Trastuzumab deruxtecan: An antibody-drug conjugate embracing its destiny in breast cancer

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In DESTINY-Breast 03, Trastuzumab Deruxtecan, a HER2-specific antibody-drug conjugate, proved superior to T-DM1 in patients with HER2+ metastatic breast cancer progressing on taxane and trastuzumab.1 This study supported its recent approval as second-line therapy in HER2+ metastatic breast cancer.

Despite numerous successes in the history of medical oncology, few have rivaled the metamorphosis that took place in breast cancer with the discovery of the HER2 gene and its subsequent targeting with trastuzumab. In 1987, Slamon and colleagues published the first clinical data of a novel gene called erb2, or HER2/neu, and significantly worse relapse-free survival and overall survival in patients with HER2-amplified breast cancer.2 Subsequent laboratory-based studies elucidated HER2’s role as a driver oncogene linked to aggressive tumor behavior. This was followed by the development of trastuzumab, a humanized anti-HER2 monoclonal antibody (mAb), that improved progression-free survival (PFS) and overall survival when combined with chemotherapy for HER2-overexpressed (HER2+) metastatic breast cancer (MBC)3 and early-stage breast cancer,4 cementing it as a core treatment and laying the foundation for several further advances in HER2-targeting approaches, including tyrosine-kinase inhibitors (TKIs), novel mAbs, and most recently, antibody-drug conjugates (ADCs). One such ADC, fam-trastuzumab deruxtecan (T-DXd), has recently been shown to prolong PFS compared with trastuzumab emtansine (T-DM1) in HER2+ MBC in the international phase 3 randomized clinical trial DESTINY-Breast 03 (DB-03), the focus of this spotlight, reported by Cortés et al.1

DB-03 enrolled HER2+ MBC patients previously progressing on taxane and trastuzumab (median 1–2 prior lines of therapy) and randomized to T-DXd versus T-DM1. Importantly, 62% of participants had prior pertuzumab, 50% were ER+, 70% had visceral metastases, and roughly 20% had stable brain metastases at enrollment. Despite this study being positioned in the “second-line” setting given the current indication for T-DM1, the ranges of prior lines of therapy were 0–16 for T-DXd and 0–14 for T-DM1, which the authors cite as due to limited availability of T-DM1 in certain countries participating in this study. With these characteristics in mind, the median PFS (mPFS) was not reached for T-DXd versus 6.8 months for T-DM1, representing a 72% improvement in PFS, with 12-month PFS rates of 75.8% and 34.1%, respectively. Equally impressive, the disease control rate, defined as partial response, complete response, or stable disease for ≥6 months, was 96.6% (T-DXd) versus 76.8% (T-DM1). All key subgroups favored T-DXd. Additional data presented at the San Antonio Breast Cancer Symposium (SABCS) in 2021 regarding participants with stable brain metastases at enrollment demonstrated a clinically significant improvement in mPFS (15 months T-DXd versus 3 months T-DM1) and intracranial objective response rates (63.9% versus 33.4%, respectively), suggesting that T-DXd crosses the blood-brain barrier.6 These data led to an updated NCCN recommendation for T-DXd as the preferred second-line therapy with category one evidence, and on May 4th, 2022, the FDA granted regular approval for T-DXd in a similar population (median seven prior lines of therapy) which yielded a 60.9% ORR and an mPFS of 16.4 months. Based on these results, the FDA granted T-DXd accelerated approval in 2019 for patients with HER2+ MBC having progressed on T-DM1.

Given its bystander effect, T-DXd was also tested in a cohort of participants with HER2- (by FISH) MBC with HER2 1+/2+ expression by immunohistochemistry (HER2 low), a population for which...
anti-HER2 therapy had historically not been effective, demonstrating an ORR of 37% and median duration of response of 10.4 months. These data provided rationale for DB-04, a randomized phase 3 trial evaluating T-DXd versus physician’s choice for HER2 low tumors, the results of which were announced in a recent press release indicating that DFS and overall survival (OS) endpoints had been met and thus potentially adding T-DXd and other ADCs with bystander effect as additional agents for triple-negative and ER+ breast cancers with low-intermediate expression of HER2.

The initial successes of T-DXd were tempered, however, by a signal for high-grade interstitial lung disease (ILD)/pneumonitis. In the phase 2 DB-01 trial, 13.6% of participants developed any-grade ILD, and 4 participants (2.2%) died from ILD. As a result of this early experience, institution of rigorous monitoring for signs and symptoms of ILD, as well as early drug interruption and steroid initiation for any-grade ILD or grade ≥2 pneumonitis, has led to lowered rates of ILD and no further grade 5 events. In DB-03, there were only 0.8% grade 3 events and no ILD-related deaths. Additional frequent toxicities noted with T-DXd in DB-03 included high rates of G ≥3 myelosuppression (including neutropenia [19%], anemia [5.8%], thrombocytopenia [7.8%], nausea [6.6%], and fatigue [5.1%], a reminder that off-target toxicity remains a challenge for the “targeted” chemo approach of ADCs.

As the field of ADCs continues to grow, several key questions remain, including: what is the optimal sequencing of ADCs in the metastatic setting, and what role will ADCs in the neo- and post-neoadjuvant setting for early stage breast cancer play (under investigation in the DB-05 study evaluating T-DXd versus T-DM1 in HER2+ breast cancer with residual disease after neoadjuvant therapy)? Given its toxicity, strategies for selecting patients most likely to benefit are key. Doing so could provide an opportunity to investigate new biomarkers, including those based on radiomics utilizing novel HER2-tracers, for in vivo assessment of target expression. Further advances in ADC technology, such as dual payloads, novel synthetic site-specific payload conjugation, and targeting of the tumor microenvironment in addition to the tumor antigen, will hopefully continue to improve efficacy and widen the therapeutic window.

The publication of DB-03 both commemorates the past successes of trastuzumab-based therapy for HER2+ breast cancer and looks forward to the next 5–10 years, which will no doubt see continued advancements in ADC technology. With 11 currently approved ADCs and several more under development, it appears we have reached another metamorphosis in oncology.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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