Novel Therapies and Multidisciplinary Strategies in Metastatic Triple-Positive Breast Cancer

PRESENTED BY DANIELLE ROMAN, PharmD, BCOP, and KAITLYN REEDER, PA-C

From Allegheny Health Network, Pittsburgh, Pennsylvania

Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

The management of metastatic hormone receptor–positive (HR+) and human epidermal growth factor receptor 2–positive (HER2+) breast cancer continues to evolve with the development of novel targeted therapies. At JADPRO Live, presenters discussed therapies for this subtype of breast cancer, adverse events, management strategies, as well as biomarkers to consider when making treatment decisions.

Metastatic triple-positive breast cancer is a biologically complex subtype. During an educational session presented on October 24, 2025, at JADPRO Live 2025, **Danielle Roman, PharmD, BCOP,** Manager of Clinical Pharmacy Services and Oncology Clinical Pharmacy Specialist at the Allegheny Health Network Cancer Institute in Pennsylvania, and **Kaitlyn Reeder, PA-C,** a hematology-oncology PA also with Allegheny Health Network, reviewed data from pivotal clinical trials as well as recent guideline updates. They also discussed newly approved therapies and their mechanisms of action, and emphasized best practices for early identification and management of treatment-related toxicities for advanced practitioners.

EPIDEMIOLOGY AND DISEASE BIOLOGY

HR+, HER2+ breast cancer accounts for approximately 9% of all breast cancer diagnoses. While overall 5-year survival is favorable in localized and regional disease, outcomes decline drastically in the metastatic setting, to just under 50% of patients alive at 5 years.

Dr. Roman noted that hormone receptor–positive tumors tend to be "overall slower growing, more indolent disease" that is responsive to endocrine therapies, whereas HER2 positivity is associated with "worse prognosis and more aggressive disease" that responds to HER2-targeted agents. "Therefore, we have a diverse biological expression with this subtype," said Dr. Roman.

There has also been crosstalk observed between hormone receptor

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and HER2 signaling pathways, which has led to dual blockade being proposed to decrease resistance mechanisms.

HER2 testing is recommended at initial diagnosis and again at the first occurrence of metastatic disease. HER2 positivity is defined by immunohistochemistry (IHC) 3+ staining or IHC 2+ with confirmatory in situ hybridization (ISH) demonstrating gene amplification.

THERAPIES

"Typically, we're looking at multimodal therapy," said Dr. Roman. This includes endocrine therapy, HER2-targeted agents, chemotherapy, and, in select cases, CDK4/6 inhibitors (Figure 1). Although CDK4/6 inhibitors have historically been used in HER2-negative disease, emerging data support their selective use in HER2-positive breast cancer. Chemotherapy continues to play an important role, particularly in patients with high disease burden or aggressive clinical features. Germline *BRCA1/2* mutations are uncommon in this population, but when present, PARP inhibitors may be considered.

HER2-directed treatments fall into three main categories: monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody-drug conjugates (ADCs). Monoclonal antibodies such as trastuzumab (Herceptin) and pertuzumab (Perjeta) bind distinct extracellular domains of the HER2 receptor and exert complementary and synergistic effects when used together. Margetuximab (Margenza), a trastuzumab-like antibody, is approved for use in later lines of metastatic disease.

Tyrosine kinase inhibitors are oral agents that inhibit intracellular HER2 signaling; among these, tucatinib (Tukysa) is the most HER2-selective, whereas lapatinib (Tykerb) and neratinib (Nerlynx) also inhibit EGFR, contributing to higher rates of diarrhea. Antibody-drug conjugates, including trastuzumab emtansine (T-DM1; Kadcyla) and trastuzumab deruxtecan (T-DXd; Enhertu), combine HER2 targeting with intracellular delivery of cytotoxic agents. While both share the same HER2-directed antibody, their payloads differ, with T-DXd inhibiting topoisomerase I and demonstrating a bystander effect that may enhance antitumor activity.

CDK4/6 inhibitors act by blocking the interaction between CDK4/6 and cyclin D1, thereby arresting the cell cycle in the G1 phase without directly inducing apoptosis. Abemaciclib (Verzenio) is administered continuously with twice-daily dosing and is associated with less myelosuppression, whereas palbociclib (Ibrance) has greater myelosuppressive effects and is given once daily on a three-weeks-on, one-week-off schedule.

KEY CLINICAL TRIALS

For more than a decade, the first-line standard for metastatic HER2-positive breast cancer has been chemotherapy with a taxane (docetaxel or paclitaxel) combined with dual HER2 blockade using trastuzumab and pertuzumab (THP), based on results from the CLEOPATRA trial (Swain et al., 2020). In this approach, patients typically receive 6 to 8 cycles of taxane in combination with HER2-targeted therapy, after which the taxane is discontinued in responders or those with stable disease, and maintenance trastuzumab and pertuzumab are continued.

"But we have some newer data here that's challenging this first line approach, and that's the DESTINY-Breast09 trial," said Dr. Roman. The DESTINY-Breast09 trial evaluated T-DXd, alone or in combination with pertuzumab, in the first-line metastatic setting and demonstrated an improvement in progression-free survival compared with standard THP therapy (Tolaney et al., 2025). Although overall survival data remain immature, these findings are expected to influence future practice.

In the second-line setting, trastuzumab deruxtecan (T-DXd) is now the preferred ADC based on efficacy data and may also be considered earlier in select patients with rapid progression following neoadjuvant or adjuvant therapy. The DESTINY-Breast03 trial demonstrated significant improvements in both progression-free and overall survival with T-DXd compared with trastuzumab emtansine (T-DM1; Hurvitz et al., 2024; Cortés et al., 2024).

In the maintenance setting, the PATINA trial evaluated the addition of the CDK4/6 inhibitor palbociclib to HER2-targeted therapy and endocrine therapy following induction THP chemotherapy (Metzger et al., 2024). This approach resulted in improved median progression-free survival.

In later lines of therapy, treatment selection is guided by prior exposure and disease characteristics, including central nervous system involvement. The triplet regimen of tucatinib, trastuzumab, and capecitabine is an option, particularly

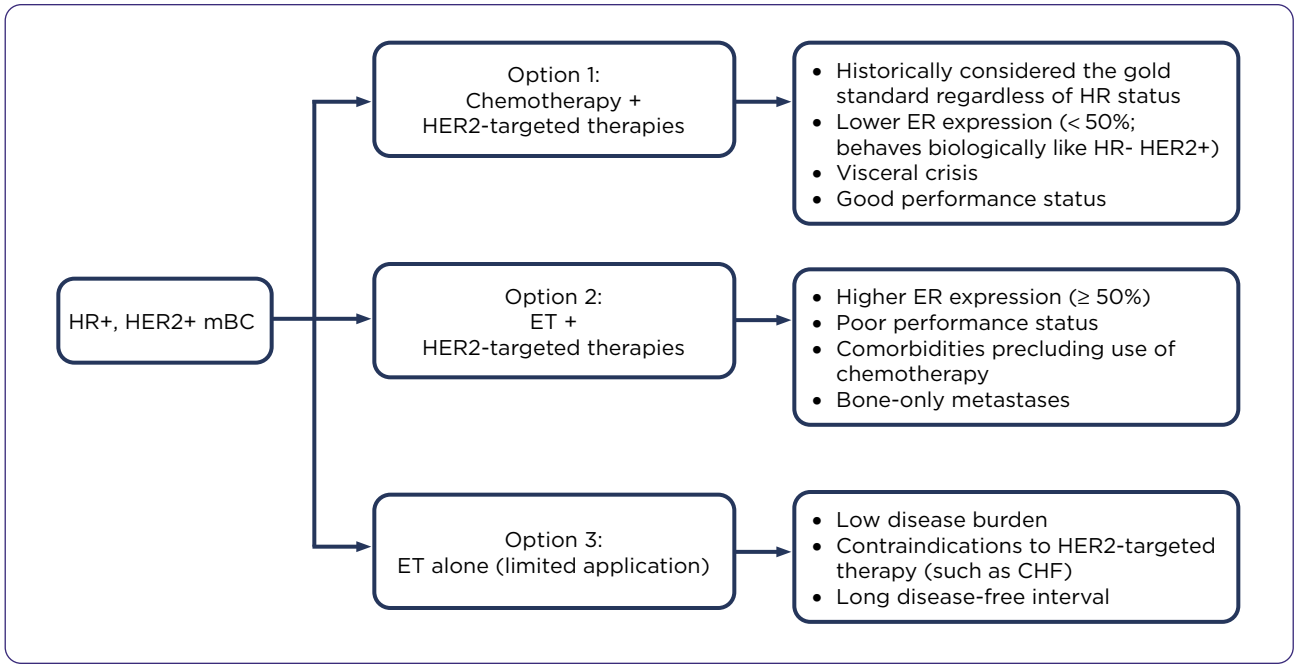

Figure 1. Treatment options in triple-positive breast cancer. CHF = congestive heart failure. Information from Al Sukhun et al. (2024); NCCN (2024).

for patients with brain metastases, given its CNS activity. Trastuzumab emtansine is an alternative in the third-line setting.

ADVERSE EVENTS

Management of metastatic HER2-positive breast cancer requires early recognition and management of toxicities. Commonly affected areas include the GI tract, cardiovascular system, liver, skin, and lungs, with interstitial lung disease (ILD) being a less frequent but notable adverse event.

Diarrhea

Diarrhea is one of the most frequently encountered toxicities with HER2-targeted agents and is mechanistically distinct from chemotherapy-induced diarrhea. Incidence varies by agent, with the highest risk observed with neratinib, followed by pertuzumab and trastuzumab. The risk is further increased when HER2-targeted therapies are combined with chemotherapy.

"We tend to see diarrhea early on in the course of treatments. Symptoms can taper off as we continue," commented Ms. Reeder.

Pertuzumab-associated diarrhea is common but usually low grade. Management focuses on supportive care rather than dose reduction, as pertuzumab dosing is not modified for diarrhea; treatment is either continued or discontinued. In contrast, neratinib is associated with a high incidence of severe diarrhea, making antidiarrheal prophylaxis essential. Strategies include scheduled loperamide during early treatment or gradual dose escalation to improve tolerability. Across agents, it is recommended to discontinue laxatives or stool softeners, recommend aggressive hydration, suggest dietary modification, and start antidiarrheal therapy early.

Cardiotoxicity

Cardiotoxicity is another consideration with HER2-targeted therapies. It commonly presents as a decrease in left ventricular ejection fraction, with or without clinical symptoms of heart failure.

"What's important to remember is that cardiotoxicity with HER2 targeted therapy is reversible. So when you stop the drug, it tends to improve," said Ms. Reeder.

Trastuzumab carries the greatest risk, and the addition of pertuzumab does not appear to significantly increase cardiotoxicity rates. Baseline and serial cardiac monitoring with echocardiography is recommended, with newer techniques such as

global longitudinal strain offering earlier detection. Therapy should be held if ejection fraction declines, with repeat imaging performed after several weeks to guide resumption.

Pneumonitis and Interstitial Lung Disease

Interstitial lung disease, including pneumonitis, pulmonary fibrosis, and organizing pneumonia, is uncommon but occurs at higher rates with trastuzumab deruxtecan. Symptoms are nonspecific and may include cough, dyspnea, hypoxia, or worsening respiratory status, which can overlap with other conditions common in patients with metastatic disease, such as pulmonary metastases, malignant pleural effusions, or pulmonary embolism.

"There is nothing specific that will point you to ILD, thus the importance of remembering that this is a possibility," said Ms. Reeder.

CT imaging is recommended when ILD is suspected. Management is grade dependent, with treatment interruption and corticosteroids considered for grade 1 events and permanent discontinuation required for grade 2 or higher toxicity.

CDK4/6 Inhibitor Toxicities

Palbociclib is associated with a high incidence of neutropenia, although febrile neutropenia is rare. Management includes routine laboratory monitoring, treatment holds, and dose adjustments rather than prophylactic growth factor use. Abemaciclib is associated with lower rates of neutropenia but higher rates of diarrhea and hepatotoxicity. A notable laboratory finding with abemaciclib is an increase in serum creatinine due to inhibition of renal tubular transporter rather than actual renal dysfunction, a distinction to be aware of to prevent unnecessary treatment interruption. ●

Disclosure

Dr. Roman has served as a consultant for Astellas, Daiichi Sankyo, and Genentech. Ms. Reeder has no relevant financial relationships to disclose.

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