Trastuzumab Deruxtecan Reshapes HER2-Low Metastatic Breast Cancer Treatment

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The classification of human epidermal growth factor receptor 2 (HER2) status in breast cancer has historically been binary: HER2-positive or HER2-negative. However, a significant proportion of breast cancers previously considered HER2-negative exhibit low levels of HER2 expression. This emerging 'HER2-low' category represents a new therapeutic target, with implications for how metastatic breast cancer is managed.

KEY TAKEAWAYS

- The Pivot: Trastuzumab deruxtecan (T-DXd) demonstrates efficacy in HER2-low metastatic breast cancer, a patient population previously lacking effective HER2-targeted options.
- The Data: In HR-positive, HER2-low metastatic breast cancer, T-DXd extended median progression-free survival to 10.1 months versus 5.4 months with chemotherapy (HR 0.51; PThe Action: T-DXd should be considered for patients with HER2-low metastatic breast cancer who have received prior lines of chemotherapy, including those with varying degrees of endocrine resistance and disease burden.

Redefining HER2 Status in Breast Cancer

For many years, HER2 status in breast cancer was categorized as either positive or negative, guiding treatment decisions with HER2-targeted therapies reserved for HER2-positive disease. However, a substantial number of breast cancers, traditionally classified as HER2-negative, express low levels of HER2. This 'HER2-low' group, defined by an immunohistochemical (IHC) score of 1+ or an IHC score of 2+ with negative in situ hybridization results, has historically not benefited from available HER2-directed treatments 1.

DESTINY-Breast04: Evaluating Trastuzumab Deruxtecan in HER2-Low Disease

The DESTINY-Breast04 trial, a phase 3 study, investigated the efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients with HER2-low metastatic breast cancer who had previously received one or two lines of chemotherapy. Patients were randomized in a 2:1 ratio to receive either T-DXd or a physician's choice of chemotherapy 1.

The study's primary endpoint was progression-free survival (PFS) in the hormone receptor-positive (HR-positive) cohort. Key secondary endpoints included PFS among all patients and overall survival (OS) in both the HR-positive cohort and the overall patient population 1.

Significant Survival Benefits Observed

Of the 557 randomized patients, 494 (88.7%) had HR-positive disease, and 63 (11.3%) had HR-negative disease. In the HR-positive cohort, T-DXd demonstrated a significant improvement in PFS, with a median of 10.1 months compared to 5.4 months in the physician's choice group (hazard ratio [HR] for disease progression or death, 0.51; P1.

Similar benefits were observed across the entire study population. The median PFS was 9.9 months with T-DXd versus 5.1 months with physician's choice chemotherapy (HR for disease progression or death, 0.50; P1.

DESTINY-Breast06: Efficacy Across Subgroups

Further analyses from the DESTINY-Breast06 trial explored T-DXd outcomes in HR-positive, HER2-low/-ultralow metastatic breast cancer across various patient subgroups. These post hoc analyses aimed to understand the treatment's effectiveness based on characteristics that influence prognosis, such as time to progression (TTP) on prior first-line endocrine therapy (ET) with a CDK4/6 inhibitor and baseline disease burden 2.

The median PFS consistently favored T-DXd over physician's choice chemotherapy regardless of TTP on prior first-line ET + CDK4/6 inhibitor. For patients with TTP 12 months, 12.9 months versus 8.2 months 2.

A consistent PFS benefit with T-DXd was also observed in patients with primary or secondary endocrine resistance, and across indicators of high or low disease burden, including visceral/non-visceral disease, presence/absence of liver metastases, number of disease sites, and baseline tumor size. Objective response rates (ORR) were higher with T-DXd (36.7% to 67.7%) compared to physician's choice chemotherapy (16.7% to 37.5%) across all subgroups, and the duration of response was longer with T-DXd. T-DXd also prolonged time from randomization until second progression or death (PFS2) across subgroups 2.

Safety Profile

In DESTINY-Breast04, adverse events of grade 3 or higher occurred in 52.6% of patients receiving T-DXd and 67.4% of those receiving physician's choice chemotherapy. A notable adverse event was adjudicated, drug-related interstitial lung disease or pneumonitis, which occurred in 12.1% of T-DXd recipients, with 0.8% experiencing grade 5 events 1. The safety profiles of T-DXd in the DESTINY-Breast06 subgroups were consistent with the overall safety population 2.

Clinical Implications

The findings from DESTINY-Breast04 and DESTINY-Breast06 indicate that trastuzumab deruxtecan offers a significant therapeutic advantage for patients with HER2-low metastatic breast cancer, a population previously underserved by HER2-targeted therapies. The consistent benefits observed across various prognostic subgroups in DESTINY-Breast06 further support its broad applicability in HR-positive, HER2-low/-ultralow metastatic breast cancer after one or more endocrine therapies.

Why this matters for clinical practice today

The concept of HER2-low breast cancer fundamentally shifts how we approach patient stratification and treatment selection. For clinicians, this means re-evaluating HER2 status beyond the traditional binary, recognizing that a substantial portion of patients previously deemed HER2-negative may now be candidates for a highly effective targeted therapy. Integrating T-DXd into treatment algorithms for these patients, particularly after progression on endocrine therapy with CDK4/6 inhibitors, could significantly improve outcomes. Careful monitoring for interstitial lung disease remains crucial, given its reported incidence.

Limitations and Next Steps

While these trials demonstrate clear benefits, the DESTINY-Breast06 subgroup analyses were post hoc, meaning they were not pre-specified as primary objectives and thus may be subject to certain limitations. Further research is needed

to refine patient selection within the HER2-low category and to explore optimal sequencing strategies for T-DXd in combination with other therapies. Continued vigilance regarding the management of interstitial lung disease is also essential as T-DXd use expands in clinical practice 1,2.

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REFERENCES

1. 1. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022;387(1):9-20. doi:10.1056/NEJMoa2203690

2. 2. Curigliano G, Hu X, Dent R, et al. Trastuzumab deruxtecan in hormone receptor-positive, HER2-low/-ultralow metastatic breast cancer (DESTINY-Breast06): outcome analyses by time to progression on prior first-line endocrine therapy with CDK4/6 inhibitor and baseline burden of disease. Ann Oncol. 2026;37(6):849-860. doi:10.1016/j.annonc.2026.02.015

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