Pharmacokinetics, Safety, and Efficacy of Trastuzumab Deruxtecan with Concomitant Ritonavir or Itraconazole in Patients with HER2-Expressing Advanced Solid Tumors

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ABSTRACT

Purpose: To evaluate drug–drug interactions between the human epidermal growth factor receptor 2 (HER2)–targeted antibody-drug conjugate trastuzumab deruxtecan (T-DXd; DS-8201a) and the OATP1B/CYP3A inhibitor ritonavir or the strong CYP3A inhibitor itraconazole.

Patients and Methods: Patients with HER2-expressing advanced solid tumors were enrolled in this phase I, open-label, single-sequence crossover study (NCT03383692) and received i.v. T-DXd 5.4 mg/kg every 3 weeks. Patients received ritonavir (cohort 1) or itraconazole (cohort 2) from day 17 of cycle 2 through the end of cycle 3. Primary endpoints were maximum serum concentration (C_{max}) and partial area under the concentration-time curve from beginning of cycle through day 17 (AUC_{17d}) for T-DXd and deruxtecan (DXd) with (cycle 3) and without (cycle 2) ritonavir or itraconazole treatment.

Results: Forty patients were enrolled (cohort 1, $n = 17$; cohort 2, $n = 23$). T-DXd C_{max} was similar whether combined with ritonavir [cohort 1, cycle 3/cycle 2; 90% confidence interval (CI): 1.05 (0.98–1.13)] or itraconazole [cohort 2, 1.03 (0.96–1.09)]. T-DXd AUC_{17d} increased from cycle 2 to 3; however, the cycle 3/cycle 2 ratio upper CI bound remained at ≤1.25 for both cohorts. For DXd (cycle 3/cycle 2), C_{max} ratio was 0.99 (90% CI, 0.85–1.14) for cohort 1 and 1.04 (0.92–1.18) for cohort 2; AUC_{17d} ratio was 1.22 (1.08–1.37) and 1.18 (1.11–1.25), respectively. The safety profile of T-DXd plus ritonavir or itraconazole was consistent with previous studies of T-DXd monotherapy. T-DXd demonstrated promising antitumor activity across HER2-expressing solid-tumor types.

Conclusions: T-DXd was safely combined with ritonavir or itraconazole without clinically meaningful impact on T-DXd or DXd pharmacokinetics.

Introduction

Trastuzumab deruxtecan (T-DXd; DS-8201a) is an antibody-drug conjugate comprising a humanized, monoclonal, anti–human epidermal growth factor receptor 2 (HER2) antibody covalently linked to a topoisomerase I inhibitor payload [deruxtecan (DXd)] through a tetrapeptide-based cleavable linker (1). T-DXd is approved in the United States, Japan, and Europe for the treatment of unresectable or metastatic HER2-positive breast cancer in patients who have received ≥2 prior anti-HER2 based regimens in the metastatic setting, and in the United States and Japan for the treatment of HER2-positive unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy (2–4). T-DXd is approved in the United States with boxed warnings for interstitial lung disease (ILD) and embryo–fetal toxicity (3). T-DXd has a drug-to-antibody ratio of approximately 8 to ensure efficient delivery of the DXd payload to HER2-expressing cells, with limited off-target toxicity (1). In a phase I study (DS8201-A-J101; NCT02564900), T-DXd demonstrated a manageable safety profile and preliminary antitumor activity across many different HER2-expressing or *HER2*-mutated advanced solid-tumor types (5–8). Recent phase I and II clinical studies have shown the antitumor activity of T-DXd in the treatment of HER2-low–expressing breast cancer (9), HER2-expressing gastric or gastroesophageal junction adenocarcinoma (9), *HER2*-mutant non–small cell lung cancer (NSCLC; ref. 10), and HER2-positive colorectal cancer (11).

The pharmacokinetics of a treatment can be altered by concomitant use of inhibitors targeting proteins involved in drug transport or metabolism (12, 13). DXd has been shown to be a substrate for organic anion transporting polypeptide 1B (OATP1B) transporters, P-glycoprotein, breast cancer resistance protein (BCRP), and cytochrome P450 3A (CYP3A) enzymes in preclinical experiments (3, 14). This study evaluated the effects of concomitant ritonavir, a dual OATP1B/CYP3A inhibitor, or itraconazole, a strong CYP3A inhibitor, on the pharmacokinetic profiles of T-DXd and DXd and the potential for drug–drug interactions (DDI) with T-DXd in patients with HER2-expressing advanced solid tumors.

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Translational Relevance

Trastuzumab deruxtecan (T-DXd) has recently been approved for patients with human epidermal growth factor receptor 2 (HER2)–positive breast and gastric cancer in the United States, Japan, and Europe and is currently under investigation in several other indications. Preclinical studies showed that DXd, a topoisomerase I inhibitor and the payload of T-DXd, is a substrate of organic anion-transporting polypeptide 1B (OATP1B) and cytochrome P450 3A (CYP3A); this study assessed the potential for T-DXd–related drug–drug interactions. Ritonavir, a dual OATP1B/CYP3A inhibitor, and itraconazole, a strong CYP3A inhibitor, were administered concomitantly with T-DXd. T-DXd combined with ritonavir or itraconazole did not result in a clinically meaningful change in the pharmacokinetics of T-DXd or DXd and did not appear to impact the safety profile of T-DXd, whose efficacy was observed across tumor indications. These results will inform physicians that patients can be treated with T-DXd concomitantly with ritonavir or itraconazole.

Patients and Methods

Study design and participants

DS8201-A-A104 (NCT03383692) was a phase I, open-label, single-sequence crossover study evaluating the DDI potential of T-DXd with concomitant ritonavir or itraconazole in patients with HER2-expressing advanced solid tumors. The study protocol was approved by the ethics committee or institutional review board at each study site. This study was conducted in compliance with its protocol, the ethical principles outlined in the Declaration of Helsinki, the International Council for Harmonisation Guideline for Good Clinical Practice (October 2013), and all applicable regulatory requirements. Written informed consent was provided by each patient prior to evaluation for eligibility. Patients were assigned first to cohort 1 (T-DXd plus ritonavir); once cohort 2 was opened, subsequent patients were assigned to cohort 2 (T-DXd plus itraconazole).

Eligible patients were aged ≥20 years and had a pathologically documented unresectable or metastatic solid-malignant tumor with HER2 expression [as per IHC (IHC 3+, IHC 2+, or IHC 1+) and/or *in situ* hybridization; archived sample was assessed by central laboratory] that was refractory or intolerant to ≥1 prior systemic chemotherapy regimen or for which no standard treatment was available. Patients also had a left ventricular ejection fraction of ≥50% within 28 days before enrollment and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were excluded if they were unable to receive ritonavir and itraconazole orally or had a contraindication to ritonavir or itraconazole according to their respective prescribing information. At the time of screening, eligible patients had investigator-assessed and documented presence of a tumor lesion as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); patients with nontarget lesions only were eligible as well. Prohibited concomitant therapies included CYP3A and OATP1B inhibitors, CYP3A inducers, OATP1B/CYP3A substrates, other anticancer treatment, other investigational therapies, radiotherapy, and systemic corticosteroids or other immunosuppressive medications (see Supplementary Appendix for a complete list of excluded therapies). Patients were excluded if they had a history of noninfectious ILD or pneumonitis that required corticosteroid treatment, current ILD, or pneumonitis. Patients could not enter the study if they had a medical history of myocardial infarction within 6 months of enrollment, troponin levels consistent with myocardial infarction within 28 days of enrollment, or symptomatic congestive heart failure. Additional criteria for exclusion were prolongation of QT interval, HIV infection, or active hepatitis B or C infection.

Patient treatment and cohorts

All patients were administered T-DXd as an intravenous infusion solution at 5.4 mg/kg once every 3 weeks (**Fig. 1**). Patients remained on T-DXd if they continued to derive clinical benefit, barring withdrawal of patient consent, progressive disease, or unacceptable toxicity (including ILD or pneumonitis). T-DXd treatment during cycle 1 was administered over 90 minutes; T-DXd treatments in subsequent cycles were given over 30 minutes if there was no initial infusion reaction. T-DXd dose was selected based on the phase I outcomes supporting 6.4 mg/kg and 5.4 mg/kg as potential phase II doses; the lower dose of 5.4 mg/kg was used in the current study to minimize the possibility of adverse events (AE) from potential DDIs (5).

Patients in cohort 1 received ritonavir 200 mg twice daily on day 17 of cycle 2 until day 21 of cycle 3. DDI analyses did not overlap with cycle 1. The OATP1B-specific inhibitors cyclosporine and rifampicin were not considered suitable for this study. Cyclosporine has immunosuppressive effects and thus its use is neither safe nor ethical in patients with cancer; rifampicin has the potential to induce CYP3A (15), and its single-dose administration does not allow for adequate DDI assessment with T-DXd, which has an elimination half-life ($t_{1/2}$) of approximately 6 days (5). Ritonavir, which inhibits both OATP1B and CYP3A4 (15–17), was chosen for its safe, ethical application in patients with cancer and for its recommended twice-daily dosing schedule (18).

Patients in cohort 2 received itraconazole 200 mg twice daily on day 17 followed by itraconazole 200 mg once daily until day 21 of cycle 3. Itraconazole, a strong CYP3A inhibitor (15), was chosen as a comparator for delineating the retrospective contributions of OATP1B and CYP3A to the elimination of T-DXd and DXd. The timing of ritonavir or itraconazole dosing on day 17 of cycle 2 and day 1 of cycle 3 followed pharmacokinetic sampling and immediately preceded T-DXd dosing, respectively (**Fig. 1**).

Key endpoints and assessments

The primary endpoints of this study were the maximum serum concentration (C_{max}) and partial area under the concentration-time curve from the start of the cycle through day 17 (AUC_{17d}) for T-DXd and DXd with (cycle 3) and without (cycle 2) treatment with ritonavir (cohort 1) or itraconazole (cohort 2). Secondary endpoints included assessments of safety and antitumor activity of T-DXd with concomitant ritonavir or itraconazole. Pharmacokinetic secondary endpoints for T-DXd included area under plasma concentration-time curve over the dosing interval (AUC_{tau}), time to maximum serum concentration (t_{max}), $t_{1/2}$, steady state clearance (CL_{ss}), apparent volume of distribution during the terminal phase (V_z), and steady state volume distribution (V_{ss}).

Blood (approximately 4 mL) was drawn for pharmacokinetic analysis within 8 hours before T-DXd infusion and within 15 minutes after the end of T-DXd infusion on cycle 1 day 1. During cycles 2 and 3, blood samples were taken on day 1 within 8 hours before infusion and again within 15 minutes after end of infusion and again 2, 4, and 7 hours after start of administration (±15 minutes); on days 2 and 4 (24 and 72 hours after start of administration ±2 hours); and on days 8, 12, and 17 (±1 day). Optional blood sampling was also done for pharmacokinetic measurements on day 22 (±2 days) if day 1 of the

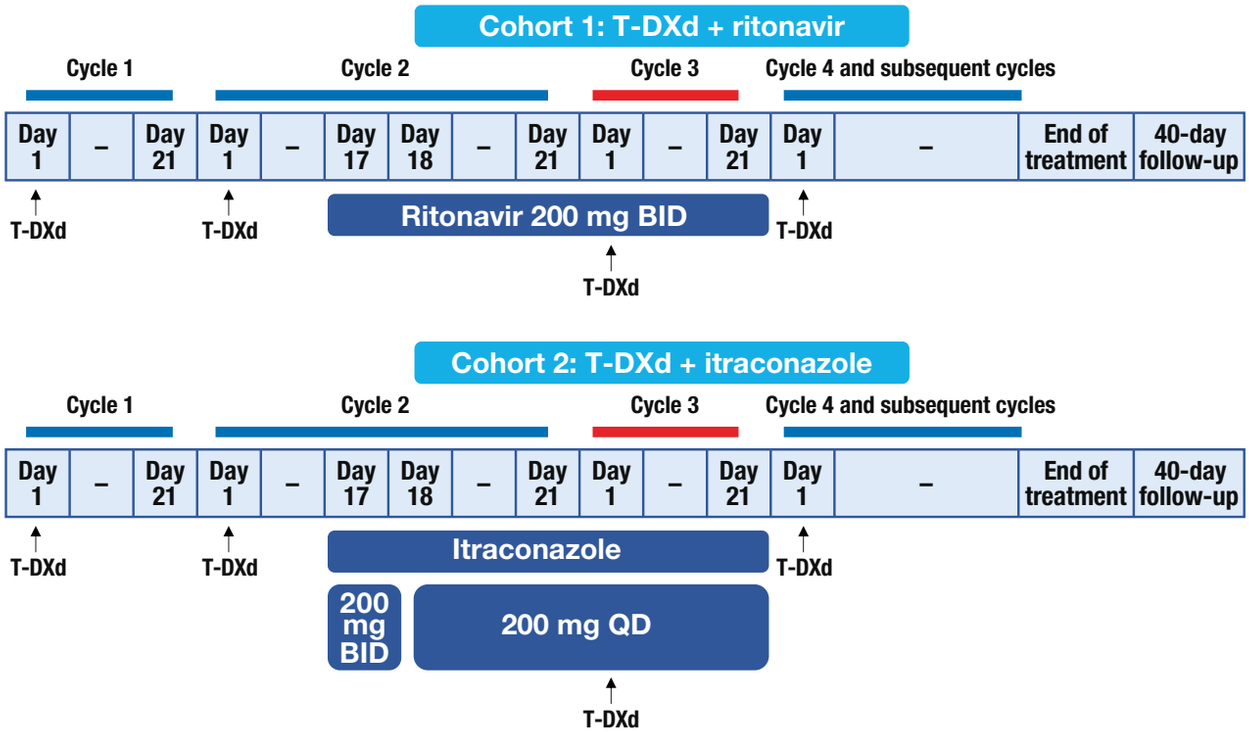

Figure 1.
Study treatment schema. BID, twice daily; QD, once daily; T-DXd, trastuzumab deruxtecan.

following cycle would be delayed for ≥3 days. During cycles 4, 6, and 8, blood collection was performed on day 1 within 8 hours before infusion and again within 30 minutes after end of infusion. Blood samples were centrifuged to separate serum and plasma and were sent to a central laboratory for analysis. Serum concentrations of T-DXd and DXd were measured by enzyme-linked immunosorbent assay and liquid chromatography with tandem mass spectrometry, respectively.

Treatment-emergent AEs (TEAE), defined as an AE that occurred after the first dose of study drug or that worsened in severity or seriousness after study drug initiation until 47 days after last dose of the study drug, were assessed. Serious AEs with an onset or worsening ≥48 days after the last dose of study drug, if considered related to the study treatment, were also considered TEAEs. TEAEs were coded based on the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 and graded as per NCI Common Terminology Criteria for Adverse Events version 4.03 by the investigator, who also determined if TEAEs were related or unrelated to T-DXd, ritonavir, or itraconazole.

TEAEs of special interest were identified based on preferred term and categorized according to the Standardized MedDRA Queries for ILD (determined by an independent ILD Adjudication Committee): pneumonitis, decreased left ventricular ejection fraction, QT prolongation, and infusion-related reactions. If ILD or pneumonitis was suspected, treatment with study drug was interrupted pending further evaluations, including high-resolution CT, pulmonologist consultation, pulmonary function tests, and pulse oximetry. Once ILD or pneumonitis was suspected, corticosteroid treatment was promptly initiated following clinical treatment guidelines. Potential ILD and pneumonitis events were evaluated by an independent adjudication committee. For confirmed grade 1 ILD or pneumonitis, T-DXd was restarted only if the event was fully resolved. If the event resolved within 28 days of onset, the dose was maintained; if it did not resolve within 28 days, the dose was reduced by one dose level. For confirmed grade ≥2 ILD or pneumonitis events, T-DXd was permanently discontinued.

Tumor assessments were performed using CT or MRI at screening and every 6 weeks in the first 24 weeks after day 1 of cycle 1, and thereafter every 12 weeks while the patient remained on study drug. The objective response rate (ORR), defined as the percentage of patients with best response of complete response (CR) or partial response (PR), was determined by the investigator based on RECIST v1.1 for subjects with measurable tumors at baseline. Confirmed ORR was not required in the protocol but was determined for some patients with CR or PR confirmation ≥4 weeks after the first documentation of response. Best ORR by HER2 IHC expression subgroups was assessed in an ad hoc analysis. Other secondary endpoints were also evaluated and included the duration of response (DOR); time to response (TTR); disease control rate (DCR), defined as the percentage of patients with best overall response of CR, PR, or stable disease (SD); clinical benefit rate (CBR), defined as the percentage of patients with a best overall response of CR, PR, or SD for ≥6 months; progression-free survival (PFS); and best (i.e., minimum) percentage change from baseline in the sum of diameters of the target lesion.

Statistical considerations

The sample size of the study was selected based on practical considerations and was confirmed to have the following precision given predicted dropout rates and degrees of variability. With an assumed intra-individual variability (i.e., coefficient of variation) estimated at 30%, a sample size of 12 patients could statistically detect a two-fold difference (geometric mean ratio of 2.0) with a 90%

confidence interval (CI) of 1.605−2.492; assuming 40% variability, the CI for a significant two-fold change would expand to 1.492−2.682. Taking into account a dropout rate of approximately 30%, a sample size of 16 patients was deemed sufficient to determine the impact of ritonavir and itraconazole on the primary endpoints of C_{max} and AUC_{17d}.

The pharmacokinetic analysis population included all enrolled patients who received T-DXd 5.4 mg/kg in cycles 2 and 3 and who had any primary endpoints assessed for cycles 2 and 3, without major deviations or events affecting pharmacokinetics. Patients were excluded from the pharmacokinetic analysis population if they forgot to take ritonavir or itraconazole and did not have both primary endpoints

Table 1. Demographics and baseline characteristics of patients receiving T-DXd plus ritonavir (cohort 1) or itraconazole (cohort 2).

Characteristic/category	Cohort 1 T-DXd + ritonavir (*n* = 17)	Cohort 2 T-DXd + itraconazole (*n* = 23)	All patients (*N* = 40)
Age, years, median (range)	57 (48–80)	57 (31–69)	57 (31–80)
<65 years, *n* (%)	10 (58.8)	18 (78.3)	28 (70.0)
≥65 years, *n* (%)	7 (41.2)	5 (21.7)	12 (30.0)
Sex, *n* (%)			
Male	5 (29.4)	13 (56.5)	18 (45.0)
Female	12 (70.6)	10 (43.5)	22 (55.0)
ECOG performance status, *n* (%)			
0	12 (70.6)	9 (39.1)	21 (52.5)
1	5 (29.4)	14 (60.9)	19 (47.5)
BMI, median (range), kg/m^2	20.9 (16.3–30.6)	23.2 (17.3–31.8)	22.0 (16.3–31.8)
Renal function, *n* (%)			
Normal	8 (47.1)	11 (47.8)	19 (47.5)
Mild/moderate impairment[a]	9 (52.9)	12 (52.2)	21 (52.5)
Hepatic function, *n* (%)			
Normal	11 (64.7)	19 (82.6)	30 (75.0)
Mild/moderate impairment[b]	6 (35.3)	4 (17.4)	10 (25.0)
Cancer type, *n* (%)			
Breast cancer	9 (52.9)	8 (34.8)	17 (42.5)
HER2-positive[c]	3 (33.3)[d]	6 (75.0)[d]	9 (52.9)
HER2-low[e]	5 (55.6)[d]	1 (12.5)[d]	6 (35.3)
IDC	8 (47.1)	4 (17.4)	12 (30.0)
IDC—papillotubular carcinoma	1 (5.9)	0	1 (2.5)
IDC—solid-tubular carcinoma	0	1 (4.3)	1 (2.5)
IDC—scirrhous carcinoma	0	3 (13.0)	3 (7.5)
Gastric cancer (intestinal type)	0	1 (4.3)	1 (2.5)
NSCLC	3 (17.6)	3 (13.0)	6 (15.0)
Colorectal cancer	0	1 (4.3)	1 (2.5)
Salivary gland cancer	3 (17.6)	6 (26.1)	9 (22.5)
Other[f]	2 (11.8)	4 (17.4)	6 (15.0)
HER2 expression, *n* (%)			
IHC 3$^+$	6 (35.3)	12 (52.2)	18 (45.0)
IHC 2$^+$	6 (35.3)	5 (21.7)	11 (27.5)
IHC 1$^+$	4 (23.5)	3 (13.0)	7 (17.5)
Not examined[g]	1 (5.9)	3 (13.0)	4 (10.0)
Prior lines of systemic cancer therapy, *n*, median (range)	5 (1–13)	4 (1–13)	4 (1–13)
Any prior cancer therapy, *n* (%)	17 (100.0)	23 (100.0)	40 (100.0)
Chemotherapy	17 (100.0)	22 (95.7)	39 (97.5)
Trastuzumab	7 (41.2)	14 (60.9)	21 (52.5)
Hormone therapy	6 (35.3)	4 (17.4)	10 (25.0)
T-DM1	4 (23.5)	6 (26.1)	10 (25.0)
Pertuzumab	4 (23.5)	2 (8.7)	6 (15.0)

Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence *in situ* hybridization; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; NGS, next-generation sequencing; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; ULN, upper limit of normal.

[a]Mild/moderate renal impairment = serum creatinine clearance ≥30, <90 mL/min.

[b]Mild/moderate hepatic impairment = total bilirubin >ULN, ≤3.0 × ULN and any AST, except for subjects with Gilbert's syndrome [total bilirubin >ULN, ≤3.0 × ULN and (AST >ULN)], or total bilirubin ≤ULN and AST >ULN regardless of Gilbert's syndrome.

[c]HER2-positive breast cancer is defined as HER2 IHC 3$^+$ or IHC2$^+$/ISH$^+$.

[d]One patient with breast cancer in cohort 1 was missing HER2 ISH expression status, and 1 patient in cohort 2 was not examined for HER2 expression by IHC.

[e]HER2-low breast cancer is defined as HER2 IHC 2$^+$/ISH$^-$ or IHC 1$^+$.

[f]Cancer types included in the Other category were cervical (*n* = 1) and vulvar (*n* = 1) for cohort 1 and bladder (*n* = 2), biliary tract (*n* = 1), and esophageal (*n* = 1) for cohort 2.

[g]HER2-positive malignancies were otherwise confirmed using FISH or NGS, as appropriate.

assessed (C_{max} and AUC_{17d}) or if they took a prohibited drug during the assessment period and did not have both primary endpoints assessed (C_{max} and AUC_{17d}). The safety population included all enrolled patients who received ≥1 dose of T-DXd. The antitumor activity population included all enrolled patients who received ≥1 dose of T-DXd and had pretreatment and posttreatment antitumor activity data.

Primary pharmacokinetic endpoints of C_{max} and AUC_{17d} were reported as the arithmetic mean and SD for each cohort during each cycle. AUC_{17d} was calculated according to the mixed-log linear trapezoidal rule (i.e., linear up and log down) using actual sampling times from the time of dosing to day 17. The geometric least squares mean ratio of cycle 3 versus cycle 2 and its two-sided 90% CI for pharmacokinetic parameters (C_{max} and AUC_{17d}) of T-DXd and DXd were calculated to evaluate DDI. Following natural log transformation, C_{max} and AUC_{17d} were analyzed separately using a mixed-effects analysis of variance model. Analysis of t_{max} was conducted using the Hodges–Lehmann median method, and the median difference between cycle 2 and cycle 3 and its 2-sided 90% CI were calculated.

ORR, DCR, and CBR are reported as point estimates, and two-sided 95% CI was calculated using the Clopper–Pearson method for each cohort. The Kaplan–Meier method was used to calculate median event times for DOR, TTR, and PFS. The two-sided CIs of quartile event times were calculated using the Brookmeyer and Crowley method. All statistical analyses were performed on SAS software version 9.4 (SAS Institute). Pharmacokinetic analyses were assessed with Phoenix WinNonlin version 8.0 or higher (Certara LP).

Results

Patients

Between January 12, 2018, and July 24, 2018, 40 patients were enrolled (cohort 1, $n = 17$; cohort 2, $n = 23$) at 10 study centers in Japan, South Korea, and Taiwan. Median patient age was 57 years

Table 2. Pharmacokinetics of T-DXd and DXd in patients receiving T-DXd alone (cycle 2) or T-DXd plus ritonavir or itraconazole (cycle 3).

	Cohort 1 T-DXd + ritonavir ($n = 12$)			Cohort 2 T-DXd + itraconazole ($n = 14$)		
Least squares mean (90% CI)	**Cycle 2 T-DXd only**	**Cycle 3 T-DXd + ritonavir**	**Cycle 3/cycle 2 ratio**	**Cycle 2 T-DXd only**	**Cycle 3 T-DXd + itraconazole**	**Cycle 3/cycle 2 ratio**
T-DXd						
C_{max}, μg/mL	131 (120–144)	138 (126–151)	1.05 (0.98–1.13)	137 (126–149)	140 (129–152)	1.03 (0.96–1.09)
AUC_{17d}, μg·d/mL	623 (544–714)	742[a] (648–851)	1.19 (1.14–1.25)	617 (536–710)	685 (595–788)	1.11 (1.07–1.15)
DXd						
C_{max}, ng/mL	8.49 (7.04–10.3)	8.38 (6.94–10.1)	0.99 (0.85–1.14)	8.43 (7.65–9.29)	8.78 (7.97–9.68)	1.04 (0.92–1.18)
AUC_{17d}, ng·d/mL	30.2 (26.8–34.0)	36.6[a] (32.5–41.3)	1.22 (1.08–1.37)	28.8 (25.4–32.7)	33.9 (29.9–38.5)	1.18 (1.11–1.25)

	Cohort 1 T-DXd + ritonavir ($n = 12$)		Cohort 2 T-DXd + itraconazole ($n = 14$)	
Arithmetic mean (standard deviation)	**Cycle 2 T-DXd only**	**Cycle 3 T-DXd + ritonavir**	**Cycle 2 T-DXd only**	**Cycle 3 T-DXd + itraconazole**
T-DXd				
C_{max}, μg/mL	133 (25.5)	140 (23.0)	139 (23.6)	142 (23.9)
AUC_{17d}, μg·d/mL	650 (168)	754 (137)[a]	644 (188)	710 (187)
AUC_{tau}, μg·d/mL	701 (185)	810 (153)[b]	706 (211)	789 (217)
t_{max}, hours	1.90 (0.37)	2.73 (1.77)	3.47 (1.77)	2.68 (1.55)
$t_{1/2}$, days	7.19 (1.31)	7.51 (1.01)[a]	7.13 (1.57)	7.50 (1.53)
CL_{ss}, mL/d/kg	8.22 (2.19)	6.87 (1.29)[b]	8.39 (2.77)	7.43 (2.37)
V_z, mL/kg	83.5 (20.7)	72.8 (17.8)[b]	84.5 (26.9)	78.4 (22.4)
V_{ss}, mL/kg	72.0 (16.2)	67.3 (14.0)[b]	71.9 (20.2)	68.9 (16.5)
DXd				
C_{max}, ng/mL	8.98 (2.83)	8.95 (3.68)	8.65 (2.03)	8.93 (1.77)
AUC_{17d}, ng·d/mL	32.7 (7.45)	37.2 (6.93)[a]	29.9 (8.31)	34.8 (8.04)
AUC_{tau}, ng·d/mL	35.0 (8.10)	39.2 (7.98)[b]	32.4 (9.21)	37.7 (8.87)
t_{max}, hours	6.30 (5.64)	11.50 (19.39)	4.11 (1.95)	5.51 (1.76)
$t_{1/2}$, days	6.62 (1.76)[c]	6.60 (0.965)[a]	8.24 (2.39)[d]	6.73 (1.52)

Abbreviations: AUC_{17d}, area under the serum concentration-time curve through day 17 of cycle; AUC_{tau}, area under plasma concentration-time curve over dosing interval; C_{max}, maximum serum concentration; CL_{ss}, steady-state clearance; $t_{1/2}$, half-life; T-DXd, trastuzumab deruxtecan; t_{max}, time to maximum serum concentration; V_{ss}, steady-state volume distribution; V_z, apparent volume of distribution during the terminal phase.

[a]Eight patients were evaluable at this timepoint.

[b]Seven patients were evaluable at this timepoint.

[c]Ten patients were evaluable at this timepoint.

[d]Thirteen patients were evaluable at this timepoint.

(**Table 1**). Breast cancer was the most common cancer type, followed by salivary gland cancer and NSCLC, and about half of patients had received trastuzumab in a prior line of therapy (**Table 1**). At data cutoff (December 13, 2019), the median duration of follow up was 289 days (range, 3–675). A total of 5 patients (29.4%) in cohort 1 and 3 patients (13.0%) in cohort 2 remained on treatment (Supplementary Fig. S1). Of 40 patients, 32 (80.0%) discontinued treatment: 20 (50.0%) due to disease progression as per RECIST v1.1, 7 (17.5%) due to an AE, 2 (5.0%) based on clinical progression, 2 (5.0%) due to withdrawal of patient consent, and 1 (2.5%) due to investigator decision (Supplementary Fig. S1).

Pharmacokinetics

A total of 26 patients were included in the pharmacokinetic analysis set (cohort 1, $n = 12$; cohort 2, $n = 14$). A total of 14 patients were excluded from the pharmacokinetic analysis set: 9 (9/40; 22.5%) because C_{max} and AUC_{17d} were not assessed in cycles 2 and 3 due to protocol deviations or because the subject had missing or incomplete dosing of an inhibitor drug and 5 (5/40; 12.5%) because the patients did not receive T-DXd at 5.4 mg/kg in cycles 2 and 3 due to a dose reduction (Supplementary Fig. S1).

The C_{max} of T-DXd was similar between cycle 2 (T-DXd alone) and cycle 3 (T-DXd plus ritonavir or itraconazole), whether T-DXd was combined with ritonavir [cohort 1, cycle 3/cycle 2 ratio (90% CI): 1.05 (0.98–1.13)] or with itraconazole [cohort 2, 1.03 (0.96–1.09); **Table 2**]. Similarly, the C_{max} of DXd was similar between cycle 2 and cycle 3, whether T-DXd was combined with ritonavir [cohort 1, cycle 3/cycle 2 ratio (90% CI): 0.99 (0.85–1.14)] or with itraconazole [cohort 2, 1.04 (0.92–1.18]; **Table 2**]. The AUC_{17d} of T-DXd increased from cycle 2 to cycle 3; however, the upper CI bound of the cycle 3/cycle 2 ratio remained at ≤1.25 [cycle 3/cycle 2 ratio (90% CI): cohort 1, 1.19 (1.14–1.25); cohort 2, 1.11 (1.07–1.15); **Table 2**]. The AUC_{17d} of DXd increased from 30.2 to 36.6 ng·d/mL [cycle 3/cycle 2 ratio (90% CI): 1.22 (1.08–1.37)] with ritonavir, and from 28.8 to 33.9 ng·d/mL [1.18 (1.11–1.25)] with itraconazole (**Table 2**).

The $t_{1/2}$ of T-DXd in this study population was 7–8 days (**Table 2**). The median of differences in t_{max} between cycles 3 and 2 for T-DXd calculated using the Hodges-Lehmann estimator method was 0.03 hours (90% CI, 0.00–1.97) and −0.22 hours (90% CI, −1.95 to −0.01) in cohorts 1 and 2, respectively, and for DXd was 0.15 hours (90% CI, −0.03 to 3.00) and 1.81 hours (90% CI, 0.07–2.96).

Safety

Safety analyses included all 40 patients who were enrolled and received at least 1 dose of T-DXd. The median duration of treatment with T-DXd was 273 days (range, 42–695) and 260 days (range, 21–631) for cohorts 1 and 2, respectively. The rates of dose reduction, dose interruption, and treatment discontinuation due to TEAEs were similar between cycles 2 and 3 for both cohorts, except for the incidence of dose interruption of T-DXd in cycle 3 for cohort 1 (Supplementary Table S1). Four patients (25.0%) had dose

Table 3. TEAE incidence during cycle 2, during cycle 3, and over the entire course of treatment with T-DXd plus ritonavir or T-DXd plus itraconazole.

	Cohort 1 T-DXd + ritonavir			Cohort 2 T-DXd + itraconazole		
Preferred term	**Cycle 2 ($n = 17$)**	**Cycle 3 ($n = 16$)**	**On treatment ($n = 17$)**	**Cycle 2 ($n = 22$)**	**Cycle 3 ($n = 22$)**	**On treatment ($n = 23$)**
Patients with ≥1 TEAE, *n* (%)	17 (100.0)	16 (100.0)	17 (100.0)	18 (81.8)	12 (54.5)	22 (95.7)
Hematologic TEAEs						
Neutrophil count decreased	4 (23.5)	4 (25.0)	6 (35.3)	5 (22.7)	3 (13.6)	10 (43.5)
Platelet count decreased	6 (35.3)	8 (50.0)	10 (58.8)	1 (4.5)	3 (13.6)	4 (17.4)
White blood cell count decreased	3 (17.6)	6 (37.5)	7 (41.2)	5 (22.7)	3 (13.6)	7 (30.4)
Anemia	1 (5.9)	1 (6.3)	7 (41.2)	1 (4.5)	1 (4.5)	5 (21.7)
Thrombocytopenia	3 (17.6)	3 (18.8)	3 (17.6)	1 (4.5)	0	1 (4.3)
Neutropenia	3 (17.6)	1 (6.3)	4 (23.5)	0	1 (4.5)	1 (4.3)
Nonhematologic TEAEs						
Nausea	10 (58.8)	4 (25.0)	17 (100.0)	6 (27.3)	2 (9.1)	16 (69.6)
Decreased appetite	7 (41.2)	3 (18.8)	13 (76.5)	3 (13.6)	2 (9.1)	11 (47.8)
Diarrhea	4 (23.5)	5 (31.3)	8 (47.1)	1 (4.5)	1 (4.5)	6 (26.1)
Constipation	3 (17.6)	1 (6.3)	8 (47.1)	2 (9.1)	0	8 (34.8)
Alopecia	3 (17.6)	0	6 (35.3)	4 (18.2)	0	8 (34.8)
Aspartate aminotransferase level increased	2 (11.8)	3 (18.8)	6 (35.3)	2 (9.1)	0	5 (21.7)
Fatigue	1 (5.9)	2 (12.5)	5 (29.4)	1 (4.5)	1 (4.5)	7 (30.4)
Vomiting	2 (11.8)	3 (18.8)	3 (17.6)	0	1 (4.5)	8 (34.8)
Alanine aminotransferase level increased	1 (5.9)	4 (25.0)	7 (41.2)	1 (4.5)	0	3 (13.0)
Headache	3 (17.6)	1 (6.3)	4 (23.5)	1 (4.5)	0	3 (13.0)
Blood alkaline phosphatase level increased	2 (11.8)	3 (18.8)	4 (23.5)	0	0	2 (8.7)
Stomatitis	2 (11.8)	0	5 (29.4)	0	1 (4.5)	3 (13.0)
Malaise	2 (11.8)	0	5 (29.4)	1 (4.5)	0	2 (8.7)
Nasopharyngitis	1 (5.9)	1 (6.3)	5 (29.4)	0	0	2 (8.7)
Cough	0	0	3 (17.6)	0	0	4 (17.4)
Weight decreased	0	0	3 (17.6)	0	1 (4.5)	2 (8.7)
Back pain	0	0	1 (5.9)	0	1 (4.5)	3 (13.0)
Pyrexia	0	1 (6.3)	2 (11.8)	0	0	2 (8.7)
Dry skin	0	0	3 (17.6)	0	0	1 (4.3)

Abbreviations: T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

interruption of T-DXd in cycle 3 of cohort 1 due to neutrophil count decrease ($n = 2$), neutrophil and white blood cell count decrease ($n = 1$), and hypokalemia ($n = 1$); no dose interruptions were observed in cycle 2 prior to ritonavir administration.

Patients in cohorts 1 and 2 experienced similar types and incidences of TEAEs (**Table 3**; Supplementary Table S1; refs. 5–9, 19). The incidence of TEAEs did not appear to increase from cycle 2 to cycle 3, when inhibitors were added (**Table 3**). Grade ≥3 TEAEs occurred in 10 patients (58.8%) in cohort 1 and in 13 patients (56.5%) in cohort 2, and serious TEAEs occurred in 4 (23.5%) and 5 patients (21.7%), respectively (Supplementary Table S1). During cycles 2 and 3, there were no cases of TEAEs of special interest, including ILD or pneumonitis, and there were no serious TEAEs deemed related to T-DXd, ritonavir, or itraconazole (Supplementary Table S1). During cycle 4 or beyond, ILD or pneumonitis occurred in 3 patients (17.6%) in cohort 1 and 4 patients (17.4%) in cohort 2 (Supplementary Table S1).

Antitumor activity

A total of 17 patients in cohort 1 and 19 patients in cohort 2 had measurable tumors at baseline and were assessed for response. The ORR was 52.9% (9/17; 95% CI, 27.8–77.0) in cohort 1 and 57.9% (11/19; 95% CI, 33.5–79.7) in cohort 2; all responses were PRs and all responses were confirmed except for those of one patient in cohort 1 (**Table 4**). Reductions in tumor burden were observed across multiple tumor types, including breast (total $n = 15$), salivary gland ($n = 7$), lung ($n = 6$), colorectal ($n = 1$), and other ($n = 6$) cancers across cohorts (**Fig. 2**). Responses were observed across all HER2 IHC expression levels, including IHC 1^+, across both cohorts (Supplementary Table S2). Across both cohorts combined, the DCR was 97.2%, CBR was 75.0%, and median DOR was 376 days (95% CI, 209–not evaluable; **Table 4**). The median TTR was 46 days (95% CI, 42–85), roughly corresponding to the first postbaseline tumor assessment, and patients achieved a median PFS of 419 days (95% CI, 260–not evaluable; **Table 4**).

Discussion

This study assessed potential pharmacokinetic alterations or DDIs when T-DXd was combined with ritonavir (a dual OATP1B/CYP3A inhibitor) or itraconazole (a strong CYP3A inhibitor); no clinically meaningful DDIs were observed. Concomitant use of ritonavir or itraconazole resulted in a minimal increase in exposure of both T-DXd and DXd, with cycle 3/cycle 2 90% CIs mostly within 80% to 125% of those measured on T-DXd alone.

A slight increase in exposure above the 125% threshold for DXd in cohort 1 (T-DXd plus ritonavir) was observed [AUC_{17d} cycle 3/cycle 2 ratio (90% CI): 1.22 (1.08–1.37)]. DXd has been shown to be a substrate for P-glycoprotein and BCRP, and also for OATP1B and CYP3A (3, 14). Considering that ritonavir has demonstrated inhibitory potential for P-glycoprotein and BCRP in addition to OATP1B and CYP3A (15–17, 20, 21), the observed increase in DXd exposure in cohort 1 could be the result of simultaneous OATP1B, CYP3A, P-glycoprotein, and BCRP inhibition resulting from concurrent ritonavir administration. Although pharmacokinetic parameters were evaluable in fewer patients in cycle 3 of cohort 1 than in cycle 2, this is unlikely to influence the assessment of T-DXd with and without ritonavir.

In clinical practice, ritonavir is frequently prescribed in a coformulation with lopinavir, another protease inhibitor. Ritonavir alone demonstrates maximal inhibition of hepatic and enteric CYP3A activity at doses of 100 mg twice daily (BID; ref. 22). Furthermore, the inhibitory effect of ritonavir/lopinavir on pravastatin (a known OATP1B substrate) was similar to that of ritonavir alone in studies of healthy volunteers (17, 23). Therefore, given that the

Table 4. Clinical response with T-DXd plus ritonavir (cohort 1) or T-DXd plus itraconazole (cohort 2) in patients with advanced solid tumors.

Investigator-assessed objective response per RECIST v1.1[a]	Cohort 1 T-DXd + ritonavir ($n = 17$)	Cohort 2 T-DXd + itraconazole ($n = 19$)	All patients ($n = 36$)
ORR[b], *n* (%; 95% CI)	9 (52.9; 27.8–77.0)	11 (57.9; 33.5–79.7)	20 (55.6; 38.1–72.1)
CR	0	0	0
PR	9 (52.9)	11 (57.9)	20 (55.6)
SD	8 (47.1)	7 (36.8)	15 (41.7)
PD	0	1 (5.3)	1 (2.8)
Confirmed ORR[c], *n* (%; 95% CI)	8 (47.1; 23.0–72.2)	11 (57.9; 33.5–79.7)	19 (52.8) (35.5–69.6)
DCR, *n* (%)	17 (100.0)	18 (94.7)	35 (97.2)
(95% CI)	(80.5–100.0)	(74.0–99.9)	(85.5–99.9)
CBR, *n* (%)	12 (70.6)	15 (78.9)	27 (75.0)
(95% CI)	(44.0–89.7)	(54.4–93.9)	(57.8–87.9)
Median DOR, days (95% CI)	378 (23–NE)[d]	376 (73–NE)[e]	376 (209–NE)[f]
Median TTR, days (95% CI)	46 (37–128)[d]	46 (37–85)[e]	46 (42–85)[f]
Median PFS, days (95% CI)	419 (252–NE)	420 (254–NE)	419 (260–NE)

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTR, time to response.

[a]Four patients did not have measurable tumors at baseline and were not assessed for response.

[b]Based on best overall response.

[c]Responses were confirmed by ≥2 postbaseline scans.

[d]Nine patients were evaluable.

[e]Eleven patients were evaluable.

[f]Twenty patients were evaluable.

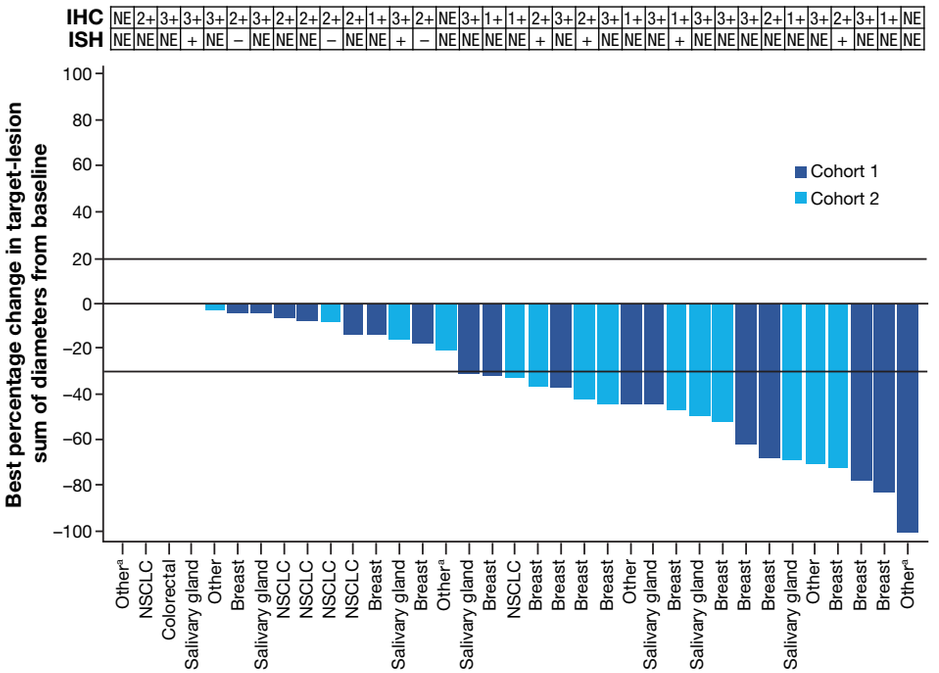

Figure 2.
Best (minimum) percentage change in target-lesion sum of diameters from baseline with T-DXd plus ritonavir (cohort 1) or T-DXd plus itraconazole (cohort 2). The best (minimum) percentage change from baseline in the sum of diameters of target lesions for patients with measurable tumors at baseline and ≥1 postbaseline scan are shown ($n = 35$). Individual bars are colored by cohort, and the cancer type for each patient is shown on the *x*-axis. The horizontal line at 20% generally indicates PD, and the horizontal line at −30% generally indicates PR. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; NE, not evaluable; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer; PD, progressive disease; PR, partial response; T-DXd, trastuzumab deruxtecan. [a]Contains *HER2* amplification as determined by NGS.

ritonavir regimen in the present study is double that needed to achieve saturating CYP3A inhibition and ritonavir/lopinavir showed a similar inhibitory effect on pravastatin to ritonavir alone (100 mg BID), the pharmacokinetics are not expected to differ from those in the present study if T-DXd were administered with ritonavir/lopinavir.

With itraconazole, an inhibitor of P-glycoprotein and CYP3A (14), DXd exposure also increased slightly [AUC_{17d} cycle 3/cycle 2 ratio (90% CI): 1.18 (1.11–1.25)]. However, the effects of P-glycoprotein inhibition and the contribution of metabolism are expected to be minimal. Increased DXd exposure could also be due to the slight increases in T-DXd exposure observed between cycle 2 and cycle 3.

This study demonstrated that T-DXd can be combined with inhibitors of OATP1B, CYP3A, P-glycoprotein, and BRCP in patients with HER2-expressing advanced solid tumors with no clinically meaningful effects on T-DXd pharmacokinetics. Although exposure to DXd was slightly elevated during inhibitor coadministration, the exposure levels of DXd detected in the blood during any cycle were negligibly small, with a maximum upper cycle 3/cycle 2 90% CI of 1.37 seen with the dual-enzyme inhibitor ritonavir.

In addition to pharmacokinetics, the safety profile did not show additional risks with the concomitant use of T-DXd and OATP1B/CYP3A inhibitors. The incidence of TEAEs did not increase in cycle 3 (T-DXd plus ritonavir or itraconazole) compared with cycle 2 (T-DXd alone), and the incidence of TEAEs of special interest, including ILD and pneumonitis, were consistent with previous studies of T-DXd (5–8). Additional follow up may be needed to assess the long-term safety of concomitant OATP1B/CYP3A inhibition on T-DXd due to the limited duration of follow up in this study.

The safety profile of T-DXd when administered concomitantly with ritonavir or itraconazole was consistent with previous studies of T-DXd in advanced solid tumors (Supplementary Table S2; refs. 5–9, 19). The most common TEAEs with T-DXd were gastrointestinal or hematologic in nature, and no new safety signals were observed with either combination. TEAEs related to ritonavir occurred more frequently than those related to itraconazole; however, no serious TEAEs related to either ritonavir or itraconazole occurred in either cohort during cycle 2 or cycle 3. Increased dose interruption of ritonavir [on treatment, 3/17 (17.6%)] may be related to the frequency of neutropenia in this group [on treatment, 4/17 (23.5%)].

T-DXd demonstrated durable antitumor responses in this study in patients with HER2-expressing advanced solid tumors, similar to activity of T-DXd monotherapy previously observed in phase I studies (5–8). Tumor regression with T-DXd was observed across various HER2-expressing tumor types, including those in breast, salivary gland, lung, and colorectal cancers. Furthermore, responses were observed across all HER2 IHC expression levels, including patients with low HER2 expression. Although pooled across tumor indications, these responses were also prolonged, with a median DOR of 376 days (95% CI: 209–not evaluable).

Given the recent approvals of T-DXd to treat HER2-positive breast and gastric cancer and the promising results emerging in additional indications, a complete understanding of the characteristics of T-DXd, including its pharmacokinetic profile, metabolism, and potential for DDI, is critical. This study investigated the DDI of OATP1B/CYP3A inhibitors with T-DXd after multiple doses in patients with HER2-expressing advanced solid tumors and did not find clinically meaningful DDIs between T-DXd and ritonavir or itraconazole.

Authors' Disclosures

S. Takahashi reports grants from Daiichi Sankyo during the conduct of the study, as well as grants and personal fees from MSD, AstraZeneca, Chugai, Bayer, Ono Pharmaceutical, and Bristol-Myers Squibb outside the submitted work. M. Takahashi reports personal fees from Daiichi Sankyo during the conduct of the study, as well as personal fees from AstraZeneca, Eli Lilly, Pfizer, and Eisai and grants from Taiho and Kyowa Kirin outside the submitted work. J. Watanabe reports personal fees from Daiichi Sankyo during the conduct of the study, as well as personal fees from Chugai Pharmaceuticals, Eisai, Eli Lilly, Novartis Pharma, Pfizer, and Taiho Pharmaceuticals

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Authors' Contributions

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References

1. Ogitani Y, Aida T, Hagihara K, Yamaguchi J, Ishii C, Harada N, et al. DS-8201a, A novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res 2016;22:5097–108.
2. ENHERTU for Intravenous drip infusion 100 mg (SPC) [prescribing information]. Chuo-ku, Tokyo: Daiichi Sankyo Co. LTD; 2020.
3. ENHERTU (fam-trastuzumab deruxtecan-nxki) [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo Inc.; 2021.
4. Enhertu 100 mg powder for concentrate for solution for infusion (SPC). Munich, Germany: Daiichi Sankyo Europe GmbH; 2021.
5. Doi T, Shitara K, Naito Y, Shimomura A, Fujiwara Y, Yonemori K, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. Lancet Oncol 2017;18:1512–22.
6. Shitara K, Iwata H, Takahashi S, Tamura K, Park H, Modi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. Lancet Oncol 2019;20:827–36.
7. Tamura K, Tsurutani J, Takahashi S, Iwata H, Krop IE, Redfern C, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. Lancet Oncol 2019;20:816–26.
8. Tsurutani J, Iwata H, Krop I, Jänne PA, Doi T, Takahashi S, et al. Targeting HER2 with trastuzumab deruxtecan: a dose-expansion, phase I study in multiple advanced solid tumors. Cancer Discov 2020;10:688–701.
9. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382:2419–30.
10. Smit EF, Nakagawa K, Nagasaka M, Felip E, Goto Y, Li BT, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with *HER2*-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung01. J Clin Oncol 2020;38:9504.
11. Siena S, Di Bartolomeo M, Raghav KPS, Masuishi T, Loupakis F, Kawakami H, et al. A phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01. J Clin Oncol 2020;38:4000.
12. Kovacsics D, Patik I, Özvegy-Laczka C. The role of organic anion transporting polypeptides in drug absorption, distribution, excretion and drug-drug interactions. Expert Opin Drug Metab Toxicol 2017;13:409–24.
13. McDonnell AM, Dang CH. Basic review of the cytochrome p450 system. J Adv Pract Oncol 2013;4:263–8.
14. Nagai Y, Oitate M, Shiozawa H, Ando O. Comprehensive preclinical pharmacokinetic evaluations of trastuzumab deruxtecan (DS-8201a), a HER2-targeting antibody-drug conjugate, in cynomolgus monkeys. Xenobiotica 2019;49:1086–96.
15. U.S. Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. 2020 [updated 03/10/2020]. Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.
16. Karlgren M, Vildhede A, Norinder U, Wisniewski JR, Kimoto E, Lai Y, et al. Classification of inhibitors of hepatic organic anion transporting polypeptides (OATPs): influence of protein expression on drug-drug interactions. J Med Chem 2012;55:4740–63.
17. Ieiri I, Tsunemitsu S, Maeda K, Ando Y, Izumi N, Kimura M, et al. Mechanisms of pharmacokinetic enhancement between ritonavir and saquinavir; micro/small dosing tests using midazolam (CYP3A4), fexofenadine (p-glycoprotein), and pravastatin (OATP1B1) as probe drugs. J Clin Pharmacol 2013;53:654–61.
18. NORVIR (ritonavir) tablets, for oral use NORVIR (ritonavir) oral solution NORVIR (ritonavir) oral powder [prescribing information]. Chicago, IL: AbbVie Inc.; 2019.

19. Modi S, Park H, Murthy RK, Iwata H, Tamura K, Tsurutani J, et al. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase Ib study. J Clin Oncol 2020;38:1887–96.
20. Bierman WFW, Scheffer GL, Schoonderwoerd A, Jansen G, van Agtmael MA, Danner SA, et al. Protease inhibitors atazanavir, lopinavir and ritonavir are potent blockers, but poor substrates, of ABC transporters in a broad panel of ABC transporter-overexpressing cell lines. J Antimicrob Chemother 2010;65:1672–80.
21. Gupta A, Zhang Y, Unadkat JD, Mao Q. HIV protease inhibitors are inhibitors but not substrates of the human breast cancer resistance protein (BCRP/ABCG2). J Pharmacol Exp Ther 2004;310:334–41.
22. Greenblatt DJ. Evidence-based choice of ritonavir as index CYP3A inhibitor in drug-drug interaction studies. J Clin Pharmacol 2016;56:152–6.
23. Chauvin B, Drouot S, Barrail-Tran A, Taburet AM. Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. Clin Pharmacokinet 2013;52:815–31.