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PHARMACOKINETICS OF TRASTUZUMAB DERUXTECAN (T-DXd) IN SUBJECTS WITH HER2-LOW METASTATIC BREAST CANCER

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Objectives

To update the previously developed PopPK model used for patients with HER2-positive breast cancer for T-DXd and DXd with pharmacokinetic (PK) data pooled from nine phase 1-3 clinical trials to:

- Update the established PopPK model for T-DXd and DXd with data from DB-04
- Evaluate the impact of potential covariates on the PK of T-DXd and DXd
- Estimate individual post hoc PK parameters used to derive exposure in subsequent exposure-response analyses
- Compare exposures among subpopulations of interest, including by HER2 status for BC subjects only, and by hepatic function, renal function, race-country and country for HER2 low BC subjects

Conclusion

T-DXd and DXd exposures were comparable across subjects with HER2-low and HER2-positive mBC, and across different hepatic and renal function, region, and race-country groups within HER2-low mBC, supporting the dosing recommendation of 5.4 mg/kg in HER2-low mBC from PK perspective.
With the newly incorporated HER2 low patients from DB-04 data, no new significant covariates in the popPK were identified and concentrations were similar to previous observed concentrations therefore HER2 low patients did not differentiate from HER2-positive patients.

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Introduction

T-DXd is an antibody-drug conjugate composed of an anti-human epidermal growth factor receptor 2 (HER2) antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload[1-3]
T-DXd is approved for the treatment of adults with:[4]

- Unresectable or metastatic HER2-postive breast cancer who previously received anti-HER2–based therapy
- Unresectable or metastatic HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/in-situ hybridization [ISH]-) breast cancer who previously received chemotherapy for metastatic disease or developed disease recurrence during or within 6 months of completed adjuvant chemotherapy
- Unresectable or metastatic non-small cell lung cancer (NSCLC) with activating ERBB2 (HER2) mutations who previously received systemic therapy
- Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma and who previously received trastuzumab-based therapy

The recommended dose of T-DXd is 5.4 mg/kg every 3 weeks (Q3W) in all approved indications, except for patients with HER2-positive gastric or gastroesophageal junction adenocarcinoma for whom the recommended dose is 6.4 mg/kg Q3W
Population PK (PopPK) analyses of T-DXd in patients with HER2-positive breast cancer and other solid tumors from phase 1 and 2 clinical trials have been previously published[5]
A large-scale, randomized, phase 3 clinical trial, DESTINY-Breast04 (DB-04) evaluated the effectiveness and safety of T-DXd for use in patients with HER2-low BC[6]

Methods

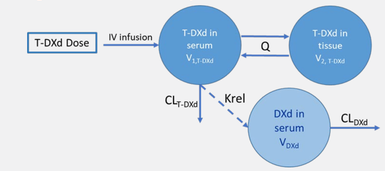
The analysis was performed using PK data from patients with HER2-expressing breast cancer or other solid tumors from four phase 1 studies (NCT02564900, NCT03366428, NCT03368196, NCT03383692), four phase 2 studies (DESTINY-Gastric01, DESTINYBreast01, DESTINY-Lung01, DESTINY-Gastric02), and two phase 3 studies (DESTINY-Breast03, DESTINY-Breast04)

- Compared with previous PopPK analyses, in the current analysis, data were added from DESTINY-Breast04
- Sparse sampling for serum T-DXd and DXd concentrations was collected from patients at least before and after the end of the infusion for up to 8 cycles across phase 2 and 3 studies. Intensive PK sampling was included in earlier phase 1 and 2 studies[5]
- All patients who received at least 1 dose of T-DXd and had 1 evaluable post-dose concentration of T-DXd or DXd were eligible for inclusion in the PopPK analysis

The PopPK analysis was performed with a nonlinear mixed-effects modeling approach using NONMEM (version 7.4.3) in which T-DXd and DXd were fitted sequentially

- Covariate effects from the previous PopPK analysis were retained in the model as pre-specified covariates unless diagnostic plots showed any indication for modification
- Additional candidate covariates were race, country (Mainland China, Hong Kong and Taiwan, Rest of World), region (Asia, North America, Europe, Rest of World), presence of ADA (Yes/No) and HER2 status (positive, negative, missing, other, mutant, HER2-low) for T-DXd.
- Creatinine clearance (CrCL), region, race, country and race-country (Asian from Japan, Asian not from Japan, non-Asian) were included in the DXd analysis.
- Significant candidate covariates ($P < 0.01$ based on univariate analysis of variance or linear regression of post hoc individual random effects and covariates) and prespecified covariates were included in the full covariate model, for which an interactive backward elimination procedure was used ($P > 0.001$)
- The effect of significant covariates was evaluated by use of univariate and multivariate analyses on steady state exposure of T-DXd and DXd

Figure 1. Structural PopPK model T-DXd and DXd



CLDXd = clearance of DXd; CLT-DXd = clearance of T-DXd; IV = intravenous; Krel = release rate constant; Q = distributional clearance for T-DXd; V1,T-DXd = central volume of T-DXd; V2,T-DXd = peripheral volume of T-DXd; VDXd = volume of DXd.

Results

Patients

Data from 1675 patients across the 10 studies were included, contributing 23,296 evaluable T-DXd concentrations and 23,245 evaluable DXd concentrations to the PopPK analysis

- T-DXd dose ranged from 0.8 mg/kg to 8.0 mg/kg across the studies
- 1128 patients (67.3%) including 362 (21.6%) patients from DB04 had breast cancer, 293 patients (17.5%) had gastric cancer, 199 patients (11.9%) had NSCLC, and 55 patients (3.3%) had other cancer types
- 919 patients (54.9%) were confirmed as HER2 positive (IHC 3+ or IHC 2+/ISH+) and 468 patients(27.9%) were HER2 low (IHC 1+ or IHC 2+/ISH-); the remaining patients (17.2%) had HER2 negative, mutant, overexpressing, or missing
- 575 patients (34.3%) had mild impairment in hepatic function and 6 patients (0.4%) had moderate impairment
- 646 patients (38.6%) had mild impairment in renal function, 251 (15.0%) had moderate impairment, and 4 (0.2%) had severe impairment
- Most patients in the pooled data set were female (79.3%), and the median age was 58.0 years
- 54.1% of the patients were Asian, 37.0% were White, 6.4% were other race, and 2.1% were African American
- Patients were included from the United States and several countries in Europe (45.8%), Japan (34.1%), and other Asian countries (20.1%)

PopPK final models for T-DXd and DXd

In the T-DXd model, the relative standard error (RSE) was <20% for all parameters and the RSE for between-patient variability of $CL_{T\text{-}DXd}$, $V_{1,T\text{-}DXd}$, $Q_{T\text{-}DXd}$, and $V_{2,T\text{-}DXd}$ was 2.1%, 1.9%, 4.3%, and 3.1%, respectively
Relationships between patient-specific covariates and T-DXd PK parameters are shown in **Equations 1-3**

- $CL_{T\text{-}DXd}$ and $V_{1,T\text{-}DXd}$ and $V_{2,T\text{-}DXd}$ were estimated at 0.410 L/d, 2.68 L, and 6.64 L, respectively

In the DXd model, the RSE was <22% for all parameters and the RSE for between-patient variability of CL_{DXd}, V_{DXd}, Krel, and fraction of Krel at cycle >1 was 3.6%, 2.6%, 3.6%, and 2.7%, respectively
Relationships between patient-specific covariates and DXd PK parameters are shown in **Equations 4-6**

- DXd elimination clearance was estimated at 19.6 L/h

Equation 1. Elimination Clearance of T-DXd

$$CL_{T\text{-}DXd} = 0.410\ L/d \times \left(\frac{Weight\ in\ kg}{57.8}\right)^{0.385} \times \left(\frac{Albumin\ in\ \frac{g}{L}}{40}\right)^{-0.480} \times \left(\frac{Tumor\ size\ in\ mm}{57}\right)^{0.0533}$$

(× 0.907, if Asian from Japan) (× 1.18, if GC) (× 1.10, if NSCLC and other cancer)

Equation 2. T-DXd Central Volume of Distribution

$$V_{1,T\text{-}DXd} = 2.68\ L \times \left(\frac{Weight\ in\ kg}{57.8}\right)^{0.430}$$

(× 1.10, if GC) (× 1.14, if male)

Equation 3. T-DXd Peripheral Volume of Distribution

$V_{2,T\text{-}DXd} = 6.64\ L$ (× 0.731, if Asian from Japan)

Equation 4. Elimination Clearance of DXd

$$CL_{DXd} = 19.6\ L/h \times \left(\frac{Weight\ in\ kg}{57.8}\right)^{0.316} \times \left(\frac{Total\ \ bilirubin\ in\ \frac{\mu mol}{L}}{8}\right)^{-0.147} \times \left(\frac{AST\ in\ \frac{U}{L}}{30}\right)^{-0.195}$$

(× 0.889, if itraconazole) (× 0.879, if ritonavir)

Equation 5. DXd Volume of Distribution

$$V_{DXd} = 17.0\ L/m^2 \times \text{Body surface area in } m^2 \times \left(\frac{Age\ in\ yr}{57}\right)^{0.630}$$

(× 1.58, if FL-DP2) (× 0.796, if NSCLC) (× 0.756, if non-Asian)

Equation 6. Release Rate Constant

$K_{rel} = 0.0196\ h^{-1} \times Cycle^{-0.158}$ (× 0.741, if Cycle >1)

Covariate effects on PK of T-DXd and DXd

The following covariates determined to be statistically significant in the previous PopPK models were retained in the updated PopPK models though only cancer type on DXd clearance was dropped from the original model:

- T-DXd: cancer type, tumor size, albumin, race-country, body weight, and sex
- DXd: age, cancer type, AST, total bilirubin, ritonavir or itraconazole use, race-country, formulation, and body weight

No new covariates were identified as statistically significant in this updated PopPK model

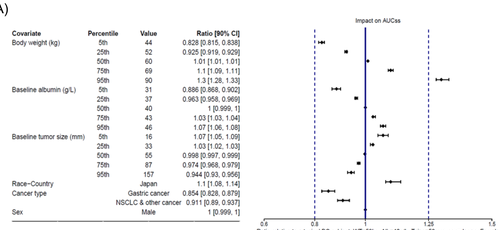
For both T-DXd and DXd area under the concentration-time curve at steady state (AUCss), most covariates effects were contained within the 0.8-1.25 exposure ratio interval relative to a reference subject with typical covariate values, suggesting there is no clinically meaningful effect of the covariates on AUCss (Figure 2)

- Subjects with low albumin (31 g/L; 5th percentile) had an approximately 21% lower Cmin,ss relative to a BC subject with an albumin value of 40 g/L. Subjects with extreme values of body weight (90 kg; 95th percentile) had a 27% higher Cmax,ss and a 30% higher AUCss relative to a BC subject with a weight of 59 kg; however, These differences in T-DXd or DXd exposures were not considered clinically meaningful based on exposure-response analyses.

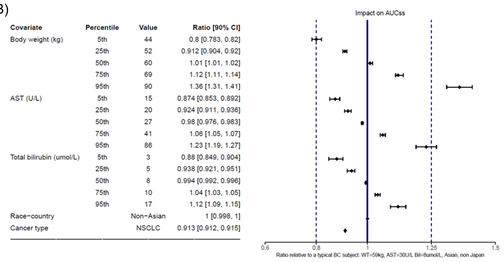
Post hoc exposure estimates of T-DXd and DXd after a dosing regimen of T-DXd 5.4 mg/kg Q3W in patients with HER2 low BC were similar to those in subjects with HER2-positive BC at the same dose (Figures 3). T-DXd exposure estimates in subjects with HER2 low BC were comparable across region, race-country, and subgroups of hepatic or renal function (Figures 4-7) .

Figure 2. Covariate Effects on AUCss of (A) T-DXd and (B) DXd

(A)



(B)



First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents the typical subject. Points and whiskers represent the median and 90% confidence interval, respectively. A typical subject is defined as a female, non-Japan with breast cancer, baseline body weight of 59 kg, albumin of 40 g/L and tumor size of 53 mm. Race-country group 'Asian not from Japan' was merged with 'non-Asian' to form a 'not from Japan' group for the T-DXd model. The 50th percentile may deviate slightly from 1 because median covariate values for a typical BC subject used as the reference differ from the covariate values used for standardization in the PopPK model.

Figure 3. Post Hoc Steady State (A) T-DXd and (B) DXd Exposure After Administration of T-DXd 5.4 mg/kg Q3W in Patients With Breast Cancer by HER2 Status

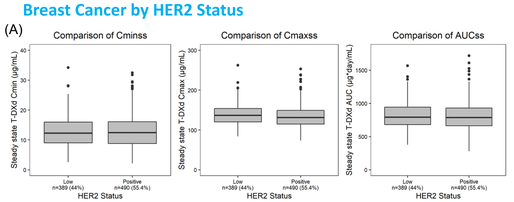


Figure 4. Post Hoc Steady State (A) T-DXd and (B) DXd Exposure After Administration of T-DXd 5.4 mg/kg Q3W in Patients With HER2 low Breast Cancer by Region

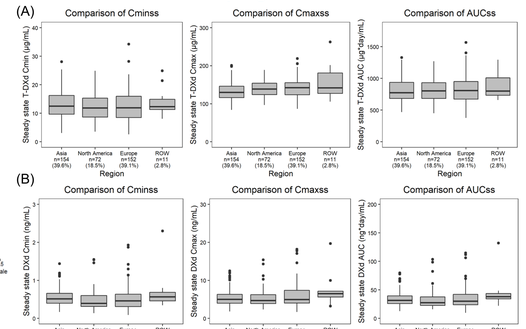


Figure 5. Post Hoc Steady State (A) T-DXd and (B) DXd Exposure After Administration of T-DXd 5.4 mg/kg Q3W in Patients With HER2 low Breast Cancer by Race-Country

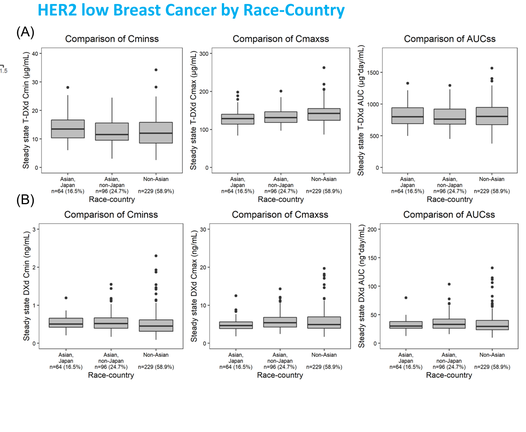


Figure 6. Post Hoc Steady State (A) T-DXd and (B) DXd Exposure After Administration of T-DXd 5.4 mg/kg Q3W in Patients With HER2 low Breast Cancer by Hepatic Function

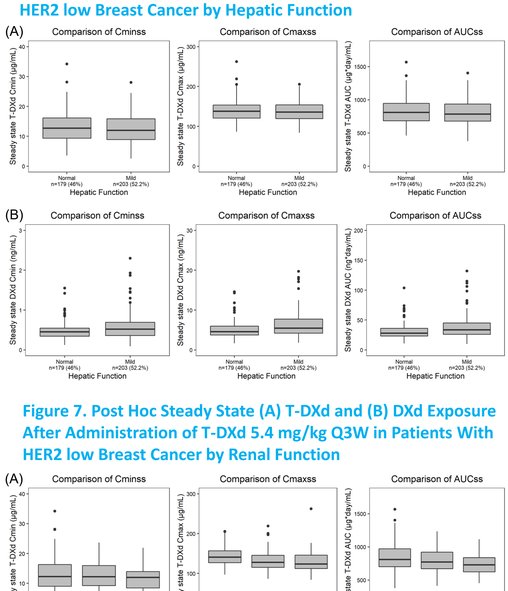
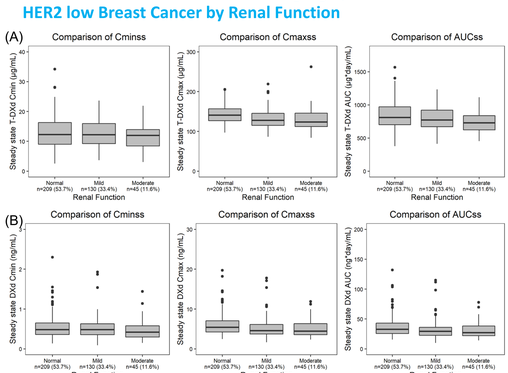


Figure 7. Post Hoc Steady State (A) T-DXd and (B) DXd Exposure After Administration of T-DXd 5.4 mg/kg Q3W in Patients With HER2 low Breast Cancer by Renal Function



Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers.

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Disclosures

Li. Li, E. Kamiyama, P. Vaddady, M. Abutarif, T. Garimella, and A. Khatri disclose employment by Daiichi Sankyo. . Zheng Lu is a former employee of Daiichi Sankyo.

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