Exposure-Response Analyses to Support Dose Justification of DS-8201a ([Fam-] Trastuzumab Deruxtecan), a HER2-Targeting Antibody-Drug Conjugate, in HER2-Positive Breast Cancer Patients

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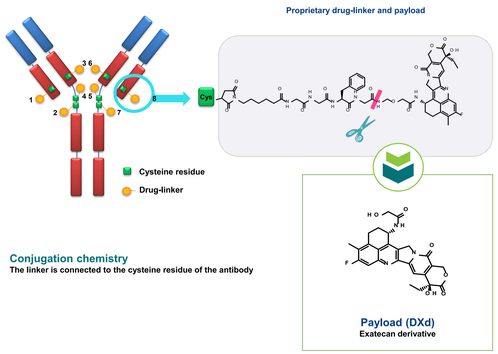
BACKGROUND

- [Fam-] trastuzumab deruxtecan (DS-8201a) is a novel human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate with a humanized anti-HER2 antibody, a proprietary cleavable peptide-based linker, a potent topoisomerase I inhibitor payload (MAAA-1181a), and a high drug-to-antibody ratio of approximately 8 (**Figure 1**)[1]
- In the ongoing, 2-part, phase 1 trial (DS8201-A-J101; NCT02564900) of [fam-] trastuzumab deruxtecan in patients with HER2-expressing solid tumors:
  - No dose limiting toxicities were observed, and the maximum tolerated dose was not reached in the dose escalation phase[2]
  - The 5.4- and 6.4-mg/kg doses were recommended for the dose expansion phase[2]
  - In the dose expansion phase, the objective response rate (ORR) was 54.5% (54/99) for HER2-positive breast cancer previously treated with ado-trastuzumab emtansine (T-DM1)[3]
- [Fam-] trastuzumab deruxtecan is currently in phase 2[4] and 3[5,6] development for the treatment of patients with HER2-positive, locally advanced or metastatic breast cancer who have been previously treated with T-DM1
- Other tumor types in clinical development include HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma,[3,7] HER2-positive or -mutated, unresectable and/or metastatic non-small cell lung cancer,[8,9] and HER2-expressing advanced colorectal cancer[10,11]

FIGURE 1. Structure of [fam-] trastuzumab deruxtecan



OBJECTIVE

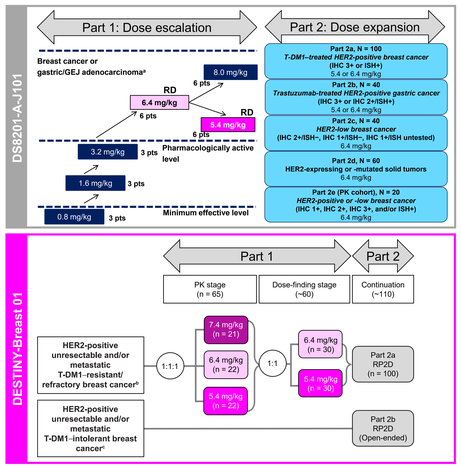
- To conduct exposure-response analyses to support [fam-] trastuzumab deruxtecan dose justification in patients with HER2-positive breast cancer

METHODS

Data Source and Study Design

- Interim data from both the first-in-human study in patients with advanced solid tumors (DS8201-A-J101)[2,3] and the pivotal phase 2 study in HER2-positive breast cancer patients (DS8201-A-U201, DESTINY-Breast01)[4] were included (**Figure 2**)
  - [Fam-] trastuzumab deruxtecan doses ranged from 0.8 to 8.0 mg/kg every 3 weeks (Q3W) in DS8201-A-J101
  - [Fam-] trastuzumab deruxtecan doses were 5.4, 6.4, or 7.4 mg/kg Q3W in DESTINY-Breast01

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+ 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.

Pharmacokinetic Exposure Measure

- The following pharmacokinetic (PK) exposure metrics of [fam-] trastuzumab deruxtecan and payload were estimated for individual patients based on the empirical Bayes estimates of PK parameters and patients' specific dosing from a pooled population PK analysis[12]
  - Maximum concentration (Cmax), minimum concentration (Cmin), and exposure (AUC) at cycle 1 and steady-state
  - Average AUC during treatment, or up to the time of event
- The above exposure metrics were tested for each endpoint; the most significant exposure metric was generally selected in the exposure-response model. Consistency across endpoints and correlation between exposure metrics were also taken into account

Exposure-Efficacy Analysis

- Evaluated in HER2-positive breast cancer patients (n = 140, 111 from DS8201-A-J101 and 29 from DS8201-A-U201)
- Efficacy endpoints included confirmed ORR, best tumor response (BTR), and progression-free survival (PFS)
- For each endpoint, linear or nonlinear logistic or Cox regression analysis was performed
- Covariates tested are shown in **Table 1**. A forward search at p <0.10, and a backward search at p <0.05 was conducted using the likelihood ratio test

Exposure-Safety Analysis

- Evaluated in patients with all tumor types (n = 276, 232 from DS8201-A-J101 and 44 from DS8201-A-U201)
- Safety endpoints included interstitial lung disease (ILD; including cases of ILD, pneumonitis, and organizing pneumonia), anemia, neutrophil count deceased, platelet count deceased, nausea, diarrhea, dose reductions due to treatment-emergent adverse events (TEAEs), and discontinuations due to TEAEs
- For the purpose of this analysis, ILD events included cases that were adjudicated as ILD and related to [fam-] trastuzumab deruxtecan by an independent adjudication committee in addition to all unadjudicated events of ILD that were reported at the time of analysis
- For each endpoint, logistic or Cox regression analysis was performed. Both linear and nonlinear functions were tested
- Covariate evaluation was performed using a similar method as is described for the exposure-efficacy analysis (**Table 1**)

TABLE 1. List of covariates evaluated in the exposure-response analysis

Covariate	Endpoint
Country (Japan vs USA) Study Age Sex Race HER2 status ECOG PS	Efficacy and safety
Tumor burden/size Number of prior HER2 therapies (≥2 vs <2) Number of prior nonhormal cancer therapies (≥6 vs <6) Hormone receptor status	Efficacy only
Number of prior therapies (≥6 vs <6) Lung metastases (yes/no)	Safety only

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2.

Dose-Response Projections

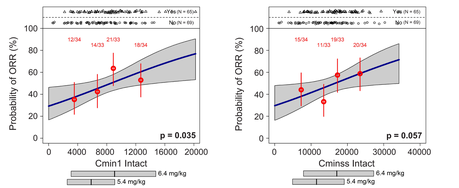
- Simulation was conducted to obtain projected event rates for the efficacy and safety parameters at 5.4- and 6.4-mg/kg doses:
  - For each endpoint, 1000 exposures were sampled with replacement from the 5.4- and 6.4-mg/kg groups
  - 1000 models were simulated from the variance-covariance matrix of the exposure-response model
  - Mean response was calculated across the 1000 exposures, and then summary statistics were calculated across the 1000 models

RESULTS

Exposure-Efficacy Relationship

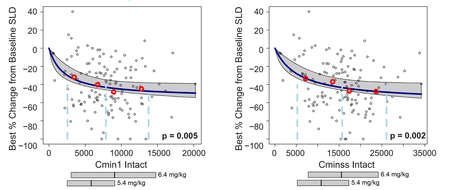
- Statistically significant exposure-response relationships were observed for ORR and BTR (**Figure 3a, 3b**)
- There was a trend of higher probability of PFS with higher [fam-] trastuzumab deruxtecan Cmin, but the relationship was not statistically significant (p = 0.238, **Figure 3c**)
- Only country was identified as a statistically significant covariate on the slope of ORR model and Emax of BTR model. Such an effect requires further evaluation due to other potential confounding factors, such as duration of exposure between J101 (Japan) and U201 (US) studies

FIGURE 3A. Logistic regression fits for ORR



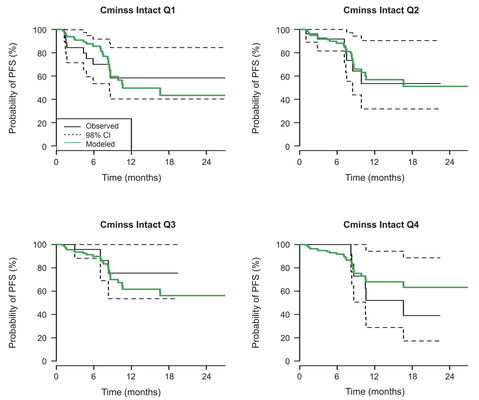
Patients are stratified into exposure quartiles. Points are mean exposure and response rate per quartile. Vertical bars are exact 90% confidence intervals. Numbers above each bar indicate number of responders and total number of patients. Solid curve is the logistic regression fit. Gray band represents the 5th–95th percentile confidence interval of the fit. Individual data (Yes/No) are shown above the plot. Horizontal bars below the plot indicate the 5th, 50th, and 9th percentile of exposures per dose group.
Cmin1, minimum concentration during cycle 1; Cminss, minimum concentration over 1 cycle at steady-state; ORR, objective response rate.

FIGURE 3B. Nonlinear regression fits for BTR



Patients are stratified into exposure quartiles. Red points are mean exposure and response rate per quartile. Gray points are individual patients. Solid curve is the nonlinear regression fit. Gray band represents the 5th–95th percentile confidence interval of the fit. Vertical dashed lines indicate the 5th, 50th, and 95th percentile of exposures. Horizontal bars below the plot indicate the 5th, 50th, and 95th percentile of exposures per dose group.
Cmin1, minimum concentration during cycle 1; Cminss, minimum concentration over 1 cycle at steady-state; SLD, sum of longest diameter.

FIGURE 3C. Cox-regression fit for PFS

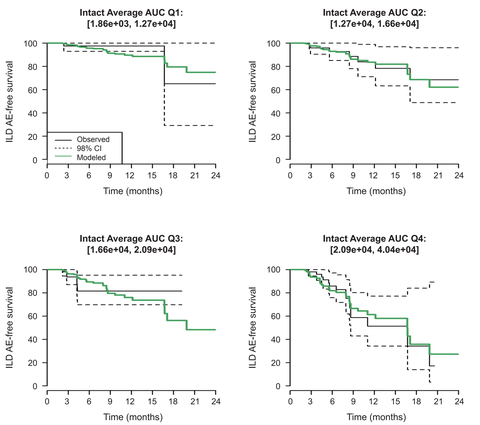


Q1–4 indicate subjects stratified by exposure quartile. Kaplan-Meier plots are stratified by exposure quartile. The solid black line is the Kaplan-Meier estimate. The dashed lines indicate 95% confidence intervals. The solid green line is the fit of the Cox-regression model.
CI, confidence interval; Cminss, trough concentration at steady-state; PFS, progression-free survival.

Exposure-Safety Relationship

- The risk of any grade ILD was increased with higher [fam-] trastuzumab deruxtecan AUC (p <0.001) (**Figure 4**). Asian race appeared to have more ILD events of any grade as compared to non-Asian race, but this effect is likely confounded
- Incidence of grade ≥3 ILD was too low to allow for a meaningful analysis
- No statistically significant exposure-response relationships were found for nausea of any grade or grade ≥3, diarrhea of any grade or grade ≥3, or platelet count decreased of grade ≥3 (all p >0.05)

FIGURE 4. Cox-regression fit for ILD of any grade



Q1–4 indicate patients stratified by AUC quartile. Kaplan-Meier plots are stratified by exposure quartile. The solid black line is the Kaplan-Meier estimate. The dashed lines indicate 95% CI. The solid green line is the fit of the cox-regression model.
AE, adverse event; AUC, area under the curve; CI, confidence interval; ILD, interstitial lung disease.

- Statistically significant exposure-response relationships identified for safety endpoints are shown in **Table 2**
- Country, study, and race were identified as statistically significant covariates for some safety endpoints (**Table 2**), but further evaluation is needed due to confounding factors in the current analysis dataset, such as duration of exposure

TABLE 2. Summary of logistic regression analyses on selected safety endpoints

Safety endpoint	Exposure variable	p-value	Slope effect	Covariates
Anemia, any grade	Payload Cycle 1 AUC	<0.001	+	Country, study on slope
Anemia, grade ≥3	Payload Cycle 1 AUC	<0.001	+	Study, race on slope
Neutrophil count decreased, any grade	Intact Cycle 1 Cmax	0.001	+	Country on slope, study on intercept
Neutrophil count decreased, grade ≥3	Intact Cycle 1 Cmax	0.015	+	Race on slope
Platelet count decreased, any grade	Payload Cycle 1 AUC	<0.001	+	Country on slope, study on slope
Discontinuations due to TEAEs	Intact Steady-State, Cmax	0.003	+	Study on slope, race on intercept
Dose reductions due to TEAEs	Intact Steady-State, Payload	0.005	+	—

The p-value is for the slope of the logistic regression model.
AUC, area under the curve; Cmax, maximum concentration; TEAE, treatment-emergent adverse event.

Integrated Dose-Response Projections

- A comparison of the projected event rates for the efficacy and safety parameters for each dose is shown in **Figure 5**
- Overall, the 2 doses were similar; however, the 6.4-mg/kg dose was projected to have higher rates of efficacy, but also higher risk of developing TEAEs or discontinuation/dose reduction due to TEAEs

FIGURE 5. Model-projected event rates for doses of 5.4 and 6.4 mg/kg

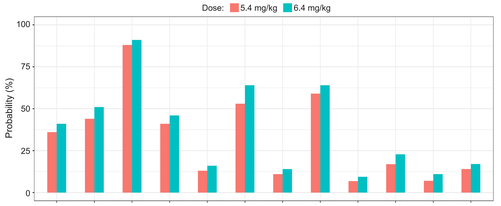


Figure previously presented at SABCS 2018, Tamura et al, Poster # P6-17-10.
ANM, anemia; BTR, best tumor response; DCAE, discontinuations due to adverse events; DRAE, dose reductions due to adverse events; Gr3+, grade ≥3; ILD, interstitial lung disease; NTP, neutrophil count decreased; ORR, objective response rate; PFS, progression-free survival; TCP, platelet count decreased.

CONCLUSIONS

- For both doses, the projected benefits of [fam-] trastuzumab deruxtecan exceeded the projected risks
- There was a statistically significant relationship between exposures vs ORR and BTR, with a trend for higher PFS at higher exposure
- Statistically significant relationships were also found for exposures and key AEs in the exposure-safety analyses
- Based on the modelling results as well as overall benefit and risk assessment, 5.4 mg/kg was chosen as the recommended dose for continued development in HER2-positive breast cancer

REFERENCES

1) Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108; **2)** Doi T, et al. *Lancet Oncol.* 2017;18:1512-1522; **3)** Iwata, et al. ASCO 2018; **4)** Basel-ga, et al. ASCO 2018; **5)** André, et al. SABCS 2018; **6)** Verma, et al. SABCS 2018; **7)** Yamaguchi, et al. ASCO 2018; **8)** Tsurutani, et al. IASLC WCLC 2018; **9)** Jänne, et al. IASLC WCLC 2018; **10)** Yoshino, et al. ESMO 2018; **11)** Yoshino, et al. ESMO GI 2018; **12)** Yin, et al. ASCPT 2019.

ACKNOWLEDGMENTS

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