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Exposure-response of Trastuzumab Deruxtecan (T-DXd) in Subjects With HER2-Low Metastatic Breast Cancer

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Objectives

- To evaluate the relationship between T-DXd pharmacokinetic exposure and efficacy endpoints in patients with HER2-low BC
- To evaluate the relationship between T-DXd pharmacokinetic exposure and safety endpoints in patients across tumor types including HER2-low BC

Conclusion

- Model-based E-R analyses support clinically meaningful efficacy (9.9-month median PFS and OS probability of 88% at 1 year) and acceptable and generally manageable safety profile at the 5.4 mg/kg T-DXd dose in HER2-low BC patients, consistent with approved dose of T-DXd in HER2-positive BC patients (5.4 mg/kg Q3W).
  - ✓ The E-R relationships for efficacy endpoints (OS and cORR) were shallow and not clinically relevant with ±6% estimated difference in OS probability at Day 360 over the extremes of T-DXd exposure (5th to 95th percentile) relative to OS probability of approximately 88% at median exposure.
  - ✓ ER relationships for safety across 10 clinical trials (phases 1-3) showed a positive correlation between T-DXd or DXd exposure and safety endpoints and comparable AE rates for 5.4 mg/kg dose in HER2-low and HER2-positive BC patients.
- Overall, these model-based analyses continue to support T-DXd 5.4 mg/kg Q3W dosing in patients with previously treated HER2-low BC.

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Introduction

- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate made up of 3 components: a humanized anti-HER2 IgG1 monoclonal antibody, a topoisomerase I inhibitor payload, and a tetrapeptide-based cleavable linker[1,2] .
- T-DXd is approved for adult patients with unresectable or metastatic HER2-positive or HER2-low breast cancer (BC), HER2-mutant NSCLC and HER2-positive gastric or gastroesophageal junction (GC or GEJ) adenocarcinoma based on the several phase 2 or phase 3 trials[3].
- Using data from 5 phase 1 and 2 clinical trials and 2 phase 3 trials, previous E-R analyses for key efficacy and safety endpoints supported the recommended dose of T-DXd 5.4 mg/kg once every three weeks (Q3W) in patients with HER2-positive BC[4,5] and an additional update to these analyses supported 6.4mg/kg Q3W dose in HER2-positive gastric or gastroesophageal junction (GC or GEJ) adenocarcinoma[6].
- An update to exposure-response analyses for T-DXd was performed including data from a large-scale, randomized, phase 3 clinical trial, DESTINY-Breast04 (DB-04) that evaluated the effectiveness and safety of T-DXd for use in patients with HER2-low BC[7].

Methods

Exposure-Efficacy Analyses

- Exposure-efficacy analyses were evaluated in 362 HER2-low BC patients, including 324 patients with Hormone Receptor (HR)-positive status, who were treated with T-DXd 5.4 mg/kg Q3W in DB-04 (Data Cutoff: 11 Jan 2022).
  - ✓ DB-04 was a phase 3, multicenter, randomized, open-label, active-controlled study of T-DXd versus treatment of physician's choice (TPC) in patients with HER2-low, unresectable and/or metastatic BC patients.
- Efficacy endpoints for exposure-efficacy analyses were PFS based on blinded independent central review (BICR) and OS, and confirmed ORR (cORR) based on BICR.
- PFS and OS were analyzed using a Cox proportional hazards model.
- The binary variable cORR was analyzed by linear logistic regression.
- T-DXd or DXd exposure metrics evaluated, included maximum serum concentration (Cmax), minimum serum concentration (Cmin) and area under the serum concentration curve (AUC) at Cycle 1 and steady-state, and the average serum concentration at the time of efficacy event (Cavg-TOE), and were calculated based on population PK model.
- Furthermore, patient-specific covariates (e.g., Age, sex, race, weight, race-country (Asian-Japan, Asian Non-Japan, Non-Asian), region (Asia, North American, Europe, Rest of World), baseline albumin, AST, total bilirubin, ECOG Performance score (0, ≥1), tumor size, baseline CNS or liver metastases, number of prior lines of therapy (chemotherapy or endocrine) in metastatic setting, HER2 IHC, HR status) were tested in the E-R relationships using a forward search at p<0.05 followed by a backward search at p<0.01 using the likelihood ratio test.

Exposure-Safety Analyses

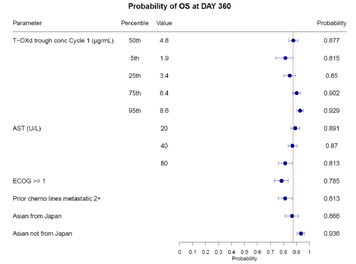
- Exposure-safety analyses were conducted using an integrated dataset across 10 phase 1 to 3 clinical trials (N=1675), including DB-04.
  - ✓ The analysis included data from patients with HER2-low and HER2-positive BC and other tumor types (NSCLC, GC or GEJ or others).
- Safety endpoints included any Grade ≥3 adverse events, Grade ≥3 anemia, Grade ≥3 neutropenia, and Grade ≥3 thrombocytopenia, any Grade and Grade ≥3 adjudicated drug-related ILD.
- ILD endpoints were analyzed by time-to-event Cox proportional hazards models and the rest of the endpoints were analyzed by logistic regression.
- T-DXd exposure metrics including Cmax and AUC at steady-state, and DXd average serum concentration to the time of safety event (Cavg-TOE) identified as significant in previous exposure-safety analyses were tested for correlation with safety endpoints, and were calculated based on population PK model.
- Furthermore, patient-specific covariates (e.g., demographics, disease and patient characteristics as included in efficacy analysis and baseline platelets (for thrombocytopenia), hemoglobin (for anemia), and neutrophils (for neutropenia), oxygen saturation, HER2 status) were tested in the E-R relationships.

Results

Exposure-Efficacy (EE) Analyses

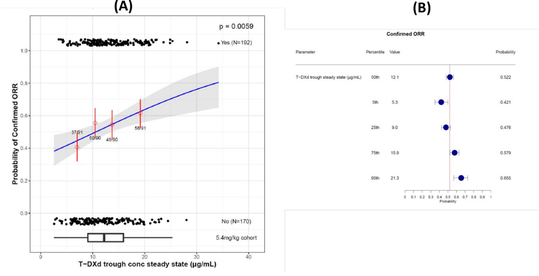
- 362 patients from DB-04 were included in the EE analyses (median age, 56 years; female, 99.4%). Patients were from Europe (42.0%), Asia (39.5%), North America (15.5%), and the rest of the world (3.0%) .
- For PFS in multivariate analysis in HER2-low BC HR-positive or in all HER2-low BC patients T-DXd was not a significant covariate, suggesting a flat exposure-response (E-R) relationship at 5.4mg/kg Q3W.
- T-DXd exposure (Cmin at Cycle 1) was a significant predictor for OS (P < 0.01) in all HER2-low BC patients; however, the OS E-R relationship was shallow and not clinically relevant, as the estimated difference in OS probability at Day 360 was small, with a range of approximately ±6% over the extremes of exposure (5th to 95th percentile) compared with the subjects with median exposure value who were estimated to have an OS probability of approximately 88% at Day 360.
  - ✓ OS was estimated to be shorter in patients with higher AST, ECOG PS ≥1, Asians from Japan, or those with ≥2 prior chemotherapy treatments (Figure 1).
- There was a significant (P < 0.01) relationship between increasing T-DXd Cmin,ss and cORR in HER2-low patients across the range of exposures at 5.4 mg/kg (Figure 2); however, the estimated differences in cORR probability were within ±14% over the extremes of exposure (5th to 95th percentile) compared to the median exposure, suggesting a shallow E-R relationship, which is not clinically meaningful.
  - ✓ No additional covariates were significant in multivariate analysis for cORR.
- HR status was not a significant predictor of any evaluated efficacy endpoint.
- Overall, these analyses support clinically meaningful efficacy (9.9-month median PFS and OS probability of 88% at 1 year and cORR 52.2% at median T-DXd exposure) across the entire exposure range with the T-DXd 5.4 mg/kg dose in HER2-low BC patients regardless of HR status.

Figure 1. Forest Plot Showing Covariate Effects on OS Probability at Day 360 in HER2-low BC (DB-04)



Dot and horizontal line corresponds to the probability estimate and 90% CI, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical patient (non-Asian, ECOG = 0, baseline AST of 34 IU/mL, <2 lines of prior chemotherapy in the metastatic setting) with indicated median T-DXd exposure for 5.4 mg/kg T-DXd of 4.8 µg/mL.

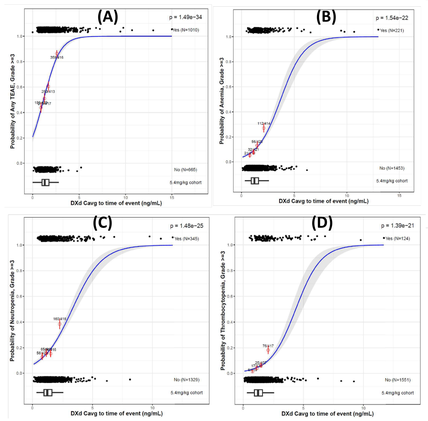
Figure 2. E-R Relationship for cORR (A) and Forest Plot Showing Covariate Effect on cORR (B) in HER2-low BC (DB-04)



conc = concentration; N = number of patients;
Note: Yes and No refer to if patients experienced or did not experience cORR. Patients are stratified into exposure quartiles. Red points and vertical bars are ORR (90% CIs) per exposure quartile. Gray band represents the 5th to 95th percentile CI of a linear logistic regression fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. Horizontal boxplot below shows the exposure distribution for the 5.4 mg/kg dose group.

CI = confidence interval; Dots and horizontal line corresponds to the probability estimate and 90% CI, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical patient with indicated median T-DXd exposure for 5.4 mg/kg T-DXd.

Figure 3. Exposure-Safety Relationships for Grade ≥3 adverse events (A), Grade ≥3 anemia (B), Grade ≥3 neutropenia (C), and Grade ≥3 thrombocytopenia (D)



Footnote (Figure 3). Plot shows probability of AE versus exposure. Yes and No refer to if patients experienced or did not experience AE. patients are stratified into exposure quartiles. Red points and vertical bars are AE rates (90% CI) per exposure quartile plotted at the median exposure of the quartile. Blue line is the linear logistic regression fit. Gray band represents the 5th to 95th percentile CI of the fit. The p-value is the significance level of the slope of the logistic regression fit using a z-test. The plot shows data for all dose groups. Horizontal boxplot below shows the exposure distribution for the 5.4 mg/kg dose group.

Figure 4. Cox Regression Fit for Any-Grade ILD (A) and Grade ≥3 ILD (B) E-S Analyses

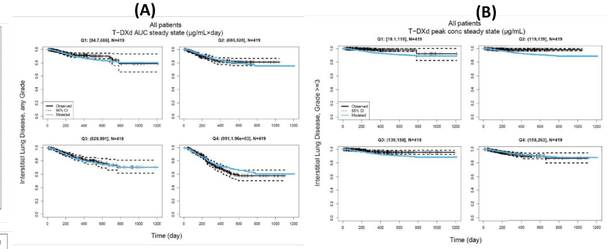
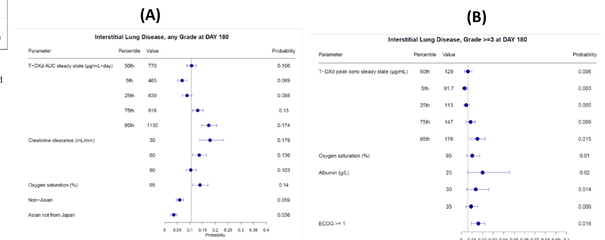


Figure 5. Covariate Effects for Any-Grade ILD (A) and Grade ≥3 ILD (B) Event Probability at Day 180



Footnote (Figure 5). Dot and horizontal line corresponds to the probability estimate and 90% CI, respectively, for 1000 simulated models incorporating parameter uncertainty. Vertical line corresponds to the model-predicted probability for a typical patient and the indicated median T-DXd exposure for T-DXd 5.4 mg/kg in the overall population including all tumor types. Typical patient for ILD Any grade (Asian from Japan, oxygen saturation of 98%, creatinine clearance of 87 mL/min) and Grade ≥3 ILD (ECOG performance status = 0, oxygen saturation of 98%, albumin = 40 g/L).

Exposure-safety (ES) Analyses

- The ES dataset comprised 1675 patients across 10 clinical trials, including
  - ✓ 1328 (79%) female and 347 (21%) male patients, 569 (34%) of whom were Asians from Japan, 337 (20%) were Asians from countries other than Japan, and 769 (46%) were non-Asians.
  - ✓ The median age was 58 years, and the median body weight was 60.0 kg.
  - ✓ Most patients had BC (67%), GC (17.5%) or NSCLC (11.9%).
  - ✓ Across tumor types, majority of patients were HER2-positive (55%), or HER2-low (22%, in BC only).
  - ✓ T-DXd doses in the range of 0.8 to 8 mg/kg
- The ES analyses showed statistically significant relationships between T-DXd exposure and ILD, and between DXd exposure (average concentration to the event time) and all other safety endpoints (Table 1 and Figure 3).
- For T-DXd, ILD is an adverse-event of special interest, For ILD, a statistically significant relationship (P < 0.001) was identified between increasing T-DXd exposures across all dose levels (0.8 to 8 mg/kg) and increasing hazard of any Grade and Grade ≥3 ILD (Figures 4 and 5).

Table 1. Significant Covariates and Exposure Metrics Identified in the ES Analyses

Safety Endpoint	Exposure Metric	Significant Covariates
Any TEAE, Grade ≥3	DXd Cavg to event time	Baseline albumin, tumor type, prior CDK4/6 treatment, baseline weight
Anemia, Grade ≥3	DXd Cavg to event time	Baseline hemoglobin, baseline weight, prior CDK4/6 treatment, tumor type, baseline CrCL, baseline total bilirubin, race-country
Neutropenia, Grade ≥3	DXd Cavg to event time	Baseline neutrophils, race-country, checkpoint therapy, baseline albumin
Thrombocytopenia, Grade ≥3	DXd Cavg to event time	Baseline CrCL, baseline platelets, race-country
Interstitial Lung Disease, Grade ≥3	T-DXd Cmax,ss	ECOG PS, oxygen saturation, baseline albumin
Interstitial Lung Disease, any grade	T-DXd AUCss	Baseline CrCL, race-country, oxygen saturation

- Findings for ILD and other safety endpoints were generally consistent with those of previous model-predicted rates of adverse events[4,5] .
- Model-predicted AE rates across all safety endpoints were similar (within ±5%) for T-DXd 5.4 mg/kg dose between HER2-low and HER2-positive BC.
- Modeled AE rates were similar (within ±5%) between patients from Europe and North America. Patients from Asia had a greater incidence of Grade ≥3 anemia, Grade ≥3 neutropenia, and Grade ≥3 thrombocytopenia relative to those from Europe or North America, with differences ranging from 1.0% to 13.1%.
- Higher bodyweight (>95th percentile; >89 kg) patients had higher T-DXd and DXd exposures (30% to 36% higher AUC) compared to typical patient; However, despite higher T-DXd or DXd exposures, high bodyweight patients had similar (<5% difference) predicted AE rates as the rest of patients, supporting T-DXd doses without any dose adjustment in heavier patients.

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Disclosures

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