

Trastuzumab-deruxtecan in breast cancer treatment: Balancing the triad of efficacy, safety and accessibility

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Trastuzumab deruxtecan (T-DXd), an anti-human epidermal growth receptor 2 (HER2) antibody-drug conjugate (ADC), has emerged as a transformative therapy for metastatic breast cancer (MBC), demonstrating efficacy across the full spectrum of HER2 expression including HER2 positive, HER2 low and HER2 ultralow disease.¹⁻⁴ This novel ADC consists of trastuzumab linked via an enzymatically cleavable disulfide linker to deruxtecan, a potent topoisomerase I inhibitor. Its high drug-to-antibody ratio (approximately 8) and membrane-permeable payload enable a bystander effect, contributing to its pronounced antitumour activity. The DESTINY-Breast03 trial redefined expectations in HER2-positive MBC, achieving a median overall survival of only over 50 months in the second-line setting, which far exceeds the 30-month benchmark set by previous gold standard therapy trastuzumab emtansine, underscoring a paradigm shift in the therapeutic landscape of this disease. While T-DXd is generally well-tolerated and allows most patients to preserve quality of life, its use is tempered by toxicities including alopecia, nausea and fatigue. The main long-term concern is interstitial lung disease (ILD), which requires careful monitoring. Despite its impressive clinical activity, the widespread adoption of T-DXd is constrained by its high cost and toxicity profile that can be clinically significant for some patients. These challenges underscore the need for strategies that enhance its generalisability, ensuring that more patients can benefit from its therapeutic potential without compromising safety or affordability.

In this issue of the *Annals*, a retrospective analysis of 87 patients with MBC treated with T-DXd by Lee et al. reported comparable real-world progression-free survival (rwPFS) between those receiving an initial relative dose intensity (RDI) of <85% versus ≥85%.⁵ T-DXd demonstrated favourable central nervous system (CNS) activity, with brain progression observed in only 16% of patients, and an incidence of ILD at 5%.

The study offers valuable real-world evidence (RWE) from a predominantly Asian population, demonstrating that reductions in RDI of T-DXd did

not significantly affect rwPFS. The authors should be commended for conducting this real-world analysis, which more closely mirrors routine clinical practice, where dose modifications are often made to mitigate toxicity and manage treatment costs. This study underscores the value of RWE in complementing clinical trial data. While trials often involve highly selected patient populations under controlled conditions, RWE captures outcomes in broader, more diverse groups including older patients, those with comorbidities and individuals receiving later-line therapies. Such data provide critical insights into how treatments perform in routine practice, helping to guide clinical decisions and advance patient-centred oncology care.

The patients included in this analysis were heavily pre-treated, with a median of 4 prior lines of therapy (ranging 2–15). Over 90% received T-DXd as a third-line treatment or later. The observed rwPFS was 8.1 months, which is consistent with other real-world data from Asian populations,⁶ but remains inferior compared to outcomes reported in non-Asian cohorts.⁷ In contrast, the DESTINY-Breast01 (DB-01) trial reported a median progression-free survival (PFS) of 16.4 months, despite patients receiving a median of 6 prior lines of therapy (ranging 2–27).¹ However, DB-01 enrolled only fit patients (Eastern Cooperative Oncology Group performance status 0–1) and excluded those with untreated or symptomatic brain metastases, which may account for the superior outcomes.

Lee et al. reported noteworthy findings on the intracranial activity of T-DXd. Among 11 patients with baseline CNS involvement, 9 achieved disease control following treatment with T-DXd. While the sample size is limited, these real-world results are consistent with previously reported studies and reinforce the growing body of evidence supporting the CNS efficacy of T-DXd, even in heavily pre-treated populations. Data from the DESTINY-Breast12 trial,⁸ which demonstrated a high intracranial objective response rate and prolonged CNS PFS, suggest that systemic therapy with T-DXd may complement local therapy in select patients. This is particularly relevant given

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the neurocognitive sequelae associated with local modalities such as whole-brain radiotherapy, which also fails to address extracranial disease burden. With newer agents showing good intracranial efficacy, the European Society for Medical Oncology Living Guidelines have recently recommended consideration of both T-DXd and the tucatinib–trastuzumab–capecitabine (TTC) combination as second-line options for patients with active brain metastases who do not require immediate local treatment.⁹ The selection between these regimens should be guided by patient-specific factors, toxicity profiles and accessibility. T-DXd is associated with risks such as ILD and fatigue, whereas TTC tends to cause gastrointestinal toxicities and hepatotoxicity. In the Singapore context, it may be more cost-effective to use T-DXd over TTC. Finally, there is retrospective evidence supporting the feasibility of sequencing TTC after T-DXd.¹⁰

The incidence of ILD in this study was 5.7%, notably lower than the 10–15% reported across the DESTINY-Breast trials.^{1,4} While earlier analyses have suggested that ILD rates may be higher among Asian patients—particularly within Japanese cohorts¹¹—emerging real-world data from broader Asian, non-Japanese populations indicate ILD incidences that are comparable to or even lower than those observed in the clinical trial setting.¹² This discrepancy highlights the complex interplay between ethnicity, patient selection, drug dosing and pharmacogenomic differences. Importantly, these real-world findings suggest that in routine practice, with appropriate monitoring strategies and individualised dose modifications, the risk of ILD associated with T-DXd may be effectively minimised. As we continue to integrate T-DXd into clinical practice, real-world pharmacovigilance will remain essential in optimising safety across diverse patient populations.

Although non-ILD-related toxicities such as nausea and fatigue were not explicitly captured in this study, it is reasonable to infer that their incidence and severity may be attenuated with lower RDI of T-DXd. This consideration is particularly relevant given that T-DXd-associated toxicities have been observed to be more pronounced when the drug is administered in later lines of therapy, as compared to earlier use in the DB clinical trials.¹³ These observations underscore the practical importance of dose optimisation where clinicians must balance drug efficacy with tolerability in more heavily pretreated and heterogeneous patient populations.

While this retrospective analysis suggests that reduced RDI does not compromise efficacy of T-DXd, prospective studies are needed to validate optimal

dosing strategies, with consideration of comparison for fixed versus adaptive dosing regimens, stratified by baseline patient characteristics, to better balance efficacy with tolerability. The current optimal systemic option for MBC with brain metastasis is not straightforward given the lack of head-to-head studies between T-DXd and other regimens with CNS activity like TTC; systemic collection and review of such data in diverse real-world populations are warranted. These studies should consider not only efficacy and safety but also patient-reported outcomes, quality of life and cost-effectiveness.

In Singapore, T-DXd was incorporated into the Cancer Drug List in November 2023 for HER2-positive advanced breast cancer and expanded in September 2024 to include HER2-low disease. These milestones represent a major step forward in improving access to a transformative therapy for breast cancer patients. While financial considerations remain for patients without Medisave or MediShield support, the progressive inclusion of T-DXd into national funding frameworks paves the way for broader adoption and integration of this therapy into mainstream clinical practice.

In summary, the study by Lee et al. contributes important RWE supporting the clinical utility and tolerability of T-DXd in a diverse, heavily pre-treated Asian population. The findings reinforce the notion that reduced dose intensity may preserve efficacy while potentially mitigating toxicity. Furthermore, the encouraging CNS activity of T-DXd, coupled with a manageable safety profile—particularly with regard to ILD—highlights its promise as systemic therapy for MBC patients with brain metastases. As T-DXd continues to be integrated into earlier lines of therapy and across the HER2 expression spectrum, real-world data such as these are invaluable. They complement clinical trial findings by offering nuanced insights into treatment outcomes in patient populations that are under-represented in trials, thereby guiding more personalised cancer care.

Ethics statement

Not applicable.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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