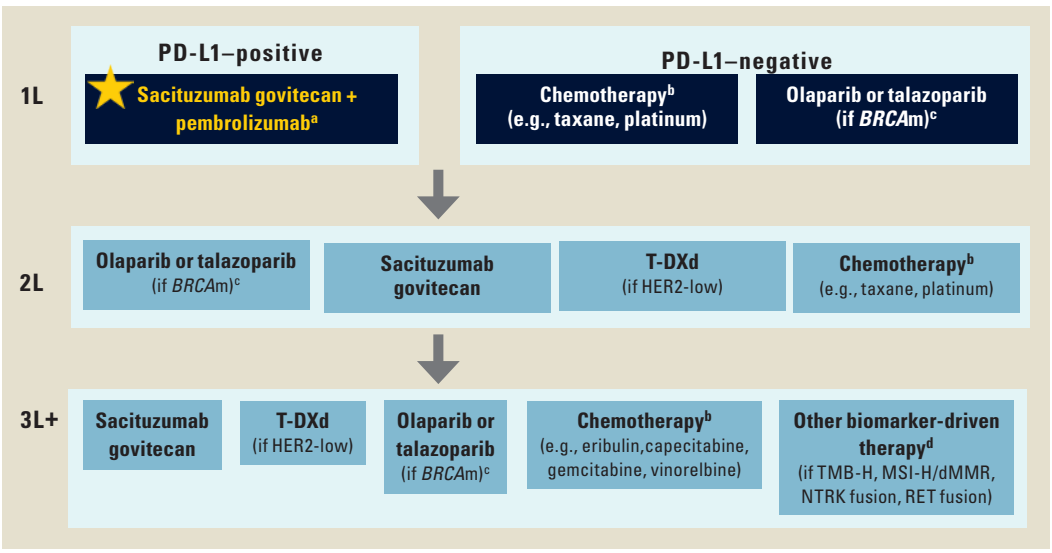
- For patients with PD-L1–negative, g*BRCA1/2*–wild-type mTNBC, treatment depends on prior therapy, disease presentation, DFI, and comorbidities. Single-agent taxane or anthracycline is preferred if not previously given in the adjuvant or neoadjuvant setting. Combination chemotherapy may be considered in patients with high tumor burden, rapidly progressing disease, and visceral crisis.
- For patients who are eligible for either immunotherapy or PARP inhibitors, chemoimmunotherapy is generally preferred because of the demonstrated OS benefit, with PARP inhibitors reserved for later lines.
- For patients with early relapse (DFI <12 months), novel strategies are still urgently needed. Most trials of first-line treatment for mTNBC have excluded such high-risk patients, with the exception of IMpassion132, which evaluated chemotherapy with or without atezolizumab in patients with mTNBC who had relapsed within 12 months of curative therapy (*Ann Oncol* 2024; 35:630). Unfortunately, in an analysis of patients with PD-L1 expression at 1% or above in immune cells (of whom 68% had DFI <6 months), atezolizumab did not improve OS.

Second-Line Treatment and Beyond

Both Trop-2- and HER2-targeted ADCs have demonstrated benefit in the second-line setting and beyond. In the ASCENT trial, conducted among patients with TNBC that was relapsed or refractory to at least 2 prior chemotherapy regimens, investigators compared the Trop-2–directed ADC sacituzumab govitecan with single-agent chemotherapy and found that it improved both median PFS (4.8 vs. 1.7 months; HR, 0.43) and OS (11.8 vs. 6.9 months; HR, 0.51; *N Engl J Med* 2021; 384:1529).

Trastuzumab deruxtecan (T-DXd), a HER2-targeted ADC, is another option for the roughly 40% of patients with HER2-low mTNBC (defined by an immunohistochemical [IHC] score of 1+ or by an IHC score

FIGURE. The Evolving Treatment Algorithm for Metastatic Triple-Negative Breast Cancer (post–ASCO 2025)



[a] This combination is not FDA approved for first-line treatment as of this writing (September 2025).
[b] In cases of visceral crisis, taxane- or anthracycline-based combinations are reasonable if not used in the adjuvant or neoadjuvant setting or if disease-free interval ≥12 months. In cases of liver visceral crisis, carboplatin is one of the preferred options.
[c] Platinum preferred if PD-L1–negative, g*BRCA1/2*-mut, and only chemotherapy available. Olaparib may be considered for g*PALB2*-mut.
[d] TMB-H (high tumor mutational burden): pembrolizumab; MSI-H (high microsatellite instability): pembrolizumab, dostarlimab; NTRK fusion: larotrectinib, entrectinib, repotrectinib; RET fusion: selpercatinib
1L — first line; 2L — second line; 3L+ — third line and beyond; HER2 — human epidermal growth factor receptor 2; T-DXd — trastuzumab deruxtecan

of 2+ with negative results on in situ hybridization [ISH]) after prior chemotherapy in the advanced setting or DFI of 6 months or less. In DESTINY-Breast04, an exploratory analysis of 58 patients with hormone receptor–negative/HER2-low tumors showed numerically longer median PFS (8.5 vs. 2.9 months; HR, 0.46) and OS (18.2 vs. 8.3 months; HR, 0.48) with T-DXd than with chemotherapy (*N Engl J Med* 2022; 387:9). DESTINY-Breast15 is investigating T-DXd in HER2-low and HER2-0 breast cancers, including mTNBC, after one to two prior lines of therapy in the metastatic setting (NCT05950945).

For patients eligible for both Trop-2- and HER2-targeted ADCs, the optimal sequence of agents is actively being investigated. For example, TRADE-DXd (NCT06533826) is a phase 2 trial evaluating the role of T-DXd followed by Dato-DXd, which has shown activity in pretreated mTNBC (*Cancer Res* 2023; 83:P6–10–03), or vice versa in metastatic HER2-negative breast cancer. Similarly, ENCORE is a registry studying the sequence of sacituzumab govitecan followed by T-DXd and vice versa in metastatic HER2-negative breast cancer (NCT06774027). (For further discussion of ADC sequencing in metastatic breast cancer, see page 13.)

For patients who have received sacituzumab govitecan or T-DXd, single-agent chemotherapy (eribulin, capecitabine, vinorelbine) can be considered. Anti-androgen therapy and PI3K/AKT inhibitors are not supported outside of clinical trials.

For patients with chemotherapy-refractory, immunotherapy-naive mTNBC, options include:

- Pembrolizumab for tumors with high microsatellite instability/mismatch repair deficiency or a high mutational tumor burden
- Tropomyosin receptor kinase (TRK) inhibitors (entrectinib, larotrectinib) for TRK fusion–positive cancers that have progressed on other treatments (*Clin Cancer Res* 2025; 31:P4–08–29 and *Ann Oncol* 2022; 33:S204)

Conclusion and Future Perspectives

Emerging strategies include bispecific antibodies, immune cell engagers, chimeric antigen receptor (CAR) T-cells, and tumor infiltrating lymphocyte (TIL) transfer. Although prior studies with anti-angiogenic therapies showed PFS benefit without OS improvement (*Ann Oncol* 2013; 24:2773), anti–vascular endothelial growth factor (VEGF) agents are now being revisited in combination with PD-1/PD-L1 inhibitors to modulate the tumor microenvironment, as shown by initial results from the phase 2 FUTURE-C-Plus and ATRACTIB trials and the development of bispecific antibodies such as ivonescimab and BNT327/PM8002 (*J Clin Oncol* 2023; 41:1086, *Nat Med* 2025; 31:2746, *Ann Oncol* 2024; 35:S360, *J Clin Oncol* 2023; 41:2536, *Clin Can Res* 2025; 31:PS3).

In summary, the treatment landscape of mTNBC is rapidly evolving, with ADCs poised to replace chemotherapy in first-line regimens, although major gaps remain in managing early relapse and overcoming ADC resistance.

Topic Update

Management of Metastatic HER2-Positive Breast Cancer

A review of current practice and the evolving treatment landscape

Candace B. Mainor, MD, and Claudine Isaacs, MD, FRCPC, FASCO

During the past 5 years, the treatment paradigm for human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer (MBC) has rapidly evolved. Here, we will review current therapies for the first line and beyond, followed by a discussion of more recent data that are challenging the existing standard.

First-Line Treatment

For more than a decade, first-line treatment for HER2-positive MBC has consisted of induction therapy with six to eight cycles of docetaxel, trastuzumab, and pertuzumab (THP) followed by maintenance trastuzumab and pertuzumab (HP). Support for this regimen comes from the phase 3 CLEOPATRA study, which demonstrated that adding pertuzumab to TH improved median progression-free survival (PFS) by 6.1 months and, most importantly, overall survival (OS) by 15.7 months (*N Engl J Med* 2012; 366:109, *N Engl J Med* 2015; 372:724). At 8 years' follow-up, 16% of patients remained progression-free (*Lancet Oncol* 2020; 21:519).

In practice, endocrine therapy is typically added during maintenance HP for those with hormone receptor (HR)–positive disease, although in the CLEOPATRA trial, it was not allowed per protocol.

Recently, the PATINA trial, a randomized, open-label, phase 3 study, demonstrated that adding the CDK4/6 inhibitor palbociclib to maintenance HP and endocrine therapy improved median PFS by 15.2 months (44.3 months with palbociclib vs. 29.1 months without; 2024 San Antonio Breast Cancer Symposium, abstract GS2-12). As of this writing, the combination of palbociclib with HP and endocrine therapy has not yet been approved by the U.S. Food and Drug Administration (FDA).

Second-Line Treatment and Beyond

In recent years, trastuzumab deruxtecan (T-DXd), an antibody–drug conjugate (ADC) composed of a humanized anti-HER2 monoclonal antibody with a topoisomerase I inhibitor payload, has replaced trastuzumab emtansine (T-DM1) as the preferred second-line therapy for HER2-positive MBC. The impetus for this shift was the DESTINY-Breast03 trial, a randomized, open-label, phase 3 study that directly compared the two agents and showed an impressive 22-month improvement in PFS with T-DXd and a 9.9-month improvement in OS (*Lancet* 2023; 401:105, *Nat Med* 2024; 30:2208).

In the third-line HER2CLIMB placebo-controlled study, the addition of the tyrosine kinase inhibitor



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(TKI) tucatinib to capecitabine and trastuzumab resulted in a 5.5-month improvement in median OS and a 2.2-month median PFS benefit (*Ann Oncol* 2022; 33:321, *N Engl J Med* 2020; 382:597). This triplet also has significant activity in the central nervous system (CNS), reducing the risk of CNS progression or death by 68% in those with CNS disease at study entry (median CNS-PFS, 9.9 months with tucatinib vs. 4.2 months without; *J Clin Oncol* 2020; 38:2610). Thus, for patients with brain metastases, this combination is also considered in the second line. T-DXd also shows intracranial activity in patients with HER2-positive MBC (*Lancet* 2023; 401:105, *Nat Med* 2022; 28:1840), with the latest such data coming from DESTINY-Breast12 trial, a larger, prospective, phase 3b/4 study (*Nat Med* 2024; 30:3717). In later settings, T-DM1, anti-HER2 monoclonal antibodies, or other TKIs in combination with chemotherapy are given sequentially.

Emerging Data

More recent data have challenged which regimen should be used in the first line. Given the exceptional results seen with T-DXd in the second-line setting, this agent was evaluated as first-line therapy for HER2-positive MBC in the DESTINY-Breast09 trial. This study randomized patients to T-DXd, either alone or with pertuzumab, or to THP. Results from two arms of this study (T-DXd + P vs. THP) were presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting and demonstrated that T-DXd plus pertuzumab improved median PFS by 13.8 months (40.7 vs. 26.9 months; *J Clin Oncol* 2025; 43:LBA1008). Based on these results, the combination of T-DXd and pertuzumab now has FDA breakthrough-therapy designation for first-line treatment in HER2-positive MBC.

Of note, the median duration of cytotoxic therapy in DESTINY-Breast09 was much longer in the T-DXd and pertuzumab arm than in the THP arm (21.7 vs. ≈5 months) because T-DXd and pertuzumab were given continuously, whereas patients in the THP arm received only six to eight cycles of cytotoxic therapy before switching to maintenance HP alone (based on the CLEOPATRA study). Although the DESTINY-Breast09 trial showed no significant differences in overall rates of adverse events between the two arms, patients receiving THP typically have an excellent quality of life while on maintenance therapy. Interstitial lung disease, a known adverse effect of T-DXd, was reported in 12% of patients, with two having grade 5 events. This trial also raises the question of whether quality-of-life concerns could be mitigated with T-DXd induction followed by anti-HER2 maintenance therapy, an approach that will be evaluated in the upcoming DEMETHER trial (*Clin Cancer Res* 2025; 31:P5-03-11).

The impressive activity of T-DXd in both the first- and second-line settings underscores its role as a highly effective therapy. However, important questions remain about optimal sequencing — namely, should all patients receive it first-line, or might selected patients achieve comparable benefit with second-line use, thereby potentially preserving quality of life? Both clinical factors and biomarkers of response could help inform this decision. Clinical factors favoring the use of T-DXd and pertuzumab as first-line treatment could include the presence of brain metastases or significant visceral disease as well as a short disease-free interval from completion of adjuvant or neoadjuvant therapy. Putative biomarkers requiring further validation include presence of a *PIK3CA* mutation, which predicts for shorter response on THP (*J Clin Oncol* 2014; 32:3753; *Lancet Oncol* 2020; 21:519), evidence of lower HER2 dependence (*Clin Cancer Res* 2025; 31:PS4-06), and dynamic measures of treatment response, such as a drop in circulating tumor DNA (*J Clin Oncol* 2025; 43:1011) or response by PET scan (*J Clin Oncol* 2024; 42:1009). For example, minimal change in ctDNA within the first 6 weeks of therapy with THP or lower HER2 dependence may lead one to favor the use of T-DXd in the first-line setting.

Several phase 3, randomized, double-blind trials are also investigating whether adding therapies during the HP maintenance phase in the first-line setting can further improve outcomes. In addition to the PATINA trial discussed above, the HER2CLIMB-05 trial is evaluating the benefit of adding tucatinib, a drug known to have potent CNS activity, to HP (*J Clin Oncol* 2023; 41:TPS1115), and the INAVO122 study is evaluating the role of inavolisib, a p110α-selective PI3K inhibitor, during maintenance HP in patients with *PIK3CA*-mutated HER2-positive MBC (*J Clin Oncol* 2024; 42:TPS1124). Both trials' primary end points are PFS, with additional secondary end points including OS. Importantly, if T-DXd is given first line, it is unclear how to incorporate data from these maintenance trials and also what the optimal second-line therapy would be. No clinical data are

currently available to guide the latter decision; however, options may include tucatinib in combination either with capecitabine and trastuzumab (HER2CLIMB; *N Engl J Med* 2020; 382:597) or with T-DM1 (HER2CLIMB-02; *Cancer Res* 2024; 84:GS01-10).

Several other therapies, including novel ADCs and bispecific antibodies, are also being evaluated in later-line therapy.

Conclusion

These emerging data are poised to reshape the treatment landscape, but they also present challenges in determining how best to integrate new options and select the optimal therapy for individual patients while balancing efficacy and quality of life. These complexities underscore the critical need for trials that address sequencing questions and incorporate biomarkers to better individualize treatment algorithms.

Two Views

Should We Sequence Antibody–Drug Conjugates for the Treatment of Metastatic Breast Cancer?

Antibody–drug conjugates (ADCs) have transformed the treatment landscape of breast cancer, demonstrating unprecedented efficacy across disease subtypes. Four ADCs are currently approved to treat metastatic breast cancer (MBC) — two targeting human epidermal growth factor receptor 2 (HER2) and two targeting Trop-2, with three carrying similar chemotherapy backbones (topoisomerase 1 inhibitors, TOPO1i) and largely overlapping in indications. As ADC use rapidly expands, oncologists now face critical questions about how best to integrate these agents into practice. In particular, should ADCs be used sequentially after progression on a prior ADC, or should they be limited to a single line of therapy? Two experts summarize the available data and highlight key arguments in favor and against ADC sequencing.

The Argument Against Sequencing ADCs

Paolo Tarantino, MD, PhD

Innovations in breast cancer treatment often come in bursts. In the 1990s, the development of three aromatase inhibitors (AIs) enabled improved treatment of both early and metastatic breast cancer; between 2015 and 2018, three cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors reshaped treatment algorithms for hormone receptor (HR)–positive/HER2-negative breast cancer; and in the early 2020s, three agents targeting the phosphatidylinositol 3-kinase (PI3K)/AKT pathway enhanced precision breast oncology, leading to FDA approvals. Now, another burst of innovation has provided three new, highly effective ADCs to treat MBC: trastuzumab deruxtecan (T-DXd), sacituzumab govitecan (SG), and datopotamab deruxtecan (Dato-DXd). These agents, which join the previously approved trastuzumab emtansine (T-DM1), have led to meaningful improvements in outcomes for patients with MBC, including when used as first-line cytotoxic treatment.

With each burst of innovation has come optimism as well as sequencing dilemmas. In the case of AIs, postapproval clinical trials have demonstrated minimal benefit when these agents are used in sequence for treating MBC (*J Clin Oncol* 2000; 18:2234). Similarly, sequencing different CDK4/6 inhibitors upon disease progression has been shown to improve progression-free survival (PFS) by only a few weeks, which is far less than the PFS seen with these drugs in CDK4/6 inhibitor–naive patients (*J Clin Oncol* 2025; 43:1101). Understanding the effects of ADC sequencing is especially important because each of the new ADCs has been associated with non-negligible rates of fatal adverse events (pneumonitis for T-DXd and Dato-DXd; sepsis for SG) as well as potential financial toxicity due to their high cost (*Value Health* 2025; 28:S402).



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Joshua Drago, MD, MS, is an Assistant Attending Physician and breast medical oncologist at Memorial Sloan Kettering Cancer Center. **Disclosures:** Dr. Drago reports consulting roles with AstraZeneca, Genagon, AmMax Bio, NuProbe, Revelio Therapeutics, MEDACorp, and Baird Conferences; and external grant support from Merck and Mars Shot.

MOLECULAR INSIGHTS

The structure of ADCs can provide some hints about their sequencing potential (*CA Cancer J Clin* 2022; 72:165). The four approved ADCs carry either a microtubule inhibitor (T-DM1) or a TOPO1i payload (T-DXd, Dato-DXd, SG) and target either HER2 (T-DM1 and T-DXd) or Trop-2 (SG and Dato-DXd; Table).

Table. Currently Approved ADCs (as of September 2025) by Antibody Target and Chemotherapy Payload

Chemotherapy Payload	Antibody Target	
	HER2	Trop-2
Topoisomerase 1	Trastuzumab deruxtecan (T-DXd)	Sacituzumab govitecan (SG)
		Datopotamab deruxtecan (Dato-DXd)
Microtubule inhibitor	Trastuzumab emtansine (T-DM1)	

Elucidating which of these components — the chemotherapy payload or the antibody target — drives the generation of resistance could theoretically guide treatment after ADC progression. To date, translational efforts have produced mixed evidence, with some studies suggesting downregulation or alteration of the ADC target upon progression (*Clin Cancer Res* 2025; 31:1268) and others demonstrating the emergence of payload-related resistance mechanisms (e.g., *TOP1* mutations, upregulation of ATP-binding cassette transporters) upon progression after a TOPO1i ADC (*Clin Cancer Res* 2025; 31:1966 and 31:PS13-09).

CLINICAL EVIDENCE

Despite conflicting translational evidence, most clinical evidence suggests that ADC resistance is largely related to chemotherapy payload rather than antibody target. Key evidence for this comes from the phase 3 DESTINY-Breast02 and DESTINY-Breast03 trials, where prior treatment with one HER2-targeted ADC did not appear to diminish the effect of the second in patients with HER2-positive MBC (*Lancet Oncol* 2024; 25:614, *ESMO Open* 2025; 10:322P). In DESTINY-Breast02, which compared T-DXd to capecitabine plus HER2-blockade among T-DM1–pretreated patients, T-DXd yielded high efficacy (response rate, 70%; PFS, 17.8 months) and improved survival. Similarly, in the DESTINY-Breast03 trial, the median duration of treatment for patients who received T-DM1 after T-DXd (7.6 months) was consistent with that seen among T-DXd–naive patients in prior studies, confirming negligible cross-resistance when two ADCs that target the same antigen are used in sequence.

Conversely, multiple studies testing the value of sequencing TOPO1i ADCs have shown relevant payload cross-resistance, even when patients are switching from a HER2-targeted ADC to a Trop-2–targeted one. The phase 1 TROPION-PanTumor01 trial evaluating Dato-DXd for MBC revealed impaired outcomes in TOPO1i ADC-pretreated patients (*J Clin Oncol* 2024; 42:2281). Ten distinct retrospective ADC-sequencing studies consistently found that the median real-world PFS achieved by a second TOPO1i ADC is shorter than that achieved with the first and is usually within the 2- to 3-month range (*Biochim Biophys Acta Rev Cancer* 2025; 1880:189369). Moreover, when our group analyzed post–T-DXd outcomes in a U.S.-based, retrospective cohort of nearly 800 patients with MBC, we found that using SG (a TOPO1i ADC) immediately after T-DXd yielded a real-world PFS of 3 months or less across MBC subtypes, whereas switching to a treatment with a different mechanism of action led to reasonable effectiveness (*J Natl Cancer Inst* 2025; djaf220).

Of note, exceptions exist, where the second TOPO1i ADC actually performs better than the first. For instance, in three separate retrospective studies, about 25% of patients experienced longer PFS with the second ADC (*Biochim Biophys Acta Rev Cancer* 2025; 1880:189369). In our retrospective study of electronic medical records, patients who discontinued T-DXd in the absence of progression achieved up to 6 months PFS with subsequent SG (*J Natl Cancer Inst* 2025; djaf220), which suggests that patients discontinuing a TOPO1i ADC for toxicity rather than tumor progression might be particularly

appropriate candidates for immediate ADC sequencing. However, additional efforts in biomarker discovery are warranted to more adequately identify which patients will benefit most from ADC sequencing.

PRACTICAL CONSIDERATIONS

Overall, the immediate sequencing of ADCs with similar payload classes appears to be associated with limited clinical value for most patients, whereas switching payload classes (e.g., from T-DXd to T-DM1) enables retained efficacy, even for ADCs sharing a targeted antigen. Given the available data, in the absence of prospective trials, routine immediate sequencing of TOPO1i ADCs cannot be justified; instead, switching the mechanism of action of treatments should be prioritized.

Ongoing phase 2 clinical trials prospectively testing ADC sequencing — for example, SATEEN (NCT06100874), TRADE-DXd (NCT06533826), and SERIES (NCT06263543) — will hopefully fill the gap of prospective evidence and help identify biomarkers for effective ADC sequencing. Until high-quality evidence emerges, sequential use of ADCs should be considered on a case-by-case scenario, such as for highly pretreated patients that require additional therapeutic options. This choice will need to be weighed against the toxicities of ADC treatment (which often require specific prophylaxis), the financial burden of novel ADCs, and each patient's unique clinical scenario and preferences.

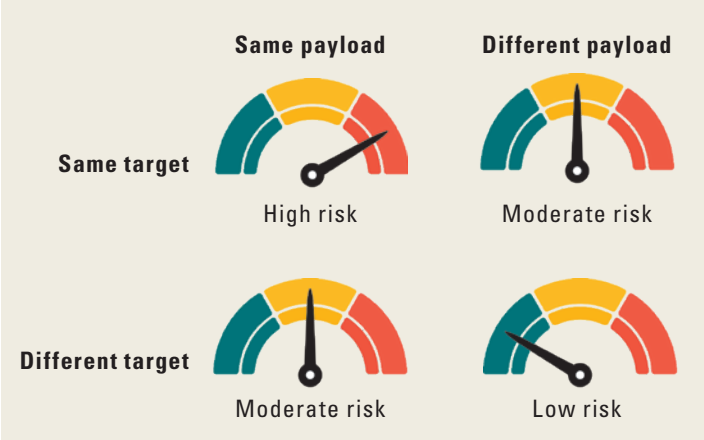
The Argument in Favor of Sequencing ADCs

Joshua Drago, MD, MS

ADCs are entering the clinic at a rapid pace, and more are currently approved for MBC than for any other solid tumor. Nearly every patient with MBC will become eligible for treatment with an ADC at some point in their disease course, and most will be eligible for two or three different ADC options based on current approvals. These developments raise pressing practical questions: Can we use ADCs sequentially in MBC? Does a second ADC have benefit after clinical resistance develops to the first? Here, I will argue that sequential ADC therapy can be a viable and advisable treatment strategy, although perhaps not with every ADC and not for every patient. The field is nascent, and better biomarkers will hopefully soon emerge to help guide individual treatment decisions, but for now, we must rely on our experience and best judgment based on available data.

As a general framework, options in ADC sequencing can be broken down into four simple categories, depending on whether the two respective ADCs share a target, a payload, both, or neither (Figure). Based on our current understanding of ADC mechanisms, it stands to reason that sequencing two agents that share the same target and payload confers the greatest risk for cross-resistance, whereas sequencing agents that share neither confers the lowest risk. Modifying only the target or only the payload carries an intermediate risk of cross-resistance, depending on patient- and drug-specific factors. Of note, this framework needs further empiric validation before being applied broadly and likely oversimplifies some subtleties about ADC design and clinical activity that may be important, including

FIGURE. Risk of Cross-Resistance with ADC Sequencing According to Whether the ADCs Share a Target, a Payload, or Both



the specifics of the monoclonal antibody target epitope and binding characteristics, the linker type, the drug-to-antibody ratio, and the pharmacologic properties of the payload beyond its mechanism (e.g., its potency and hydrophobicity). Despite these shortcomings, this framework can facilitate both clinical decision making and research efforts until prospective data are available to better guide decision making. Here, I will focus primarily on sequencing agents that differ in either target or payload (i.e., the moderate-risk combinations), because they apply most directly to the decisions we make every day in clinic based on the available ADCs.

PAYLOAD ROTATION

The strategy of payload rotation encompasses perhaps the best proven example we have of the potential for benefit from sequential ADC therapy: the clinical activity of T-DXd after receipt of T-DM1 in metastatic HER2-positive breast cancer. T-DM1 and T-DXd are built on the same antibody backbone of trastuzumab but differ significantly in their linker and payload mechanisms. In the DESTINY-Breast01 Trial, 184 patients with metastatic HER2-positive breast cancer who received prior T-DM1 therapy were treated with T-DXd (*N Engl J Med* 2020; 382:610). The overall response rate was 61%, and median PFS was 16.4 months, substantially outpacing the clinical benefit of T-DM1 even when given in earlier lines of therapy. These results provide a clear example of how one ADC can work after another, even if they share the same target.

Indeed, payload-mediated resistance has been documented for ADCs and likely plays a role in many cases (*Cancer Discov* 2021; 11:2436, *Clin Cancer Res* 2025; 31:1966). Broadly speaking, we have observed for decades that metastatic solid tumors ultimately develop resistance to single-agent chemotherapeutics in nearly all cases, and the same is likely true for ADC payloads, strengthening the argument for payload rotation. Nevertheless, sequentially targeting the same tumor antigen carries some risk. For example, if target expression is downregulated or lost, subsequent ADCs may have less chance of benefit. So why does T-DXd work so well after T-DM1? Evolutionary pressure may protect against uniform HER2-loss in the case of HER2-amplified cancers (*Cancer Drug Resist* 2022; 5:971, *Cancer Res* 2025; 85:LB280), but even if target downregulation occurs, T-DXd has activity at low levels of HER2 expression (*N Engl J Med* 2022; 387:9). This illustrative example can help shed light on conditions for favorable outcomes with a payload rotation strategy. Importantly, the converse with T-DXd and T-DM1 is not necessarily true. Although there are no prospective studies on this topic, existing reports show mixed results about the activity of T-DM1 after T-DXd (*ESMO Open* 2025, *Clin Cancer Res* 2025; 31:P5-03-09, *J Natl Cancer Inst* 2025; djaf220). Thus, ADC sequencing needs to be considered on a case-by-case basis.

TARGET ROTATION

Target rotation is another strategy that can be used when sequencing ADCs. Several emerging studies suggest that target loss occurs frequently in patients treated with ADCs, especially when the target is not an oncogenic driver (*Clin Cancer Res* 2025; 31:1268 and 85:LB280, *Nat Med* 2023; 29:2110). If insufficient target is present on the tumor cell, ADC engagement and thus activity could be compromised. In these cases, rotation of the ADC target may circumvent this mechanism of resistance. Several retrospective real-world studies have evaluated clinical outcomes for this strategy, with similar findings. Patients with MBC who received both sacituzumab govitecan (targeting Trop-2) and T-DXd (targeting HER2) during their clinical course tend to have diminishing benefit with the second ADC, regardless of which one that is (*J Natl Cancer Inst* 2025; djaf220, *JCO Precision Oncology* 2025; 9:PO-24-00898, *Brit J Can* 2024; 131:702). However, these are limited studies with heavily pretreated patients, where subsequent treatments tend to have less benefit in general. Notably, there is a subset of patients who clearly benefit from this strategy, experiencing far greater activity with the second ADC than with the first (*JCO Precision Oncology* 2025; 9:PO-24-00898). The central clinical challenge is how to best identify these patients, so we can rationally offer treatments that have the best chance of success and

spare our patients from unnecessary toxicity. Ongoing studies, such as TRADE-DXd (NCT06533826), which incorporate translational science into tightly controlled sequential ADC treatment, are poised to shed significant light on these questions.

MAXIMIZING BENEFIT FOR OUR PATIENTS

At this time, the choice of whether and how to sequence ADCs for our patients is complex, involving patient-specific factors, and informed by the best available data. Although ADC cross-resistance undoubtedly occurs, it is not by any means universal. With the arrival of new ADCs will come greater diversity in target antigen and payload mechanisms, and we will assuredly be able to find highly active sequencing approaches. Even with our current clinical tools, for the right patients and with the right medications, sequential ADC therapy can have dramatic clinical benefits. As clinicians and investigators, we need to work to better understand ADC resistance so that we can develop clear strategies for therapeutic sequencing and improve outcomes for our patients.

NEJM Research Summary

Elinzanetant for Vasomotor Symptoms from Endocrine Therapy

Cardoso F et al. 10.1056/NEJMoa2415566

WHY WAS THE TRIAL DONE?

For women with hormone receptor (HR)–positive breast cancer, guidelines recommend endocrine therapy for at least 5 years, which has been shown to substantially reduce disease recurrence and mortality. Vasomotor symptoms (also known as hot flashes) are common adverse reactions to endocrine therapy that can negatively affect quality of life and lead to nonadherence. In previous trials, elinzanetant — a neurokinin-targeted therapy — was shown to be effective in treating vasomotor symptoms associated with menopause.

HOW WAS THE TRIAL CONDUCTED?

Women who were receiving endocrine therapy to treat or prevent HR-positive breast cancer and had moderate-to-severe vasomotor symptoms were randomly assigned to receive either 120 mg of elinzanetant once daily for 52 weeks or placebo once daily for 12 weeks followed by 120 mg of elinzanetant once daily for 40 weeks. The primary end points were the change in the mean daily frequency of moderate-to-severe vasomotor symptoms at week 4 and week 12.

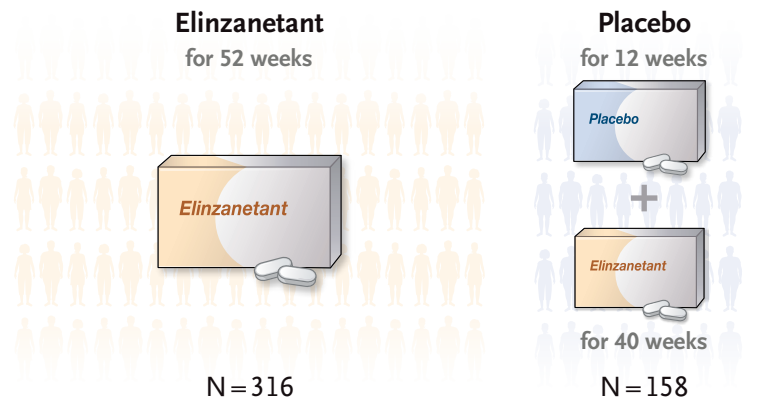
TRIAL DESIGN

- Phase 3
- Randomized
- Double-blind
- Placebo-controlled
- Location: 90 sites in Europe, Canada, Israel, and Kazakhstan

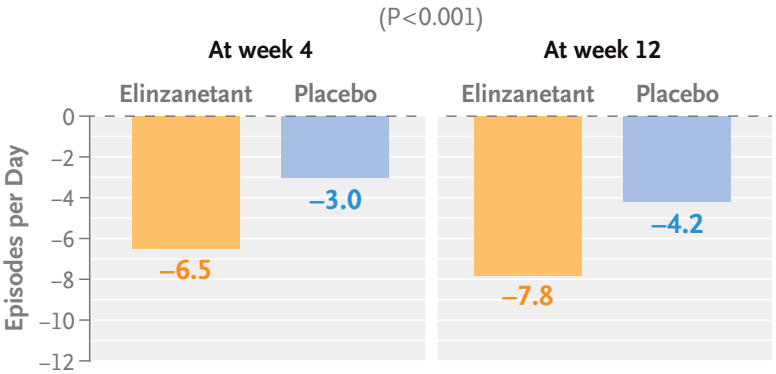
Participants

- 474 women
- Mean age, 51 years





Mean Change in Frequency of Vasomotor Symptoms

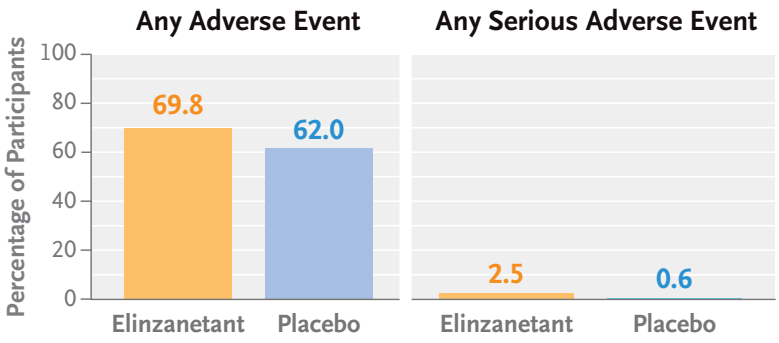


RESULTS

At weeks 4 and 12, treatment with elinzanetant resulted in greater decreases in the daily frequency of vasomotor symptoms than placebo. The frequency of adverse events was similar in the two groups, and most events were mild or moderate in severity.

LIMITATIONS AND REMAINING QUESTIONS

- Most of the participants were White.
- Because only one participant received elizanetant for prevention of breast cancer, conclusions regarding its efficacy in this population cannot be drawn.
- Survival and recurrence of breast cancer were not prespecified outcomes in this trial.



CONCLUSIONS

Among women who were receiving endocrine therapy for HR-positive breast cancer, elinzanetant significantly reduced the frequency of moderate-to-severe vasomotor symptoms.

Interview

Inavolisib for *PIK3CA*-Mutated Advanced Breast Cancer

As part of NEJM Group's coverage of the American Society of Clinical Oncology's annual meeting, Dr. Inas Abuali interviewed Dr. Komal Jhaveri, lead investigator of the INAVO120 trial, which assessed the efficacy of the PI3Kα inhibitor inavolisib in patients with *PIK3CA*-mutated, advanced breast cancer. The results were presented at ASCO and published in the *New England Journal of Medicine* (*N Engl J Med* 2025; 393:151).

Dr. Jhaveri is a breast medical oncologist at Memorial Sloan Kettering Cancer Center. Dr. Abuali is a hematologist and oncologist at Massachusetts General Cancer Center.

Their conversation has been edited for length and clarity.



Dr. Inas Abuali (left) interviews Dr. Komal Jhaveri

Abuali: Thank you so much for taking the time to chat with me today. Can you tell us what you and your colleagues hoped to learn from this study?

Jhaveri: I think, just born out of preclinical data when we had seen synergistic activity when you combine PI3K inhibitors with CDK4/6 inhibitors and endocrine therapy, we had learned in a phase 1 study that preceded this registrational phase 3 trial that such a triplet regimen could be safe and certainly efficacious for hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer, and *PIK3CA* tumors. Shortly after that safety and efficacy was determined, this registrational phase 3 study was designed in order to address the question, can a triplet really provide more benefit than our control arm, which is a CDK4/6 inhibitor with fulvestrant, for endocrine-resistant *PIK3CA*-mutated tumors? So what we had tried to do is we had patients who would recur on or within 12 months of their endocrine therapy whose tumors harbored *PIK3CA* mutations, and with no other treatment for advanced breast cancer. We randomized about 325 patients to the triplet of fulvestrant with palbociclib and inavolisib at 9 mg orally daily, which is the dose that was determined to be the recommended phase 3 dose, and the control arm — what would've been something we would've done otherwise, which is fulvestrant with the CDK4/6 inhibitor, in this case, palbociclib. So when this study was designed, palbociclib was the most commonly utilized CDK4/6 inhibitor. Our practice patterns have changed a little bit since. However, this is reflective of what we were doing then. And so that's the control arm.

The idea was, can, in *PIK3CA*-mutated tumors, this triplet regimen be safe and more efficacious? Our primary end point was investigator-assessed PFS (progression-free survival). We had met the primary end point and presented and published those results late last year. That already led to the approval of this triplet regimen in the first-line metastatic setting for *PIK3CA*-mutated, hormone receptor–positive, HER2-negative endocrine-resistant breast cancers.

But now, what is more exciting is that our secondary end point of overall survival, really the holy grail of end points if you will, gold standard that we would love to achieve for all our patients, is also statistically significant and clinically meaningful. And I would want to highlight, for the

very first time reported with any PI3K inhibitor in breast cancer. So, very exciting times.

Abuali: This is amazing in the ever-changing landscape of breast cancer management. How would you describe this in layman's terms to our patients, the significance of those results?

Jhaveri: I think for our patients, I always try and say that we try to learn within the tumor if there is a particular alteration, a particular tumor biology, that we can understand or identify, which we know could drive tumor growth and make the cancer grow in the metastatic setting or spread in the metastatic setting. If we were to identify that alteration and are able to then target that specifically, perhaps we can shut down that tumor growth that is utilizing that pathway. So that's a good example for precision medicine in general, but in estrogen receptor (ER)–positive breast cancer particularly so because approximately 40% of ER-positive breast cancers can harbor a mutation in a gene called *PIK3CA*. And so inavolisib is a targeted therapy. It's a PI3K inhibitor that goes specifically and targets these mutations. This is why we're able to see benefits when we're trying to utilize this drug.

More importantly in this setting, we know that our current standard of care otherwise would've been a CDK4/6 inhibitor and endocrine therapy, and we use that regardless of any biomarker or regardless of any alterations as long as the patient's tumors are ER-positive. But what we've been able to achieve from our prior experiments in the lab and now in clinic is that when you combine a PIK3CA inhibitor with a CDK4/6 inhibitor and endocrine therapy, that that is much better in terms of making patients live longer, and making their cancers not grow for a particular period of time, what we call progression-free survival.

Abuali: Can you briefly comment on the side effects observed from the trial and if there was anything unexpected?

Jhaveri: So certainly, more drugs means more toxicity. We've seen that when you use two drugs compared with one, we've seen more toxicity. Certainly, with three drugs, we also see more toxicity. And the common toxicities that we are seeing with PIK3CA inhibitors in general include hyperglycemia, diarrhea, and rash. In this particular case, given that we're combining palbociclib and inavolisib, we're also seeing more stomatitis in our patients. This is what we need to really keep an eye on. Certainly, fatigue is something that we can also see some patients report, but the most common ones are hyperglycemia, diarrhea, rash, and stomatitis. So we did see more of that with this triplet regimen as well.

However, reassuringly, we also learned that despite this, the discontinuation rates were very low, at 6.8%, and it was 6% related to the PI3K inhibitor drug inavolisib. So that was very reassuring that despite using these three drugs and certainly seeing the expected toxicities that we see with this class of drugs, the discontinuation rates were low, so patients were able to stay on this therapy for a long time. We've also presented long-term safety data with this triplet combination, which is nice to see.

Having said that, one has to be very vigilant about how to manage hyperglycemia better because that's an on-target side effect that we see due to the wild-type PI3K getting inhibited. And so certainly, we need to keep a very close eye on the sugar levels. We need to monitor the hemoglobin A1c before patients start it. Of note, in the INAVO120 study, we had stringent criteria for eligibility in that patients were only eligible if their baseline hemoglobin A1c was less than 6% and their fasting blood glucose was less than 126 milligrams per deciliter. So certainly something we want to do in practice. We want to identify patients who could be potentially at higher risk. Prediabetics, for instance, can have a higher incidence of hyperglycemia. We really want to intervene early, offer them antihyperglycemic medications, and monitor them very closely, use the help of our endocrinologists if we had to.

Luckily, unlike what we've seen with approved agents like capivasertib and alpelisib, we did not see grade 3 rash with inavolisib. We do see low-grade rash, which was easily manageable. Similarly, grade 3 diarrhea rates were very low, and

diarrhea could otherwise be managed with antidiarrheals like loperamide.

Stomatitis, we saw 27% in the control arm with palbociclib and fulvestrant, 51% all-grade with the triplet regimen and very low grade 3 stomatitis rates. And patients were not necessarily initiating primary prophylaxis with a dexamethasone mouthwash. But now, because we know that that works, because we know we use that for CDK4/6 inhibitors, drugs like everolimus, this would be something that we are now using in clinic when we start patients on inavolisib. That will help manage stomatitis better as well. So we really have to be vigilant about management.

Outside of that, there were no surprises. I think the surprise was that this was well tolerated. And it was a good surprise to have that the discontinuation rates were low, the dose intensity for taking inavolisib was really maintained, and the results are very promising, both for primary and secondary end points.

Abuali: Thank you for that summary. At this time, what questions remain, and where is your research taking you next?

Jhaveri: Certainly, the triplet strategy is an unprecedented way of studying a triplet in the first-line setting. Now we're changing our practice patterns and making sure we're aware whether a tumor harbors *PIK3CA* mutation or not even earlier than what we used to do in the hormone receptor–positive landscape. But I think some questions that still remain are what happens when there is progression after this therapy? We've seen overall survival benefit, we're going to see what kind of treatment regimens patients do receive, but one question that comes to mind is what if we were to utilize such a triplet strategy in the second-line metastatic setting? Do patients certainly benefit in the first line? It seems compelling from the INAVO120 that given that the longer follow-up has, if anything, improved the primary end point, even more numerically, the hazard ratio is still maintained, we're seeing an overall survival benefit that we want to use our best therapies upfront and not necessarily hold onto them for the second-line setting, but that's certainly a question.

And more importantly, this study focused only on endocrine-resistant tumors. So these are tumors recurring on or within 12 months of endocrine therapy. But now we're also trying to see can we expand the patient population that can benefit from such a regimen? And in fact, INAVO123 is a clinical trial in the first-line metastatic setting that will study the same question with letrozole in an endocrine-sensitive, high-risk patient population. So it's really important to see if we can expand the benefits of this approach beyond endocrine-resistant tumors, to even endocrine-sensitive tumors in the first-line metastatic setting.

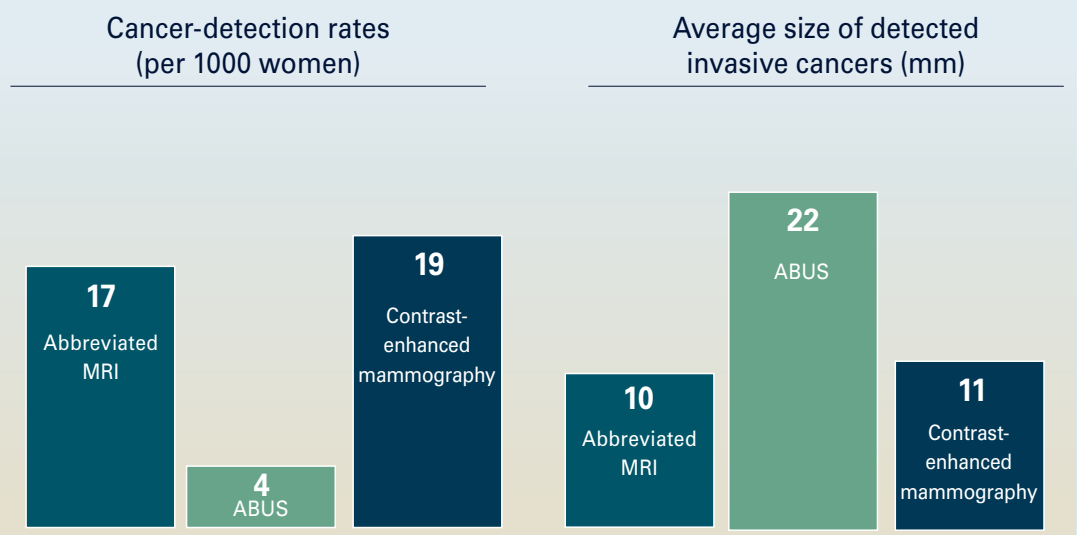
Abuali: Thank you so much. This was such a wonderful summary, and it's been wonderful chatting with you. I hope you enjoy the conference, and I wish you all the best with your upcoming research.

Jhaveri: Thank you very much, Dr. Abuali. It's a pleasure.

Visual Summary

Comparing Supplemental Imaging Modalities in Women with Dense Breasts

In a U.K.-based trial, researchers evaluated cancer detection in 6300 middle-aged women (age range, 50–70), who had heterogeneously or extremely dense breasts and negative baseline mammography findings. Participants were randomized to receive one of the following: abbreviated contrast-enhanced magnetic resonance imaging (MRI); automated whole-breast ultrasound (ABUS), which uses an automated, rather than hand-held, transducer; or iodinated contrast-enhanced mammography.



Comment

Abbreviated MRI and contrast-enhanced mammography seemingly can detect cancers, including small and early-stage cancers, that would be missed by mammography alone or mammography plus ABUS; however, they also led to more false-positive results and adverse events. Although these findings are intriguing, the survival benefit for cancer detected in this way has not been established; moreover, these modalities are not available widely and generally are not covered by insurance for screening.

Sarah E. Post, MD, reviewing Gilbert FJ et al. *Lancet* 2025 May 31

Dr. Post is a primary care physician and medical educator at Atrius Health in Boston, Massachusetts. She reports no disclosures.