Population Pharmacokinetic Analysis of DS-8201a ([Fam-] Trastuzumab Deruxtecan), a HER2-Targeting Antibody-Drug Conjugate, in Patients with HER2-Positive Breast Cancer or Other Solid Tumors

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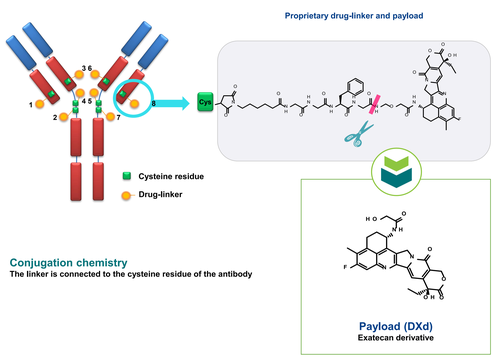
BACKGROUND

- [Fam-] trastuzumab deruxtecan (DS-8201a) is a novel human epidermal growth factor receptor 2 (HER2)-targeting antibody-drug conjugate with a humanized anti-HER2 antibody, a proprietary cleavable peptide-based linker, a potent topoisomerase I inhibitor payload (DXd) and a high drug-to-antibody ratio of approximately 8 (**Figure 1**)[1]
- [Fam-] trastuzumab deruxtecan is currently in clinical development for the treatment of patients with HER2-positive, locally advanced or metastatic breast cancer who have been previously treated with ado-trastuzumab emtansine (T-DM1)[2-4]
- Studies evaluating the safety and efficacy of [fam-] trastuzumab deruxtecan in HER2-expressing advanced gastric or gastroesophageal junction adenocarcinoma,[5,6] HER2-positive or -mutated, unresectable and/or metastatic non-small cell lung cancer,[7,8] and HER2-expressing advanced colorectal cancer are also ongoing[9,10]

FIGURE 1. Structure of [fam-] trastuzumab deruxtecan



OBJECTIVE

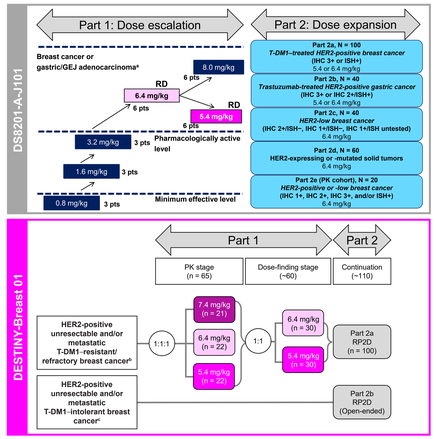
- To characterize population pharmacokinetics (PK) of [fam-] trastuzumab deruxtecan and payload in patients with HER2-positive breast cancer or other HER2-expressing solid tumors

METHODS

Data Source and Study Design

- Interim data from the first-in-human study in patients with advanced solid tumors (DS8201-A-J101),[5,11] and the phase 2 study in HER2-positive breast cancer patients (DS8201-A-U201, DESTINY-Breast01),[2] were included (**Figure 2**)
  - 232 patients from DS8201-A-J101; [fam-] trastuzumab deruxtecan doses ranged from 0.8 to 8.0 mg/kg every 3 weeks (Q3W), in the forms of frozen liquid drug product 1 (FL-DP1) and frozen liquid drug product 2 (FL-DP2)
  - 46 patients from DESTINY-Breast01; [fam-] trastuzumab deruxtecan doses were 5.4, 6.4, or 7.4 mg/kg Q3W, in the form of FL-DP2
- In both studies, relatively dense PK samples were collected after the first dose in cycle 1, and sparse samples were collected in subsequent cycles
- Serum concentrations of intact [fam-] trastuzumab deruxtecan were determined by a validated electrochemiluminescence assay, with lower limit of quantification (LLOQ) of 400 ng/mL
- Serum concentrations of payload were determined by a liquid chromatography-tandem mass spectrometry method, with LLOQ of 0.01 ng/mL

FIGURE 2. Study design for DS8201-A-J101 and DESTINY-Breast01 studies

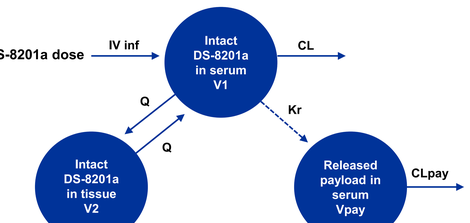


[a]Patients in Part 1 of DS8201-A-J101 were not required to have HER2-positive tumors.[b]HER2-positive is defined as IHC 3+ or IHC2+/ISH-positive and confirmed by a central laboratory for DESTINY-Breast01.
GEJ, gastro-esophageal; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PK, pharmacokinetic; pts, patients; RD, recommended dose for dose expansion; RP2D, recommended phase 2 dose; T-DM1, ado-trastuzumab emtansine.

Population PK Analysis

- Serum concentration data of intact [fam-] trastuzumab deruxtecan and the payload were analyzed using nonlinear mixed effects modeling (NONMEM version 7.3, ICON Development Solutions, Ellicott City, MD), with a sequential 2-step approach as follows:
  - PK profiles of intact [fam-] trastuzumab deruxtecan were fitted to the model first
  - PK parameter estimates including the fixed and random-effects terms of [fam-] trastuzumab deruxtecan were fixed, and payload parameters were then estimated
- The structural PK model for intact [fam-] trastuzumab deruxtecan was a 2-compartment model with linear clearance. The payload model was a 1-compartment model with first-order release from intact [fam-] trastuzumab deruxtecan and first-order elimination (**Figure 3**)
- A list of covariates evaluated is shown in **Table 1**. They were based on the known characteristics of [fam-] trastuzumab deruxtecan and prior knowledge about T-DM1.[12,13] A significance level of $p \leq 0.01$ (objective function value [OFV] ≥6.63) and $p \leq 0.001$ (OFV ≥10.83) was used in the forward addition and backward elimination step, respectively
- The final selected model was assessed by goodness-of-fit plot and visual predictive check

FIGURE 3. PK model structure



CL, clearance of intact [fam-] trastuzumab deruxtecan; CLpay, clearance of payload; IV inf, intravenous infusion; Kr, release rate constant from intact [fam-] trastuzumab deruxtecan to payload; PK, pharmacokinetic; Q, intercompartment clearance of intact [fam-] trastuzumab deruxtecan; DS-8201a, [fam-] trastuzumab deruxtecan; V1, central volume of distribution of intact [fam-] trastuzumab deruxtecan; V2, peripheral volume of distribution of intact [fam-] trastuzumab deruxtecan; Vpay, volume of distribution of payload.

TABLE 1. List of covariates evaluated

	Covariate	PK Parameter
Intact [fam-] trastuzumab deruxtecan	Baseline body weight, age, sex, race	Clearance, volume of distribution
	Baseline tumor size, tumor type (breast vs gastric vs other), HER2 status[a]	Clearance
	Baseline albumin	Clearance
	Prior HER2 therapy (no/yes)	Clearance
	Formulation (FL-DP1 vs FL-DP2)	Clearance, volume of distribution, release rate constant[b]
Payload	Baseline body weight, age, sex, race	Clearance, volume of distribution
	Baseline liver function parameters (ALT, AST, TBIL)	Clearance
	Baseline renal function parameters (CrCL)	Clearance
	Baseline tumor size	Release rate constant[b]
	Formulation (FL-DP1 vs FL-DP2)	Clearance, volume of distribution

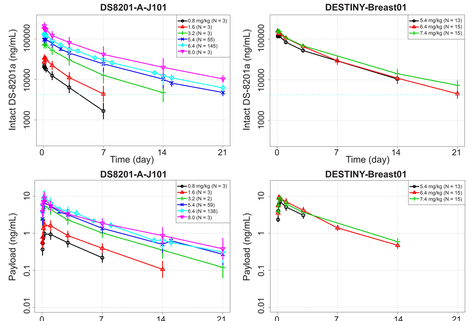
[a]HER2 status was defined as HER2 positive [IHC 3+; IHC 2+/ISH+; or ISH+], negative [IHC 2+/ISH–; IHC 1+; or IHC 0], or unknown.
[b]Covariates tested on release rate constant were based on drug characteristics and biology.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCL, creatinine clearance; FL-DP1, frozen liquid drug product 1; FL-DP2, frozen liquid drug product 2; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PK, pharmacokinetic; TBIL, total bilirubin.

RESULTS

Population PK Analysis

- A total of 4334 intact [fam-] trastuzumab deruxtecan concentrations and 4291 payload concentrations collected from 278 patients were available for analysis
- Observed PK profiles after first dose (**Figure 4**) suggested:
  - A 2-compartment model can describe the observed PK profiles of intact [fam-] trastuzumab deruxtecan
  - Payload profiles appeared to be driven by intact [fam-] trastuzumab deruxtecan and release from intact [fam-] trastuzumab deruxtecan (ie, formation related kinetics)

FIGURE 4. Observed PK profiles after first dose for intact [fam-] trastuzumab deruxtecan (upper panels) and payload (lower panels)



Points are geometric mean concentrations at nominal time points after the first dose. Vertical lines are ±1 standard error in the log-domain. PK, pharmacokinetic; DS-8201a; [fam-] trastuzumab deruxtecan.

- Covariate effects on intact [fam-] trastuzumab deruxtecan:
  - No statistically significant effects of formulation, tumor type, and HER2 status were observed
  - Identified covariates on CL and V1 were (**Table 2**):

$$CL = 0.39 \times (Weight/56.85)^{0.553} \times (Albumin/39)^{-0.510} \times (Tumor\ Size/59)^{0.098} \times (1 + 0.213 \times (Sex = Male))$$

$$V1 = 2.72 \times (Weight/56.85)^{0.503} \times (1 + 0.280 \times (Sex = Male))$$

  - Overall covariate effects on intact [fam-] trastuzumab deruxtecan steady state exposure (AUCss) were <20% (**Figure 5a**)
- Covariate effects on payload:
  - Identified covariates on CLpay were (**Table 2**):

$$CLpay = 19.4 \times (Age/58.5)^{-0.623} \times (AST/29)^{-0.316} \times (TBIL/8.55)^{-0.224}$$

  - Effects of these covariates on payload AUCss ranged from 20% to 35% (**Figure 5b**)

TABLE 2. Parameter estimates from the final population PK model for intact [fam-] trastuzumab deruxtecan and payload

Variable	Parameter estimate (%RSE)	Between-subject variability %CV (%RSE)	Shrinkage %
Intact [fam-] trastuzumab deruxtecan			
Clearance (CL, L/d)	0.390 (2.20)	25.7 (9.70)	7%
Central volume of distribution (V1, L)	2.72 (1.50)	17.0 (8.20)	6%
Inter-compartment clearance (Q, L/d)	0.200 (3.20)	32.2 (19.6)	30%
Peripheral volume of distribution (V2, L)	3.80 (6.10)	62.2 (17.8)	30%
Residual proportional error SD	0.164 (0.70)	--	--
Residual additive error SD (ng/mL)	1243 (4.70)	--	--
Weight on CL	0.553 (17.0)	--	--
Albumin on CL	−0.510 (25.7)	--	--
Tumor size on CL	0.098 (25.2)	--	--
Weight on V1	0.503 (12.3)	--	--
Sex on CL	0.213 (31.3)	--	--
Sex on V1	0.280 (14.4)	--	--
Payload			
Release rate constant (Kr, 1/h)	0.0149 (3.30)	42.2 (12.1)	10%
Payload CL (CLpay, L/h)	19.4 (3.50)	40%	16%
Residual proportional error SD (ng/mL)	0.315 (0.700)	--	--
Age on CLpay	−0.623 (22.4)	--	--
AST on CLpay	−0.316 (21.0)	--	--
TBIL on CLpay	−0.224 (30.8)	--	--

RSE is the standard error of the estimate divided by the estimate times 100%. Between-subject variability %CV is the square root of the variance for that parameter. Shrinkage is (Estimated variance – variance(post hocs))/Estimated variance x 100%. The correlation between CL and V1 is 0.577.
AST, aspartate aminotransferase; CL, clearance; CLpay, clearance of payload; CV, coefficient of variation; Q, intercompartment clearance of [fam-] trastuzumab deruxtecan; RSE, relative standard error; SD, standard deviation; TBIL, total bilirubin; V1, central volume of distribution; V2, peripheral volume of distribution.

FIGURE 5A. Forest plot of covariate effects on steady state AUC of intact [fam-] trastuzumab deruxtecan

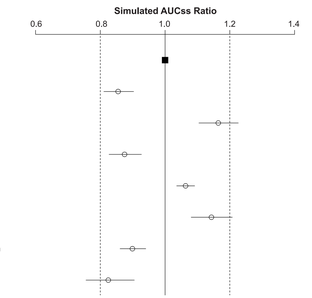
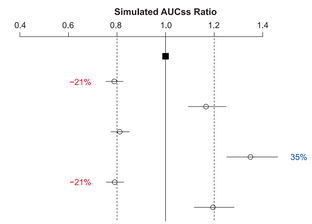


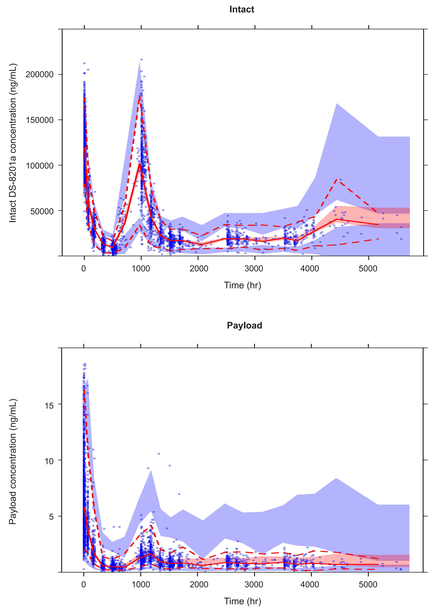
FIGURE 5B. Forest plot of covariate effects on steady state AUC of payload



Typical patient in (A) is female with median covariate values of body weight of 57 kg, albumin of 39 g/L, and tumor size of 59 mm. Typical patient in (B) has median covariate values of age of 59 years old, AST of 29 U/L, and TBIL of 0.50 mg/dL. Open circle and horizontal line are mean and 90% confidence interval.
AST, aspartate aminotransferase; AUCss, steady state exposure; TBIL, total bilirubin.

- Overall, visual predictive check suggested that the final model described the observed data well; a slight over-prediction of payload was noted (**Figure 6**)

FIGURE 6. Prediction-corrected visual predictive check of observed vs simulated exposure to intact [fam-] trastuzumab deruxtecan and payload



Dots are the individual observations, solid lines are the 50th percentile, and dashed lines are the 2.5 and 97.5 percentiles of the observed data. The shaded areas are the 95% confidence intervals around the 2.5, 50th, and 97.5 prediction intervals of the simulated data.
DS-8201a; [fam-] trastuzumab deruxtecan.

PK Simulations

- Based on the final model and simulations, steady state trough concentration of intact [fam-] trastuzumab deruxtecan is predicted to exceed the preclinical efficacious trough level (4260 ng/mL) in >90% of patients at the 5.4-mg/kg dose

CONCLUSIONS

- A population PK model was successfully developed for [fam-] trastuzumab deruxtecan and payload. Identified covariate relationships are consistent with the known characteristics of the drug
- The model was utilized to generate individual exposure metrics in subsequent exposure-response analyses

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