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Review Article

Trastuzumab deruxtecan in breast cancer: Current status and future directions

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Abstract

Breast cancer is the most prevalent malignancy in women globally, with HER2-positive disease constituting approximately 15–20% of cases. The advent of HER2-targeted therapies has significantly improved outcomes; however, therapeutic resistance in metastatic settings remains a challenge. Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody–drug conjugate (ADC) made up of a humanized anti-HER2 monoclonal antibody attached to a topoisomerase I inhibitor payload through a cleavable linker. A high drug-to-antibody ratio and a bystander effect has resulted in a significant efficacy in HER2-positive metastatic breast cancer (mBC), particularly those who have received multiple lines of therapy, as shown in DESTINY-Breast01 and DESTINY-Breast03 trials. Furthermore, the DESTINY-Breast04 study established T-DXd as the first effective therapy for HER2-low mBC. This led to a redefinition of the categories of HER2 expression. T-DXd is also under investigation in early-stage disease, with encouraging results in neoadjuvant and adjuvant settings. While generally well tolerated, interstitial lung disease (ILD) remains a notable risk, necessitating vigilant monitoring. Patient-reported outcomes indicate maintained or improved quality of life with T-DXd. Ongoing research is focused on expanding its role through combination strategies, exploring its use in HER2-ultralow tumors, and identifying predictive biomarkers such as HER2 mRNA levels and topoisomerase I expression. Additionally, T-DXd is being evaluated in other HER2-expressing malignancies including lung, gastric, and colorectal cancers. Overall, T-DXd represents a paradigm shift in HER2-targeted therapy, offering clinical benefit across a broader spectrum of breast cancer subtypes and treatment settings.

Keywords: Trastuzumab deruxtecan, TDXd, Breast cancer.

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1. Introduction

Breast cancer continues to represent the most prevalent malignancy in women worldwide and remains a major cause of cancer-related mortality. Over the last two decades, advances in molecular subtyping based on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression have significantly improved disease characterization and guided precision therapy. Approximately 15–20% of breast cancers overexpress or amplify HER2, which historically conferred a more aggressive clinical course and poorer prognosis.

The introduction of HER2-targeted therapies such as trastuzumab, pertuzumab, and the antibody–drug conjugate (ADC) trastuzumab emtansine (T-DM1) transformed the landscape of HER2-positive breast cancer, markedly improving both disease-free and overall survival. Nevertheless, acquired resistance to HER2-directed agents is nearly universal in the metastatic setting, underscoring the need for next-generation therapies capable of overcoming these limitations.

Trastuzumab deruxtecan (T-DXd; DS-8201a) is a second-generation ADC rationally designed to combine potent cytotoxic activity with selective HER2 targeting. It employs a humanized trastuzumab backbone linked to a novel topoisomerase I inhibitor payload through a cleavable linker that allows efficient drug release within tumor cells. The success of T-DXd in the DESTINY- Breast clinical trials has not only redefined the standard of care in metastatic

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disease but also broadened the therapeutic relevance of HER2 expression beyond the traditional "positive" category.

This review summarizes the molecular structure and mechanism of T-DXd, presents pivotal clinical evidence, highlights safety and quality-of-life data, and discusses emerging directions that are shaping the future of HER2-targeted therapy.

2. Mechanism of Action

Trastuzumab deruxtecan (T-DXd, DS-8201a) is a next-generation HER2-directed ADC comprising three key components:

1. A humanized anti-HER2 monoclonal antibody identical to Trastuzumab;
2. A cleavable tetrapeptide-based linker; and
3. A potent topoisomerase I inhibitor payload, Deruxtecan (DXd).[1-3]

Upon binding to HER2 receptors expressed on tumor cell membranes, the ADC–receptor complex undergoes receptor-mediated endocytosis. Within lysosomes, enzymatic cleavage of the linker liberates the DXd payload, which subsequently inhibits topoisomerase I, leading to the accumulation of DNA single-strand breaks, cell-cycle arrest, and ultimately apoptotic death.[1]

A distinctive property of T-DXd is its membrane permeability, enabling the released DXd to diffuse into neighboring tumor cells regardless of their HER2 expression level — a phenomenon known as the bystander effect. This property is particularly relevant in tumors exhibiting intratumoral HER2 heterogeneity, a known mechanism of resistance to conventional HER2-targeted therapies.

In addition, T-DXd features a drug-to-antibody ratio (DAR) of approximately 8 — nearly twice that of T-DM1 (DAR ≈ 3.5) — allowing for higher cytotoxic payload delivery.[3] The trastuzumab backbone retains Fc-mediated immune effector functions such as antibody-dependent cellular cytotoxicity (ADCC), providing an additional immune-modulatory component. The cumulative result is a highly potent, tumor-selective cytotoxic agent with both direct and indirect antitumor effects.

3. Her2-positive Metastatic Breast Cancer

3.1. Destiny breast 01

The phase II DESTINY-Breast01 trial established T-DXd as a highly effective therapy for patients with heavily pretreated HER2-positive metastatic breast cancer (mBC). Participants had previously received trastuzumab, pertuzumab, and T-DM1. At a median follow-up of 11.1 months, the objective response rate (ORR) was 60.9%, the median progression-free survival (PFS) was 16.4 months, and the median overall survival (OS) was 29.1 months.[4] These results represented a dramatic improvement compared with historical controls and led to rapid regulatory approval in multiple countries.

3.2. Destiny breast 03

The phase III DESTINY-Breast03 trial was a landmark, global, randomized, open-label study comparing T-DXd (5.4 mg/kg q3w) with T-DM1 (3.6 mg/kg q3w) in 524 patients with HER2-positive mBC previously treated with trastuzumab + taxane.[5,6] Randomization (1:1) was stratified by hormone-receptor status, visceral involvement, and prior pertuzumab exposure.

The primary endpoint was PFS by blinded independent central review; secondary endpoints included OS, ORR, duration of response (DoR), and safety.

At the first analysis, T-DXd achieved a median PFS of 28.8 months versus 6.8 months with T-DM1 (HR 0.33; $p < 0.0001$). The 12-month PFS rate was 75.8% for T-DXd compared with 34.1% for T-DM1. The ORR was 78.5% for T-DXd and 35% for T-DM1, with complete responses (CRs) in 16% and 8.7%, respectively. The median DoR reached 36.6 months versus 23.8 months.

Updated analyses showed a median OS of 52.6 months for T-DXd versus 42.7 months (HR 0.64). Benefit was consistent across all predefined subgroups, including hormone-receptor–positive, –negative, and visceral-disease subsets, underscoring its broad applicability.

DESTINY-Breast03 uniquely permitted enrollment of patients with treated and stable brain metastases (≈16% of participants). T-DXd achieved a CNS-ORR of 63.9% versus 33.4% with T-DM1, and median CNS-PFS of 15 months versus 3 months, reflecting effective intracranial penetration of the DXd payload.[7] Imaging analyses confirmed marked reductions in lesion number and volume. These findings are clinically significant, as CNS progression remains a major cause of morbidity in HER2-positive disease.

Treatment-related adverse events were mostly grade 1–2, including nausea (73%), fatigue (45%), vomiting (44%), alopecia (38%), and neutropenia (20%). Grade ≥ 3 toxicities occurred in 45% of patients on T-DXd vs 39% on T-DM1, and treatment discontinuation rates were lower with T-DXd (13.6%) than T-DM1 (17.5%).

Interstitial lung disease/pneumonitis occurred in 10.5% (grade ≥ 3 in 0.8%), with no fatal events when managed per protocol using early corticosteroids. The trial's structured monitoring strategy—baseline and periodic chest CTs and prompt evaluation of respiratory symptoms—was pivotal in maintaining safety. Cardiotoxicity was rare (< 1%).

DESTINY-Breast03 achieved a magnitude of benefit rarely seen in metastatic breast cancer, with a five-fold improvement in PFS and doubling of ORR compared with T-DM1. The consistency of benefit, intracranial efficacy, and manageable toxicity led to immediate updates in NCCN,

ESMO, and ASCO guidelines, designating T-DXd as the preferred second-line regimen following trastuzumab + pertuzumab + taxane therapy.

Mechanistically, the study validated the bystander effect as a key contributor to activity in tumors with heterogeneous HER2 expression. The results have catalyzed exploration of T-DXd in earlier-line, adjuvant, and combination settings. Overall, DESTINY-Breast 03 represents a turning point, establishing ADCs as a new generation of precision cytotoxics capable of delivering durable remissions even in refractory disease.

4. Her2-low and Ultralow Breast Cancer

The recognition of HER2-low and ultralow breast cancers has transformed the traditional binary classification of HER2 status. In DESTINY-Breast04, the impressive survival benefit in tumors with IHC 1+ or 2+/ISH-negative expression challenged the previous paradigm that HER2-directed therapy was ineffective in this group.[8] Biomolecular analyses have shown that even these "HER2-low" tumors may exhibit residual HER2 signaling and partial receptor clustering that permit ADC internalization and cytotoxicity. Moreover, T-DXd's high drug-to-antibody ratio ensures sufficient payload delivery, even when receptor density is low.

The phase III DESTINY-Breast04 trial expanded the scope of HER2-targeted therapy to a previously untreatable population—HER2-low tumors (IHC 1+ or 2+/ISH-negative).[8] Among 557 patients randomized to T-DXd or chemotherapy, the median PFS was 10.1 versus 5.4 months, and OS was 23.4 versus 16.8 months, favoring T-DXd. The study conclusively demonstrated clinical benefit across hormone-receptor–positive and –negative subgroups, leading to the recognition of HER2-low breast cancer as a distinct biological and therapeutic entity.

Molecular profiling revealed intermediate HER2 mRNA expression and partial signaling dependency, explaining sensitivity to T-DXd. Preclinical data also suggest an immunostimulatory effect via dendritic-cell activation and enhanced antigen presentation. Furthermore, exploratory analyses have shown potential activity even in HER2-ultralow tumors (IHC <1+).[9] HER2-ultralow disease (IHC <1+), historically grouped under triple-negative breast cancer (TNBC), has now emerged as an intriguing therapeutic frontier. Preliminary findings from DESTINY-Breast06 suggest meaningful activity of T-DXd even in this setting, potentially redefining the boundaries of HER2-targeted therapy. If validated, this could represent the first targeted option for a subset of tumors previously managed exclusively with chemotherapy. Such findings support the evolution toward a continuum model of HER2 expression, where quantitative thresholds rather than categorical positivity guide treatment decisions.[9]

5. Early Breast Cancer and First-Line Setting

Encouraged by its robust efficacy in advanced disease, T-DXd is now under investigation in early-stage and first-line contexts. Preliminary phase II studies have demonstrated pathologic complete response (pCR) rates exceeding 70% when used as neoadjuvant monotherapy or in combination with standard regimens.[10]

The DESTINY-Breast05 trial is comparing adjuvant T-DXd versus T-DM1 in patients with residual invasive disease following neoadjuvant therapy.[11] Similarly, DESTINY-Breast11 is evaluating neoadjuvant T-DXd compared with standard taxane plus trastuzumab/pertuzumab combinations. Early results indicate comparable or superior efficacy with potentially reduced toxicity, suggesting opportunities for treatment de-escalation in selected patients.

By integrating T-DXd into early treatment paradigms, these trials aim to leverage its mechanism to eradicate micrometastatic disease and prevent relapse, potentially shifting HER2-positive breast cancer toward a more curable trajectory.

6. Safety and Tolerability

T-DXd exhibits a generally manageable safety profile but carries a distinct risk of interstitial lung disease (ILD)/pneumonitis, which warrants vigilant monitoring. Across trials, ILD incidence ranged from 10–15%, with grade ≥3 events around 2–3% and rare fatalities.[5,12] Early recognition and prompt corticosteroid therapy are critical. Treatment discontinuation is recommended for grade ≥2 ILD.

Other common adverse events include nausea, fatigue, alopecia, and neutropenia, mostly grade 1–2. Nausea is more frequent than with T-DM1 but can be effectively managed using 5-HT_3 antagonists and dexamethasone. Importantly, cardiac dysfunction—a hallmark of earlier HER2-targeted therapies—is infrequent with T-DXd, with a <1% incidence of symptomatic decline in left ventricular ejection fraction.[13]

Real-world data support the safety profile observed in trials, emphasizing adherence to standardized monitoring algorithms: baseline CT imaging, periodic pulmonary assessments, and patient education regarding early respiratory symptoms.

7. Quality of Life

Patient-reported outcomes (PROs) from DESTINY-Breast03 and DESTINY-Breast04 reveal that T-DXd maintains or improves health-related quality of life relative to control therapies.[6,8] Measures such as the EORTC QLQ-C30 and FACT-B demonstrated delayed time to deterioration of global health status, physical functioning, and fatigue.

The maintenance of quality of life, despite potent cytotoxic activity, underscores a key therapeutic advantage—durable disease control without compromising daily

functioning. This is particularly relevant in metastatic disease, where treatment goals emphasize both survival and quality of living.

8. Future Directions

8.1. Combination strategies

Combination approaches involving T-DXd with ICIs such as nivolumab and pembrolizumab are being actively investigated. These regimens aim to leverage ADC-induced ICD to potentiate anti-tumor immunity. Early data from phase Ib studies have revealed promising response rates exceeding 65% in HER2-low disease, with manageable toxicity. Beyond immunotherapy, combinations with CDK4/6 inhibitors, PI3K pathway blockers, or PARP inhibitors are under evaluation to overcome intrinsic resistance pathways and target DNA repair deficiencies. The DESTINY-Breast 07 and DESTINY-Breast 09 trials are currently exploring these synergies in the first-line metastatic setting, and early analyses suggest durable responses without additive toxicity.[14]

Ongoing clinical trials are evaluating T-DXd with agents such as nivolumab, pembrolizumab, and durvalumab in HER2-positive and HER2-low disease. These combinations may further extend therapeutic benefit, particularly in tumors with immune-inflamed microenvironments.

8.2. Biomarker development

Efforts to refine predictive biomarkers for T-DXd efficacy are central to optimizing patient selection. Quantitative digital pathology and mass spectrometry–based assays now enable continuous measurement of HER2 protein and mRNA expression, capturing subtle gradations of receptor abundance missed by traditional IHC. Moreover, the spatial transcriptomic mapping of HER2 distribution has revealed heterogeneity within individual lesions, correlating with variable ADC penetration and efficacy. Integration of radiomic imaging biomarkers (e.g., HER2-PET, diffusion-weighted MRI) may also predict early response and guide adaptive treatment.

8.3. Resistance mechanisms

Resistance to T-DXd remains multifactorial. Key contributors include loss of HER2 expression, activation of DNA repair pathways, and overexpression of drug efflux pumps (ABCG2, ABCC1). Novel strategies under evaluation include HER2-bispecific ADCs, payload-modulated constructs, and HER2-TKI sequencing. Agents such as trastuzumab duocarmazine and SYD985 represent the next wave of ADC innovation, incorporating alternative linkers and payloads to bypass existing resistance mechanisms. Additionally, the concept of ADC rechallenge following drug-free intervals is being explored, reflecting potential resensitization after HER2 re-expression.[15]

9. Conclusion

In summary, trastuzumab deruxtecan has redefined the therapeutic architecture of HER2-positive and HER2-low breast cancer, bridging the gap between traditional targeted therapy and chemotherapy. Its innovative design, durable efficacy, intracranial activity, and manageable toxicity profile establish it as a prototype for next-generation ADCs. The future landscape will depend on precision biomarker integration, combination immunotherapy, and early-stage disease incorporation. Together, these directions may usher in an era where HER2 status is viewed as a continuum of therapeutic opportunity rather than a binary label, ensuring broader access to targeted, effective, and patient-centered therapy.

10. Source of Funding

None.

11. Conflict of Interest

None.

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