HER2-Expressing Breast Cancer: Advancements in Targeted Therapies

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> Managing HER2-expressing breast cancer continues to present challenges, particularly in advanced and resistant settings. Recent presentations at ASCO 2026 highlight the evolving landscape of targeted therapies, offering new avenues for improving patient prognosis and treatment efficacy.1

KEY TAKEAWAYS

- The Pivot: Novel antibody-drug conjugates (ADCs) and tyrosine kinase inhibitors (TKIs) are expanding treatment options beyond standard trastuzumab and pertuzumab.
- The Data: Specific trials demonstrated hazard ratios for progression-free survival (PFS) as low as HR 0.65 (95% CI 0.52-0.81, p in certain patient populations.
- The Action: Clinicians should consider integrating these newer agents into treatment algorithms for HER2-expressing breast cancer, especially in cases of progression on established regimens.

HER2-expressing breast cancer, characterized by overexpression of the human epidermal growth factor receptor 2, accounts for approximately 15-20% of all breast cancers.1 While the introduction of trastuzumab significantly improved outcomes, resistance mechanisms and disease progression remain critical clinical issues.2 Current standard of care often involves dual HER2 blockade with trastuzumab and pertuzumab in the early and metastatic settings, alongside chemotherapy.3 However, a substantial proportion of patients eventually experience disease progression, necessitating further therapeutic innovation.4

New Treatment Approaches Across Disease Settings

Several studies presented at ASCO 2026 focused on novel therapeutic strategies for HER2-expressing breast cancer, spanning early-stage, metastatic, and brain metastasis settings. One notable area of advancement involves antibody-drug conjugates (ADCs), which deliver cytotoxic agents directly to HER2-expressing cells.5 A phase 3 trial investigating a novel HER2-directed ADC in patients with unresectable or metastatic HER2-low breast cancer previously treated with at least two lines of chemotherapy demonstrated a statistically significant improvement in progression-free survival (PFS). The median PFS was 9.9 months in the ADC arm compared to 5.6 months in the physician's choice chemotherapy arm (HR 0.65, 95% CI 0.52-0.81, P6 The objective response rate (ORR) was 52.1% versus 16.3%, respectively.6

Another significant development was observed with a new generation of tyrosine kinase inhibitors (TKIs) designed to overcome resistance to earlier TKIs and improve central nervous system (CNS) penetration.7 A randomized phase 2 study evaluated a novel oral TKI in patients with HER2-positive metastatic breast cancer with active brain metastases who had progressed on prior HER2-directed therapy. The intracranial objective response rate (ORR) was 42% (95% CI

32-52%) with the new TKI, compared to 18% (95% CI 10-28%) with standard lapatinib.8 The median intracranial PFS was 6.8 months versus 3.2 months (HR 0.58, 95% CI 0.41-0.82, P=.002).8 These data suggest a potential new standard for managing brain metastases in this patient population.

Furthermore, combination strategies incorporating immunotherapy with HER2-targeted agents were explored. A phase 3 trial in the neoadjuvant setting for high-risk HER2-positive breast cancer investigated the addition of a PD-1 inhibitor to dual HER2 blockade and chemotherapy. The pathological complete response (pCR) rate was 68% in the immunotherapy arm versus 55% in the control arm (odds ratio 1.75, 95% CI 1.15-2.67, P=.009).9 While these results are promising, long-term survival data are still maturing, and the optimal patient selection for such intensive regimens requires further investigation.9

The safety profiles of these new agents warrant careful consideration. The ADC trial reported common adverse events including nausea (58%), fatigue (45%), and alopecia (35%), with grade 3 or higher adverse events occurring in 28% of patients.6 Interstitial lung disease (ILD) was observed in 3% of patients, with 1% being grade 3 or higher.6 For the novel TKI, common adverse events included diarrhea (65%), rash (48%), and elevated liver enzymes (22%), with grade 3 or higher adverse events in 20% of patients.8 These adverse event profiles are generally manageable but necessitate vigilant monitoring.

Limitations across these studies include the relatively short follow-up periods for some of the trials, particularly for long-term survival outcomes. Additionally, the generalizability of findings from highly selected patient populations, such as those with specific resistance patterns or active brain metastases, requires validation in broader real-world settings. Future research should focus on identifying predictive biomarkers to optimize patient selection for these advanced therapies and to further refine combination strategies to maximize efficacy while minimizing toxicity. Head-to-head comparisons between different novel ADCs and TKIs are also needed to establish their relative benefits.

To further explore the principles behind targeted therapies discussed here and broader oncology topics, we recommend the comprehensive Oxford Handbook of Oncology.

CLINICAL IMPLICATIONS

The data presented at ASCO 2026 for HER2-expressing breast cancer underscore a significant shift in therapeutic options beyond the established trastuzumab and pertuzumab backbone. The emergence of highly potent antibody-drug conjugates and brain-penetrant tyrosine kinase inhibitors means clinicians must now navigate a more complex, yet potentially more effective, treatment landscape. Integrating these agents will require careful consideration of patient-specific factors, prior treatment history, and the precise disease setting, moving away from a one-size-fits-all approach. The observed intracranial activity of the new TKI, for instance, offers a tangible improvement for patients with brain metastases, a population historically difficult to treat.

For the pharmaceutical industry, these advancements highlight the continued value of targeted drug development, particularly in refining delivery mechanisms and overcoming resistance. Companies like AstraZeneca and Daiichi Sankyo, with their focus on ADCs, and those developing novel TKIs, will likely see increased market penetration as these drugs move into earlier lines of therapy or become preferred options in specific refractory settings. The challenge will be demonstrating superior long-term outcomes and managing the cost-effectiveness of these often-expensive therapies within healthcare systems already strained by rising drug prices. Guideline bodies such as ESMO and NCCN will need to rapidly update their recommendations

> to incorporate these new evidence-based strategies, providing clear guidance for clinicians.
> Patients stand to benefit from these innovations through improved progression-free survival and, potentially, overall survival, particularly in advanced disease where options were previously limited. The ability to effectively manage brain metastases, a devastating complication, represents a substantial quality-of-life improvement. However, the increased complexity of treatment regimens and the potential for novel adverse events, such as interstitial lung disease with ADCs, necessitate thorough patient education and shared decision-making. Ensuring equitable access to these advanced therapies across different healthcare settings will also be a critical consideration, preventing a two-tiered system of care.

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