Trastuzumab Deruxtecan for the Treatment of HER2-low Advanced or Metastatic Breast Cancer

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Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate widely used in human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC), based on the results of the DESTINY-Breast 01, 02 and 03 studies. The data show the efficacy of T-DXd in HER2-low (defined as HER2 expression of 1+, 2+ and ISH [in situ hybridization]-) breast cancer. The DESTINY-Breast04 trial, a randomized trial comparing T-DXd with the treatment of physician's choice (TPC) in pretreated MBC with low HER2 expression, showed higher efficacy for T-DXd than for TPC. Because of its landmark results, the DESTINY-Breast04 trial was simultaneously published in the *New England Journal of Medicine* when presented at the 2022 American Society of Clinical Oncology Annual Meeting. T-DXd is now being used for HER2-low-expressing breast cancer as the second-line treatment and beyond. The DESTINY-Breast06 trial, which evaluated the efficacy of T-DXd as the first-line treatment, has completed the enrolment and is awaiting results. This article reviews the findings on T-DXd in advanced recurrent breast cancer with low HER2 expression.

Keywords

Anti-HER2 antibody–drug conjugate, brain metastasis, breast cancer, HER2-low, metastatic breast cancer, trastuzumab deruxtecan

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Trastuzumab deruxtecan (T-DXd) is a novel human epidermal growth factor receptor 2 (HER2)-targeted antibody–drug conjugate (ADC) designed to effectively deliver a potent topoisomerase I inhibitor (exatecan derivative) to HER2-expressing cancer cells and limit potential systemic toxicity.[1] T-DXd has shown remarkable efficacy against recurrent HER2-positive breast cancer in many trials.[2–5] This payload, an exatecan derivative, is highly active among camptothecins and linked to the humanized anti-HER2 antibody by a peptide-based linker that is stable in the plasma and cleaved by lysosomal cathepsins, whose expression is increased in cancer cells.[6] After cleavage, the released drug is permeable to the cell membrane, allowing the released payload to have a bystander effect on the neighbouring tumour cells, regardless of the HER2 expression status.[7] The antitumour activity in HER2-low tumours may be due to the combination of the bystander effect and a high drug-to-antibody ratio of T-DXd.[7,8]

Efficacy and safety

In preclinical studies, T-DXd demonstrated antitumour activity in a variety of tumour types, including HER2-low tumours.[9,10] This finding led to clinical trials in HER2-low tumours. A phase I study of T-DXd determined the recommended extended dose and evaluated safety, tolerability and clinical activity in patients with advanced HER2-expressing (low or high) or HER2-mutated solid tumours.[10] A total of 54 patients with advanced breast cancer with low HER2 expression were enrolled and received at least one dose of 5.4 mg/kg (n=21) or 6.4 mg/kg (n=33) of T-DXd. The median duration of treatment in the overall population was 6.1 (range, 0.7–29.2) months, with no significant differences between treatment groups. The enrolled patients with HER2-low breast cancer were heavily pretreated, with 83.3% having received five or more prior therapies; 10 patients had received prior HER2-targeted therapy. Nine of these 10 patients had previous HER2-positive biopsies, and the most recent biopsy showed low HER2 levels. All patients had visceral disease at baseline (BL). The common metastatic sites were bones (63.0%), liver (53.7%) and lungs (25.9%). The majority of patients (87.0%) were hormone receptor (HR)-positive. Based on the local assessment of the target tumours, HER2 expression was immunohistochemically (IHC) 1+ in 51.9% of patients and IHC 2+ in 48.1% of patients. When target tumours were evaluated retrospectively at a central laboratory, HER2 expression was IHC 0 in 5 of 54 (9.3%), IHC 1+ in 30 of 54 (55.6%) and IHC 2+ in 14 of 54 (25.9%) patients. For five patients, tissue samples were either not submitted or not available at the central institution. The concordance rate was 70.8% for IHC 1+ and 40.0% for IHC 2+.[10]

A study was conducted in Japan to evaluate the effect of T-DXd on the QT/QTc (corrected QT) interval and pharmacokinetics. T-DXd at a concentration of 6.4 mg/kg was intravenously administered on day 1 of each 21-day cycle.[8] The primary endpoints were the QTcF (Fridericia corrected QT) interval and pharmacokinetic parameters. The secondary endpoints were safety events, serum concentrations of T-DXd and deruxtecan during electrocardiography measurements and antitumour activity parameters. Of the total 51 patients, 47 (92.2%) had HER2-low breast

cancer (IHC 1+ or 2+ and *in situ* hybridization negative/unidentifiable/deleted). The QT interval and concentration of T-DXd or deruxtecan analysis showed no clinically meaningful QTcF prolongation (change from the baseline (BL) of >10 ms) after the administration of 6.4 mg/kg of T-DXd. Antitumour activity was assessed with the efficacy analysis set (n=51), with an overall response rate (ORR) of 37.0% confirmed by an independent central review and 44.4% by investigator-reported ORR. The median duration of response (DoR) was 10.4 months, the median progression-free survival (PFS) was 11.1 months and the median overall survival (OS) was 29.4 months (95% confidence interval [CI]: 12.9–29.4).[11]

These findings led to the DESTINY-Breast04 trial (A Phase 3, Multicenter, Randomized, Open-label, Active Controlled Trial of DS-8201a, an Anti-HER2-antibody Drug Conjugate (ADC), Versus Treatment of Physician's Choice for HER2-low, Unresectable and/or Metastatic Breast Cancer Subjects; ClinicalTrials.gov identifier: NCT03734029), which was a global, randomized, open-label phase III trial of T-DXd in advanced recurrent breast cancer with low HER2 expression.[12] In this study, 557 patients with advanced breast cancer who had received one to two lines of prior chemotherapy and were centrally adjudicated to have low HER2 expression were randomized to receive either T-DXd (5.4 mg/kg every 3 weeks) or treatment of physician's choice (TPC; capecitabine, eribulin, gemcitabine, paclitaxel and nab-paclitaxel) in a 2:1 ratio. Low HER2 expression was defined as IHC 2+/ISH- or IHC 1+. The enrolment of patients with negative HR was capped at 11%, reflecting the distribution of the metastatic breast cancer (MBC) population. The primary endpoint was PFS in patients with positive HR by blinded, independent, central adjudication; key secondary endpoints were PFS in all randomized patients, OS in patients with positive HR and OS in all randomized patients; other endpoints were ORR, DoR, PFS and safety. An efficacy analysis was also performed in patients with negative HR.[12] The study randomized 373 patients (88.7% HR-positive) into T-DXd and 184 (88.6%) into TPC. In the TPC group, 51.1% used eribulin, 20.1% used capecitabine, 10.3% used nab-paclitaxel, 10.3% used gemcitabine and 8.2% used paclitaxel. At the data cut-off median follow-up period of 18.4 months, 58 patients in the T-DXd group and 3 patients in the TPC group were still receiving study treatment. Results showed that the primary endpoint of the median PFS in patients with positive HR was 10.1 months in the T-DXd group and 5.4 months in the TPC group, with a hazard ratio of 0.51 (95% CI: 0.40–0.64, p<0.0001). The median PFS for all randomized patients was 9.9 months in the T-DXd group and 5.1 months (95% CI: 4.2–6.8) in the TPC group, with a hazard ratio of 0.50 (95% CI: 0.40–0.63), p<0.0001, which was significantly longer in the T-DXd group.[12] The median OS for patients with positive HR was 23.9 months in the T-DXd group and 17.5 months (95% CI: 15.2–22.4) in the TPC group, with a hazard ratio of 0.64 (95% CI: 0.48–0.86), p=0.0028, which was significantly longer in the T-DXd group. The median OS for all patients was 23.4 months in the T-DXd group and 16.8 months in the TPC group, with a hazard ratio of 0.64 (95% CI: 0.49–0.84), p=0.0010, which was significantly longer in the T-DXd group. The median PFS in patients with negative HR was 8.5 months in the T-DXd group and 2.9 months in the TPC group, with a hazard ratio of 0.46 (95% CI: 0.24–0.89). In patients with positive HR, the confirmed ORR was 52.6% in the T-DXd group and 16.3% in the TPC group, and the median DoR was 10.7 months in the T-DXd group and 6.8 months in the TPC group. While in patients with negative HR, the confirmed ORR was 50.0% in the T-DXd group and 16.7% in the TPC group, the median DoR was 8.6 months in the T-DXd group and 4.9 months in the TPC group.[12]

During drug administration, grade 3 or higher adverse events were observed in 53% of the T-DXd treatment group and 67% of the TPC group.[12] The median duration of treatment was 8.2 months for the T-DXd group and 3.5 months for the TPC group. The most common treatment-emergent adverse events (TEAEs) related to treatment discontinuation were interstitial lung disease (ILD)/pneumonia for the T-DXd group (8.2%) and peripheral sensory neuropathy for the physician's choice group (2.3%). Based on independent adjudication, drug-related ILD/pneumonia was observed in 45 patients (12.1%) in the T-DXd treatment group, with 10.0% classified as grade 1 or 2, 1.3% as grade 3 and 0.8% as grade 5. No new safety concerns were identified.[12] Detailed safety data were reported at European Society for Medical Oncology (ESMO) Breast Cancer 2023.[13] In the exposure-adjusted incidence rate comparison, TEAEs were 1.30 in the T-DXd group and 2.66 in the TPC group for any-grade patients and 0.69 in the T-DXd group and 1.82 in the TPC group for patients with grade ≥3. The number of patients who underwent dose reduction due to nausea and vomiting was 17 (4.6%) and 3 (0.8%) in the T-DXd group and 4 (2.3%) and 1 (0.6%) in the TPC group, respectively. The incidence of any-grade drug-related neutropaenia and febrile neutropaenia was lower in the T-Dxd group compared with the TPC group, and the subsequent granulocyte colony-stimulating factor use was 6.7 and 19.8%, respectively.[13]

The results of a subgroup analysis of the DESTINY-Breast04 trial were reported at ESMO Breast Cancer 2023 to determine whether T-DXd is equally effective in patients with low oestrogen receptor (ER) expression.[14] Low ER expression was defined as the presence of 1–10% ER-positive cells by the IHC method. The data cutoff was 11 January 2022. Overall, 35 of the 52 patients with low ER levels were randomized to the T-DXd group and 17 to the TPC group, and patients with low ER expression tended to be more likely to have received CDK (cyclin-dependent kinase)4/6 inhibitors, to have received only one line of overall therapy and to have had liver metastases at BL. The median PFS in patients with low ER expression was 8.4 months (95% CI: 5.6–12.2) in the T-DXd group and 2.6 months (95% CI: 1.2–4.6) in the TPC group, with a hazard ratio of 0.24 (95% CI: 0.12–0.48). The median OS was 20.0 months (95% CI: 13.5-not estimable) in the T-DXd group and 10.2 months (95% CI: 7.8–14.5) in the TPC group, with a hazard ratio of 0.35 (95% CI: 0.16–0.75). The confirmed ORR in patients with low ER expression was 57.1% (95% CI: 39.4–73.7) in the T-DXd group and 5.9% (95% CI: 0.1–28.7) in the TPC group, with efficacy similar to that in patients with negative ER. The safety profile in patients with low ER expression was generally consistent with the results obtained in the main analysis.[14]

The updated (median 32 months) OS, PFS and safety results from the DESTINY-Breast04 trial were presented at ESMO Congress 2023.[15] The median OS was 23.9 months in the T-DXd group and 17.6 months in the TPC group in the HR-positive cohort with a hazard ratio of 0.69 (95% CI: 0.55–0.87) and 22.9 months versus 16.8 months for all patients with a hazard ratio of 0.69 (95% CI: 0.55–0.86), and the median PFS for HR-positive and all patients was significantly improved in the T-DXd group. The median PFS by physician was 9.6 months in the T-DXd group and 4.2 months in the TPC group in the HR-positive cohort, with an HR of 0.37 (95% CI: 0.30–0.46), and 8.8 months versus 4.2 months for all patients, with an HR of 0.36 (95% CI: 0.29–0.45). The T-DXd group showed a significant improvement. As an exploratory analysis, the median OS in patients with negative HR was 17.1 months in the T-DXd group and 8.3 months in the TPC group, with an HR of 0.58 (95% CI: 0.31–1.08), and the median PFS by the investigator was 6.3 months versus 2.9 months, with an HR of 0.29 (95% CI: 0.15–0.57).[15] The incidence of TEAEs of grade 3 or higher was 54.4% in the T-DXd group and 67.4% in the TPC group. The most common treatment discontinuation-related TEAEs were ILD/pneumonia (10.2%) in the T-DXd group and peripheral sensory neuropathy (2.3%) in the TPC group. The most common weight

loss-related TEAEs were nausea (4.6%) and thrombocytopaenia (3.0%) in the T-DXd group and neutropaenia (10.5%) and hand–foot syndrome (5.2%) in the TPC group, with a safety profile similar to the results of the initial analysis. There were no new reports of drug-related ILD/pulmonary inflammation since the initial analysis.[15]

Patient-reported outcomes

An analysis of patient-reported outcomes (PROs) in the DESTINY-Breast04 trial has been reported at the ESMO Congress 2022.[16] PRO was measured using quality-of-life questionnaires (QLQ) from the European Organization for Research and Treatment of Cancer (EORTC) and EuroQol (EQ) group: EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D-5L questionnaires every cycle up to cycle 3, every two cycles thereafter, 40 days and 3 months after the treatment completion.[17,18] The change from BL and time to definitive deterioration (TDD) were assessed. Worsening was defined as an increase of 10 or more points. The HR-positive cohort consisted of 331 patients in the T-DXd group and 163 in the TPC group. The median age was 56.8 versus 55.7 years, about 58% of patients in both groups had IHC 1+ and about 70% were pretreated with CDK4/6i. Both groups had a questionnaire compliance rate of >92% at BL and >80% for cycles 2–27. The mean GHS (global health status) scores at BL were 36.3 ± 21.8 in the T-DXd group and 37.8 ± 22.5 in the TPC group. The mean change in GHS/QOL (quality of life) on the QLQ-C30 remained stable (±10 points) through 27 cycles in the T-DXd group and 13 cycles in the TPC group. For fatigue, the QLQ-C30 score change remained stable at <10 points throughout all cycles of treatment in both groups. For nausea, the T-DXd group had an increase in score of <10 points in the early cycles, and the score decreased and remained stable after cycle 7. The median TDD for GHS/QOL was 11.4 months in the T-DXd group and 7.5 months in the investigator's choice group (hazard ratio [HR]: 0.69, 95% CI: 0.52–0.92, p=0.0096), and TDD was longer for T-DXd in all pre-specified QLQ-C30 subscales except nausea, with a median TDD for pain of 16.4 months in the T-DXd group and 6.1 months in the investigator's choice group (HR: 0.40, 95% CI: 0.30–0.54, p<0.0001).[16]

Biomarker

An exploratory biomarker analysis of BL samples of HER2-low, HR-positive MBC patients from the DESTINY-Breast04 trial is reported at the 2023 American Society of Clinical Oncology Annual Meeting.[19] Biopsy specimens collected from 326 patients after pretreatment were analyzed using RNA sequencing to estimate intrinsic subtypes from PAM50 (prediction analysis of microarray 50) gene expression, *ESR1* (estrogen receptor 1) and *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutations and known genetic alterations associated with resistance to CDK4/6 inhibitor, evaluated in 414 BL circulating tumour DNA (ctDNA) samples by Guardant OMNI™ (Guardant Health, Redwood City, CA, USA). Associations with ORR and PFS were evaluated. The results showed that the frequency of BL intrinsic subtype in the T-DXd and TPC groups were 41.3 and 46.6% for luminal A, 48.0 and 37.9% for luminal B and 9.0 and 11.7% for HER2 enriched in the T-DXd and TPC groups, respectively. The ctDNA results for the T-DXd and TPC groups showed that *ESR1* mutations were detected in 51.3 and 54.0%, *PIK3CA* mutations in 36.1 and 41.6% and at least one CDK4/6 inhibitor resistance marker in 71.5 and 70.2%. The improved efficacy of T-DXd was independent of the intrinsic subtypes (luminal A, luminal B and HER2 enriched), the presence of *ESR1* mutation, *PIK3CA* mutation and CDK4/6i resistance markers.[19]

The DAISY study (Phase II, Open Label Study of DS-8201a, an Anti-HER2-antibody Drug Conjugate [ADC] for Advanced Breast Cancer Patients, With Biomarkers Analysis to Characterize Response/Resistance to Therapy; ClinicalTrials.gov identifier: NCT04132960) was a multicentre, open-label, phase II trial that evaluated the efficacy of T-DXd in breast cancer with metastases in three groups: high-HER2 expression group (IHC 3+ or IHC 2+/ISH+), low-HER2 expression group (IHC 2+/ISH- or IHC 1+) and HER2-negative group (IHC 0), and a biomarker analysis was performed.[20] T-DXd uptake into tumour cells was analysed by multiplex assay (HER2, T-DXd, gamma-H2AX and pan-CK) and IHC staining of 10 paired tumour biopsy tissue samples before and during treatment (2–4 days). T-DXd was taken up even in HER-low cells but not in HER-zero. T-DXd uptake was shown to be moderately correlated with HER2 expression level (r=0.75, p=0.053). The spatial distribution of HER2 was classified into seven clusters by cluster analysis using an artificial intelligence (AI)-based unsupervised learning algorithm (k-means) from pretreatment tissue slide images of HER2-high (61 cases), with one cluster significantly associated with no response to T-DXd (p=0.0008). The spatial distribution of HER2 was classified into eight clusters by cluster analysis using k-means from pretreatment tissue slide images of HER2-high (61 cases), with one cluster significantly associated with no response to T-DXd. This cluster was characterized by low HER2 staining (median 0.19; interquartile range: 0.10–0.47) and moderate cell density. Using this model, 65 HER2 pathology slides in cohort 2 (HER2-low MBC) were analyzed, and there was no significant association with T-DXd efficacy. The immune effects of T-DXd were explored by the fluorescence multiplex assay (cluster of differentiation [CD]3, CD4, CD8, CD68, FoxP3 [forkhead box P3], PD-1 [programmed cell death 1], PD-L1 [programmed cell death ligand 1] and cytokeratin [CK]/Sry-related HMG box10 [SOX10]) using 31 paired tumour biopsy tissue samples before and during treatment (22–43 days). T-DXd treatment resulted in a significant decrease in PD-L1 expression only in 18 patients with high HER2 expression. However, PD-L1 expression was not reduced in 10 patients with low HER2 and 3 patients with zero HER2 expression. No T-cell or macrophage modulation was observed in any of the three cohorts. The mechanism of secondary resistance was investigated by IHC in 25 paired tumour tissue samples at BL and at progression, and 13 of 25 patients showed decreased HER2 expression at progression. *SLX4* mutations were detected in 4 of 20 (20%) samples at disease progression; two were undetected in BL samples and two had no BL samples. SLX4 loss of function has been considered as one of the possible mechanisms of resistance to T-DXd.[20]

Effect on brain metastases

The efficacy of T-DXd for brain metastatic lesions in HER2-positive breast cancer has been reported in several cases.[21–23] However, the effect of T-DXd on brain metastases (BM) in breast cancer with low HER2 expression has been less well reported. Preclinical studies using PDX (patient-derived xenograft) models have shown that T-DXd inhibits tumour growth and prolongs the survival in PDX models of HER2-low breast cancer BM.[24]

The DEBBRAH trial (Multicenter, Open-Label, Single-Arm, Multicohort Phase II Clinical Trial of Trastuzumab Deruxtecan [DS-8201a] in Human Epidermal Growth Factor Receptor 2 HER2+ Advanced Breast Cancer With Brain Metastases and/or Leptomeningeal Carcinomatosis; ClinicalTrials.gov identifier: NCT04420598) is a multicentre, open-label, five-cohort, open-comparison phase II trial evaluating the efficacy and safety of T-DXd in patients with HER2-positive and HER2-low MBC with BM and/or a history of leptomeningeal carcinomatosis (LMC).[25] Thirty-nine patients were enrolled in five cohorts: (1) HER2-positive MBC with non-progressive BM after radiation therapy and/or surgery, (2) HER2-positive or HER2-low MBC with asymptomatic untreated BM, (3) HER2-positive MBC with progressive BM after local treatment, (4) HER2-low MBC with progressive BM after local therapy and (5) HER2-positive or HER2-low

MBC with LMC. The primary endpoint for cohorts 2 and 4 was the intracranial overall response rate (ORR-IC) with Response Assessment in Neuro-Oncology-BM. [26] Six and seven patients were assigned to cohorts 2 and 4.[25] One patient with LMC included in cohort 4 was excluded from the analysis. The ORR-IC for cohort 2 was 66.7% (four of six patients had intracranial partial response [PR], 95% CI: 22.3–95.7). In cohort 4, ORR-IC meeting the primary endpoint was 33.3% (two of six intracranial PR; 95% CI: 4.3–77.7; p=0.033). Overall, ORR-IC in all patients was 50% (6 of 12; 95% CI: 21.1–78.9) and clinical benefit rate (CBR) was 66.7% (8 of 12; 95% CI: 34.9–90.1). Combining patients with measurable intracranial or extracranial lesions in cohorts 2 and 4, the ORR, CBR and median DoR were 41.7% (5 of 12; 95% CI: 15.2–72.3), 50.0% (6 of 12; 95% CI: 21.1–78.9) and 7.2 months (95% CI: 2.5–16.4). The median PFS for these patients was 5.7 months (95% CI: 4.7-not estimable).[27]

A subgroup analysis of patients with BM at BL in the DESTINY-Breast04 trial was reported at ESMO Congress 2023.[28] The median PFS for patients with HER2-low MBC with investigator-assessed BM at BL was 8.1 months for T-DXd and 4.8 months for TPC (hazard ratio, 0.71; 95% CI: 0.28–1.80). This exploratory study examined serial brain scans of all patients with asymptomatic BM at BL (35 [24 T-DXd and 11 TPC]) evaluated in the blinded independent central review (BICR) of the DESTINY-Breast04 trial. Confirmed intracranial ORR, CBR and disease control rate were 25.0, 58.3 and 75.0% for the T-DXd group, respectively, versus 0, 18.2 and 63.6% for the TPC group. The median central nervous system PFS for patients treated with T-DXd was 9.7 months, and the median OS was 16.7 months. Although only a small number of patients were included in this exploratory study, the intracranial efficacy data suggest a benefit of T-DXd compared with TPC.[28]

DESTINY-Breast06

DESTINY-Breast06 is a multicenter, randomized, open-label, phase III trial comparing T-DXd versus physician's choice of chemotherapy for patients with HER2-low-expressing HR-positive MBC who are chemotherapy-naïve as advanced or recurrent therapy and had progressed on endocrine therapies. Approximately 850 patients (low HER2, n=700; IHC >0 <1+, n=150) from approximately 300 sites worldwide will be randomized 1:1 to receive T-DXd 5.4 mg/kg every 3 weeks or the investigator's choice of chemotherapy (paclitaxel, nab-paclitaxel and capecitabine). The secondary endpoints are OS in the low HER2 and intent-to-treat (ITT; low HER2 and HER2 IHC >0 <1+) populations and PFS by BICR in the ITT population. Other secondary endpoints include ORR by BICR and investigator assessment, DoR by BICR and investigator assessment, PFS by investigator assessment in the low-HER2 population, safety, pharmacokinetics and PRO. In addition, the study features the primary endpoint of evaluating the efficacy and safety of T-DXd in patients with low HER2 levels as well as in the ultra-low IHC >0 <1+ (detectable HER2 staining <1+) patient population that would have previously been classified as HER2 0.[1]

Conclusions

T-DXd has dramatically changed the treatment of breast cancer, not only in patients with positive HER2 but also in patients with low HER2 expression. There are widespread debates as to whether T-DXd is an independent entity in HER2-low expression breast cancer.[29–31] There are some published data that both support and do not support this, and so far, no conclusion has been reached. However, as T-DXd can prolong the OS in patients with low HER2 expression, the clinical classification of HER2 in breast cancer has definitely changed with the introduction of HER2 low. ❑

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