PO3-04-01

Population Pharmacokinetics of Trastuzumab Deruxtecan (T-DXd) in HER2-Positive Breast Cancer Subjects: Analysis Across Twelve Phase 1-3 Studies

Claire Li,[1] Stefanie Hennig,[2] Kashyap Patel,[2] Katrina Hui,[2] Gerly van der Vleuten,[2] Malaz Abutarif,[1] Tushar Garimella,[1] Amit Khatri[1]

[1]Quantitative Clinical Pharmacology, Daiichi Sankyo, Basking Ridge, NJ, USA; [2]Certara, Inc, NJ, USA

Objectives

- The purpose of this analysis is to update the previously developed population pharmacokinetic (PopPK) model used for patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer for T-DXd and DXd (topoisomerase I inhibitor payload) with pharmacokinetic (PK) data pooled from twelve phase 1-3 clinical trials and to obtain model-based exposures for all patients to:
  - Update the established PopPK model for T-DXd and DXd with data from DESTINY-Breast02
  - 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
  - Assess exposure in subgroups of interest according to hepatic function, renal function, region, race-country, HER2 status, and line of therapy

Conclusions

- T-DXd and DXd exposure was similar for patients with breast cancer regardless of category of race-country, hepatic function, renal function, HER2 status (HER2+, HER2-low), region, or line of therapy after receiving the recommended dose of T-DXd 5.4 mg/kg every 3 weeks (Q3W); this is in line with previous results[5]

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials.

Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from SABCS® and the authors of this poster.

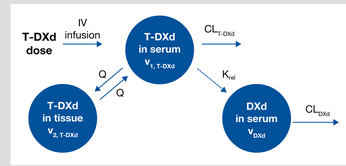
Introduction

- T-DXd is an antibody-drug conjugate composed of an anti-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-positive 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
- PopPK data of T-DXd in patients with HER2-positive breast cancer and other solid tumors from phase 1 and 2 clinical trials have been published[5]

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), five phase 2 studies (DESTINY-Gastric01, DESTINY-Breast01, DESTINY-Lung01, DESTINY-Gastric02, DESTINY-Lung02), and three phase 3 studies (DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast04)
  - Compared with previous PopPK analyses, in the current analysis, data were added from DESTINY-Breast02, a phase 3 study designed to assess T-DXd in patients with HER2-positive, unresectable and/or metastatic breast cancer who were previously treated with trastuzumab emtansine
  - 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 use of a nonlinear mixed-effects modeling approach using NONMEM (version 7.4.3; Icon) where T-DXd and DXd were fitted sequentially
  - Covariate effects were used from the previous PopPK analysis unless they were poorly estimated or the effect size was <10%
  - Additional candidate covariates were Eastern Cooperative Group performance status and presence of anti–T-DXd antibodies. Creatinine clearance was 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 for T-DXd and DXd[5]



Printed with permission from Yin O et al. *Clin Pharmacol Ther*. 2021;109:1314-1325. Published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

Results

Patients

- Data from 2216 patients across the 12 studies were included, contributing 29,000 evaluable T-DXd concentrations and 28,948 evaluable DXd concentrations to the PopPK analysis
  - T-DXd dose ranged from 0.8 mg/kg to 8.0 mg/kg across the studies
  - 1522 patients (68.7%) had breast cancer, 293 patients (13.2%) had gastric cancer, 346 patients (15.6%) had NSCLC, and 55 patients (2.4%) had other cancer types
  - 1313 patients (59.3%) were confirmed as HER2 positive (IHC 3+ or IHC 2+/ISH+) and 468 patients (21.1%) were HER2 low (IHC 1+ or IHC 2+/ISH–); the remaining 435 patients (19.6%) had HER2 IHC 0, *HER2*-mutant, HER2-overexpressing (HER2 IHC 3+ or 2+), or missing status
  - 811 patients (36.6%) had mild impairment in hepatic function and 10 patients (0.5%) had moderate impairment
  - 841 patients (38.0%) had mild impairment in renal function, 313 (14.1%) had moderate impairment, and 4 (0.2%) had severe impairment
  - 652 patients (29.4%) were on second-line therapy and 1202 (54.2%) were on third-line therapy
  - Most patients in the pooled data set were female (81.9%), and the median age was 57.0 years
  - 50.3% of the patients were Asian, 40.5% were White, 6.8% were other race, and 2.1% were African American
  - Patients were included from the United States and several countries in Europe (49.6%), Japan (30.1%), and other Asian countries (20.4%)

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 1.5%, 1.0%, 4.2%, and 2.8%, 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 0.402 L/d, 2.68 L, and 5.91 L, respectively
- In the DXd model, the RSE was <20% for all parameters and the RSE for between-patient variability of CL_{DXd}, V_{DXd}, K_{rel}, and fraction of K_{rel} at cycle >1 was 4.1%, 2.0%, 3.3%, and 2.2%, respectively
- Relationships between patient-specific covariates and DXd PK parameters are shown in **Equations 4-6**
  - DXd elimination clearance was estimated at 18.4 L/h

Equation 1. Elimination Clearance of T-DXd

$$CL_{T\text{-}DXd} = 0.402\ \text{L/d} \times \left(\frac{Weight\ in\ kg}{57.8}\right)^{0.395} \times \left(\frac{Albumin\ in\ g/L}{40}\right)^{-0.416} \times \left(\frac{Tumor\ size\ in\ mm}{57}\right)^{0.0565}$$

$$\times\ 0.926\ (\text{if Asian from Japan}) \times 1.20\ (\text{if GC}) \times 1.11\ (\text{if NSCLC})$$

Equation 2. T-DXd Central Volume of Distribution

$$V_{1,T\text{-}DXd} = 2.68\ \text{L} \times \left(\frac{Weight\ in\ kg}{57.8}\right)^{0.442} \times 1.13\ (\text{if GC}) \times 1.10\ (\text{if male})$$

Equation 3. T-DXd Peripheral Volume of Distribution

$$V_{2,T\text{-}DXd} = 5.91\ \text{L} \times 0.812\ (\text{if Asian from Japan})$$

Equation 4. Elimination Clearance of DXd

$$CL_{DXd} = 18.4\ \text{L/h} \times \left(\frac{Weight\ in\ kg}{57.8}\right)^{0.321} \times \left(\frac{Total\ bilirubin\ in\ \mu mol/L}{8}\right)^{-0.153} \times \left(\frac{AST\ in\ U/L}{30}\right)^{-0.176}$$

$$\times\ 0.894\ (\text{if itraconazole}) \times 0.883\ (\text{if ritonavir})$$

Equation 5. DXd Volume of Distribution

$$V_{DXd} = 17.0\ \text{L/m}^2 \times \text{body surface area in millimeters squared} \times \left(\frac{Age\ in\ yr}{57}\right)^{0.521} \times 1.39\ (\text{if FL-DP2})$$

$$\times\ 0.658\ (\text{if NSCLC}) \times 0.831\ (\text{if non-Asian})$$

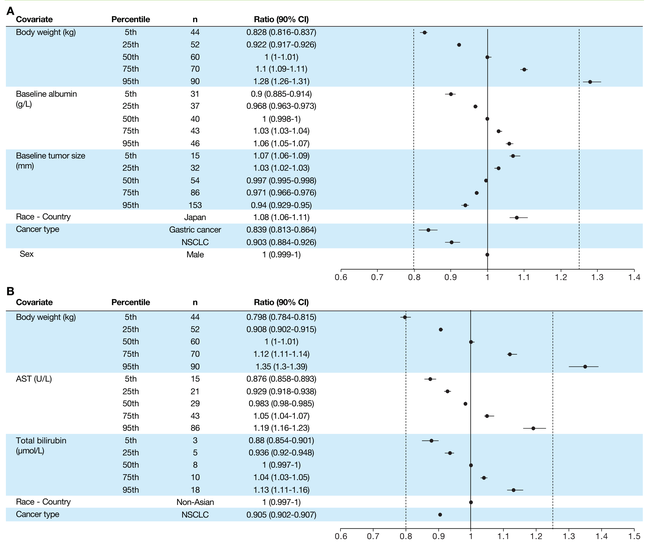
Equation 6. Release Rate Constant

$$K_{rel} = 0.0177\ \text{h}^{-1} \times \text{cycle}^{-0.137} \times 0.729\ (\text{if cycle} > 1)$$

Covariate effects on PK of T-DXd and DXd

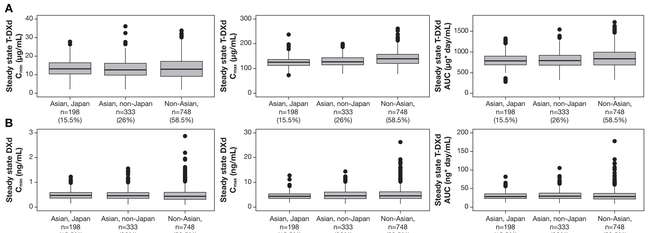
- The following covariates determined to be statistically significant in the previous PopPK models were retained in the updated PopPK models:
  - **T-DXd:** cancer type, tumor size, albumin, race-country, body weight, and sex
  - **DXd:** age, cancer type, AST, total bilirubin, ritonavir or itraconazole use, race-country, formulation, and body weight
- No new covariates were identified as statistically significant in this PopPK model after addition of DESTINY-Breast02 data
- For both T-DXd and DXd area under the concentration-time curve at steady state (AUC_{ss}), 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 AUC_{ss} (**Figure 2**)
  - In patients with high body weight (90 kg; 95th percentile), a 28% higher T-DXd AUCss and 35% higher DXd AUC_{ss} were detected relative to a typical patient with breast cancer and a median body weight of 60 kg; however, this difference was not clinically relevant to require a different dosing level
- Post hoc exposure estimates of T-DXd and DXd after a dosing regimen of T-DXd 5.4 mg/kg Q3W in patients with breast cancer were consistent across subgroups of race-country and hepatic function (**Figures 3,4**) and across subgroups of renal function, region, and line of therapy (data not shown); similarly, exposures were comparable in patients with HER2-positive and HER2-low status (**Figure 5**)

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



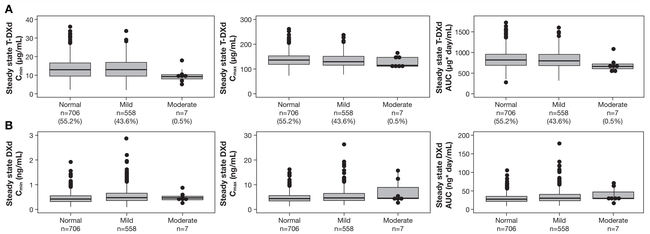
First and second dashed vertical lines correspond to ratios of 0.8 and 1.25, respectively. The solid vertical line corresponds to a ratio of 1 and represents a typical patient. Points and whiskers represent the median and 90% CI, respectively. The 50th percentile may deviate slightly from 1 because median covariates for the typical patient with breast cancer who is used as the reference are different from the covariate values used for standardization in the PopPK model; for T-DXd, a typical patient is defined as female, with breast cancer and not from Japan, and having a baseline body weight of 60 kg, albumin of 40 g/L, and tumor size of 51 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; for DXd, a typical patient is defined as Asian, with breast cancer and not from Japan, and having a baseline weight of 60 kg, AST level of 32 U/L, and total bilirubin level of 8.0 µmol/L.

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 Race-Country



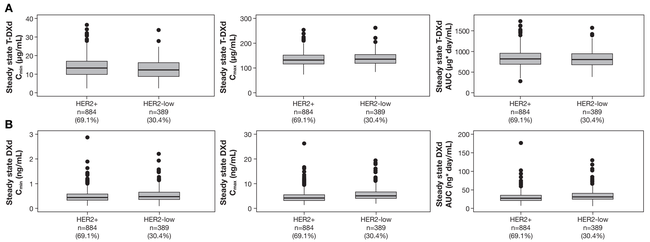
Boxes show the median and interquartile range of data. Whiskers represent the extent of data within 1.5 times the interquartile range. Points represent data outside the whiskers.

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 Breast Cancer by Hepatic 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 or all individual data for moderate hepatic impairment. Hepatic function was categorized using the NCI ODWG criteria.[6]

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 Breast Cancer by HER2 Status



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. HER2+ is defined as IHC 3+ or IHC 2+/ISH+, HER2-low is defined as IHC 1+ or IHC 2+/ISH- (5 patients who had HER2 ICH 0 status are not shown).

Abbreviations

AST, aspartate aminotransferase; AUC, area under the serum concentration-time curve; AUC_{ss}, area under the serum concentration-time curve at steady state; C_{max}, maximum serum concentration; $C_{max,ss}$, maximum serum concentration at steady state; C_{min}, minimum serum concentration; $C_{min,ss}$, minimum serum concentration at steady state; CL_{DXd}, elimination clearance of DXd; $CL_{T\text{-}DXd}$, elimination clearance of T-DXd; DXd, released payload; FL-DP2, frozen liquid drug product 2; GC, gastric cancer; K_{rel}, release rate constant; NCI, National Cancer Institute; NSCLC, non–small cell lung cancer; ODWG, Organ Dysfunction Working Group; Q, distributional clearance; $Q_{T\text{-}DXd}$, distributional clearance of T-DXd; Q3W, every 3 weeks; SE, standard error; T-DXd, trastuzumab deruxtecan; V_{DXd}, volume of DXd distribution; $V_{1,T\text{-}DXd}$, T-DXd central volume of distribution; $V_{2,T\text{-}DXd}$, T-DXd peripheral volume of distribution.

References

1. Nakada T et al. *Chem Pharm Bull*. 2019;67:173-185.
2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108.
3. Trail P et al. *Pharmacol Ther*. 2018;181:126-142.
4. ENHERTU (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Prescribing information. Daiichi Sankyo; 2022.
5. Yin O et al. *Clin Pharmacol Ther*. 2021;109:1314-1325.
6. Mansfield A et al. *Clin Cancer Res*. 2016;22(22):5472-5479.

Acknowledgments

We thank the patients who participated in the studies, as well as their families and caregivers. This study is sponsored by Daiichi Sankyo, in collaboration with AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for T-DXd (DS-8201). Under the guidance of authors, medical writing and editorial support was provided by Andre Wang, PharmD, and Sara Duggan, PhD, of ApotheCom and funded by Daiichi Sankyo, Inc.

Disclosures

Dr. Claire Li is an employee of Daiichi Sankyo Inc.

Poster presented at the San Antonio Breast Cancer Symposium (SABCS) Annual Meeting; December 5-9, 2023; San Antonio, Texas