COMMENTARY

# Beyond HER2-Positive: The ADC Revolution in Breast Cancer Care

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Dear Colleagues,

Antibody-drug conjugates (ADCs) have emerged as one of the most transformative innovations in the treatment of breast cancer, particularly in human epidermal growth factor receptor-2 (HER2)-positive and HER2-low subtypes. By combining the specificity of monoclonal antibodies with the cytotoxic potency of chemotherapy, ADCs offer a targeted approach that has reshaped expectations for efficacy and tolerability. Trastuzumab deruxtecan (T-DXd), with its high drug-to-antibody ratio and membrane-permeable payload, exemplifies this evolution and has demonstrated superiority over previous standards in landmark trials.[1-3] Most notably, its efficacy in HER2-low breast cancer, a group previously considered HER2-negative, has prompted a fundamental rethinking of how HER2 expression is classified and acted upon in clinical practice.

The distinction between HER2-positive and HER2-negative disease is no longer binary. HER2-low, defined as IHC 1+ or 2+ with negative in situ hybridization, encompasses a substantial proportion of breast cancers that may now benefit from HER2-targeted strategies. Clinical trials such as DESTINY-Breast04[4] and DESTINY-Breast06[5] have shown that patients with HER2-low or HER2-ultralow expression can derive meaningful benefit from T-DXd, leading to its incorporation into treatment guidelines. This shift not only broadens therapeutic options but also places new demands on pathology services to provide consistent and reproducible HER2 scoring.

Recent data presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting, including the ASCENT-04[6] and DESTINY-Breast09[7] trials, have also demonstrated the benefit of ADC use in the first-line setting. As these agents move earlier into the treatment paradigm, questions regarding optimal sequencing, resistance and patient selection

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become increasingly important. While the efficacy of ADCs has been demonstrated in both hormone receptor-positive and triple-negative settings, managing evolving resistance and identifying which patients are most likely to benefit from specific agents will be essential to maximizing the long-term potential of ADCs.

Toxicity management is equally critical. While ADCs offer targeted delivery, they are not without risks. Interstitial lung disease, neutropenia and gastrointestinal side effects require careful monitoring and proactive intervention. The integration of pharmacogenetic screening and supportive care protocols will play an essential role in ensuring safety and maintaining treatment intensity.

These developments and challenges were brought into sharp focus at the recent Fourth Swiss Annual Meeting on HER2-Positive Breast Cancer, held in Basel on April 11, 2025. The meeting convened leading experts to explore the expanding role of ADCs across HER2-positive, HER2-low and triple-negative disease. Discussions ranged from novel trial data and evolving treatment algorithms to the practicalities of managing toxicity and resistance. The meeting served not only as a platform for sharing data but as a reflection of the rapidly shifting therapeutic landscape that demands both scientific precision and clinical agility.

As ADCs continue to redefine standards across disease stages, the future of breast cancer therapy will depend on our ability to integrate biomarker-driven decision-making, refine diagnostic categories and anticipate patterns of response and resistance. With several new ADCs in development and ongoing trials exploring their use in neoadjuvant and adjuvant settings, the pace of innovation shows no sign of slowing. What remains essential is a sustained commitment to thoughtful implementation, balancing innovation with pragmatism and promise with precision.

Sincerely,

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## *Conflict of interest*

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