New Generation of Antibody-Drug Conjugates Shows Unprecedented Promise in Early-Stage Breast Cancer

Enhertu before or after surgery shows potential as a new standard of care for patients with early HER2-positive breast cancer.

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Lugano/Berlin — In a landmark moment at the ESMO Congress 2025, pivotal studies have unveiled compelling evidence that a new class of anti-cancer agents—antibody-drug conjugates (ADCs)—can dramatically improve outcomes for patients with early-stage HER2-positive breast cancer.

The results from the Phase III DESTINY-Breast05 and DESTINY-Breast11 trials, presented in a Presidential Symposium, mark a paradigm shift in breast cancer treatment, positioning ADCs not only as powerful therapeutic agents when the disease has already progressed but also as potential new standards of care in patients with early disease.

“There is a particular need for therapies to ensure patients with HER2-positive early breast cancer achieve pathological complete response following neoadjuvant therapies—i.e., delivered before surgery—and a high unmet need to treat residual disease in those who do not, to prevent the development of metastasis,” explains Dr Evandro de Azambuja from the Jules Bordet Institute, Brussels, Belgium.

Currently, trastuzumab emtansine (T-DM1) [Kadcyla] is the only ADC approved for patients with HER2-positive early breast cancer who show residual invasive disease after neoadjuvant therapy and are at a high risk of recurrence.

In the DESTINY-Breast05 trial, trastuzumab deruxtecan (T-DXd) [Enhertu, froom AstraZeneca and Daiichi Sankyo], a new-generation ADC delivering a topoisomerase I inhibitor, was shown to improve invasive disease-free survival and disease-free survival by 53% compared with T-DM1 (for both: hazard ratio [HR] 0.47; 95% confidence interval [CI] 0.34–0.66; $p<0.0001$). Also, T-DXd confirmed its high brain activity, demonstrating a clinically meaningful improvement in brain metastasis-free interval over T-DM1 (HR 0.64; 95% CI 0.35–1.17).

“The generally manageable safety profile and the superior efficacy data suggest that T-DXd should

replace T-DM1 as the new standard of care for patients with HER2-positive, residual invasive breast cancer after neoadjuvant therapy," notes de Azambuja.

The use of T-DXd also showed impressive findings earlier in the treatment pathway—before surgery—as reported in the DESTINY-Breast11 trial where 927 untreated patients with high-risk HER2-positive early breast cancer received either the ADC followed by standard HER2-targeted therapy (THP) or the conventional anthracycline-based regimen (ddAC-THP). The cycles of T-DXd, sequenced with THP, led to a significant increase in the rate of pathological complete response at surgery (67.3% versus 56.3%; p=0.003).

"The T-DXd regimen has also the added advantage of an improved safety profile compared with the anthracycline-containing regimen," comments de Azambuja noting the relevant reduction in cardiac toxicities which was observed with the ADC compared with the conventional treatment.

"In conjunction, these two studies establish T-DXd as a critical treatment option for early-stage HER2-positive breast cancer, ultimately providing a new tool for treatment tailoring for what was once considered the most aggressive subtype of breast cancer, and which today represents the one with the highest chance of cure," highlights Dr Paolo Tarantino from the Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA.

After having reshaped the treatment of multiple types of metastatic cancers over the last few years, novel ADCs such as T-DXd are now "raising the bar" in the curative setting due to innovations in their design and mechanism of action. However, their use presents new challenges that need to be addressed.

"For instance, toxicity profiles must be carefully defined and substantial effort to prevent permanent or fatal toxicities is required. Dosing, duration and sequencing of ADCs must also be optimised to achieve maximal efficacy with the least side-effects, and equally critical is the identification of predictive biomarkers that may allow better tailoring of ADC therapy and minimise overtreatment," clarifies Tarantino.

The presentation of the DESTINY-Breast05 and DESTINY-Breast11 trials results at the ESMO Congress 2025 cements the event's role as a catalyst for global oncology progress. With ADCs now demonstrating superiority in both pre- and post-surgical settings, the oncology community stands at the threshold of a new chapter—one defined by smarter targeting, earlier intervention and deeper biological understanding.

"Besides the immediate practical impact, in fact, data presented today are expected to have a broader impact on the future of ADC research, marking the formal entrance of the new generation of drugs in the curative arena. This is a therapeutic strategy with tremendous potential, which we are only just starting to unleash, promising to reduce rates of recurrence and improve survival across multiple cancers in the years to come," concludes Tarantino.

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