

SUPPLEMENTARY INFORMATION

SUPPLEMENTARY TABLES

Table S1. Summary of studies included in the analysis

Study identifier	Study design	Study drug administration	Patients, N	Patient diagnosis	Sampling schedule
DS8201-A-J101 (Study J101)	Phase 1, 2-part, multicenter, nonrandomized, open-label, multiple-dose, first-in-human study	FL-DP1 or FL-DP2 T-DXd IV infusion Q3W <u>Dose escalation (part 1)</u> 0.8, 1.6, 3.2, 5.4, 6.4, or 8.0 mg/kg <u>Dose expansion (part 2)</u> 5.4 or 6.4 mg/kg	<u>Planned</u> Dose escalation (part 1): ≥ 18 Dose expansion (part 2): ≈ 260 <u>Treated</u> Part 1: 27 Part 2: 262	Part 1: advanced breast cancer or gastric/gastroesophageal junction adenocarcinoma Part 2a: T-DM1-treated HER2-overexpressing breast cancer Part 2b: Trastuzumab-treated HER2-overexpressing gastric or gastroesophageal junction adenocarcinoma Part 2c: low HER2-expressing breast cancer Part 2d: other HER2-expressing solid malignant tumors Part 2e: HER2-expressing breast cancer	Prior to and after the infusion for cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 hours after start of infusion on cycle 1; on day 2, 4, 8, and 15 of cycle 1; and on day 8 and 15 of cycle 3 ^{a,b}
DS8201-A-U201 (Study U201)	Phase 2, 2-part, global, multicenter, randomized, open-label, multiple-dose study	FL-DP2 or Lyo-DP T-DXd IV infusion Q3W <u>Part 1</u> 5.4, 6.4, or 7.4 mg/kg <u>Part 2</u> 5.4 mg/kg	<u>Planned</u> Part 1: ≈ 120 Part 2: ≥ 100 <u>Treated</u> Part 1: 119 Part 2: 134	T-DM1-treated HER2-positive, unresectable and/or metastatic breast cancer	Prior to and after the infusion on cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 hours after start of infusion on cycle 1; on days 8 and 15 of cycle 1; and at 4 and 7 hours after the start of infusion in cycle 3 ^{b,c}
DS8201-A-J102 (Study J102)	Phase 1, multicenter, nonrandomized, open-label, multiple-dose study	Lyo-DP T-DXd 6.4 mg/kg IV infusion Q3W	<u>Planned</u> 50 <u>Treated</u> 51	HER2-expressing metastatic and/or unresectable breast cancer	Similar to the PK stage of study U201 but with additional collection points at 2 hours after the start of infusion and days 2, 4, 8, and 15 of cycle 3
DS8201-A-A103 (Study A103)	Phase 1, multicenter, nonrandomized, open-label study	Lyo-DP T-DXd 6.4 mg/kg IV infusion Q3W	<u>Planned</u> 12 <u>Treated</u> 12	HER2-positive, advanced, unresectable and/or refractory gastric/gastroesophageal junction adenocarcinoma or breast cancer	Similar to the PK stage of study U201 but with additional collection points at 2 hours after the start of infusion and days 2, 4, 8, and 15 of cycle 3
DS8201-A-A104 (Study A104)	Phase 1, multicenter, nonrandomized, open-label, single-sequence crossover DDI study	Lyo-DP T-DXd 5.4 mg/kg IV Q3W <u>Cohort 1</u> + ritonavir 200 mg BID on day 17 of cycle 2 until day 21 of cycle 3 <u>Cohort 2</u> + itraconazole 200 mg BID on day 17 of cycle 2 followed by 200 mg once daily until day 21 of cycle 3	<u>Planned</u> Cohort 1: 16 Cohort 2: 16 <u>Treated</u> Cohort 1: 17 Cohort 2: 23	HER2-expressing advanced solid tumors	Prior to and after the infusion on cycles 1, 2, 3, 4, 6, and 8; at 2, 4, and 7 hours after the start of infusion on cycles 2 and 3; and at days 2, 4, 8, 12, and 17 of cycles 2 and 3 ^b

BID, twice daily; DDI, drug-drug interaction; FL-DP1, frozen liquid drug product 1; FL-DP2, frozen liquid drug product 2; HER2, human epidermal growth factor receptor 2; IV, intravenous; Lyo-DP, lyophilized powder drug product; PK, pharmacokinetics; Q3W, every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

^a Additional PK samples were collected at 4 hours from the start of infusion in cycle 3 during dose-escalation phase.

^b PK samples were also conditionally collected on day 22 if day 1 of the next cycle was delayed by ≥ 3 days or the patient could not continue to the next cycle.

^c Additional sampling at days 2 and 4 of cycle 1 was performed for the PK stage of Part 1.

The following time window was allowed for PK samples collected beyond day 1 of cycle 1: ± 2 hours for days 2 and 4; ± 1 day for days 8, 12, 15, and 17; and ± 2 days for day 22.

Table S2. List of covariates

Intact T-DXd
Formulation (FL-DP1, FL-DP2, Lyo-DP)
Baseline tumor size (ie, sum of diameters of target lesions at baseline)
Baseline albumin
Baseline LDH
HER2 status (positive vs negative vs unknown)
Tumor type (breast vs gastric vs other)
Baseline body weight
Age
Sex
Race (white, black or African American, Asian, other)
Country (Japan vs non-Japan Asia vs non-Japan other)
Prior HER2 therapy (no vs yes)
Released Drug
Formulation (FL-DP1, FL-DP2, Lyo-DP)
Baseline body weight
Age
Sex
Race (white, black or African American, Asian, other)
Country (Japan vs non-Japan Asia vs non-Japan other)
Baseline liver function parameters (alanine aminotransferase, AST, total bilirubin [TBIL])
Hepatic impairment/function by National Cancer Institute organ dysfunction working group [NCI ODWG] criteria)
Baseline renal function parameters (creatinine clearance)
Baseline tumor size
OATP1B/CYP3A inhibitor

CYP3A, cytochrome P450 gene, 3A subfamily; FL-DP1, frozen liquid drug product 1; FL-DP2, frozen liquid drug product 2; HER2, human epidermal growth factor receptor 2; LDH, lactate dehydrogenase; Lyo-DP, lyophilized powder; OATP1B, organic anion transporting polypeptide 1B transporter.

Table S3. Summary of baseline categorical covariates by study

Covariate category	Count (%) ^a					
	Study J101 (N = 286)	Study U201 (N = 250)	Study J102 (N = 51)	Study A103 (N = 12)	Study A104 (N = 40)	Overall (N = 639)
Formulation						
FL-DP1	265 (92.7)	0	0	0	0	265 (41.5)
FL-DP2	21 (7.3)	142 (56.8)	0	0	0	163 (25.5)
Lyo-DP	0	108 (43.2)	51 (100)	12 (100)	40 (100)	211 (33.0)
Sex						
Female	224 (78.3)	250 (100)	51 (100)	12 (100)	22 (55.0)	559 (87.5)
Male	62 (21.7)	0	0	0	18 (45.0)	80 (12.5)
Race						
Asian	190 (66.4)	101 (40.4)	51 (100)	12 (100)	40 (100)	394 (61.7)
White	80 (28.0)	132 (52.8)	0	0	0	212 (33.2)
Black or African American	8 (2.8)	5 (2.0)	0	0	0	13 (2.0)
Other	8 (2.8)	7 (2.8)	0	0	0	15 (2.3)
Unknown	0	5 (2.0)	0	0	0	5 (0.8)
Country						
Japan	177 (61.9)	53 (21.2)	51 (100)	0	31 (77.5)	312 (48.8)
Non-Japan Asia	14 (4.90)	49 (19.6)	0	12 (100)	9 (22.5)	84 (13.2)
Other	95 (33.2)	148 (59.2)	0	0	0	243 (38.0)
Hepatic function						
Normal	169 (59.1)	141 (56.4)	26 (51.0)	9 (75.0)	30 (75.0)	375 (58.7)
Mild impairment	117 (40.9)	105 (42.0)	25 (49.0)	3 (25.0)	10 (25.0)	260 (40.7)
Moderate impairment	0	1 (0.40)	0	0	0	1 (0.2)
Unknown	0	3 (1.20)	0	0	0	3 (0.5)
Tumor type						
Breast cancer	182 (63.6)	250 (100)	51 (100)	12 (100)	17 (42.5)	512 (80.1)
Gastric/gastroesophageal cancer	47 (16.4)	0	0	0	1 (2.5)	48 (7.5)
Colorectal cancer	20 (7.0)	0	0	0	1 (2.5)	21 (3.3)
NSCLC	18 (6.3)	0	0	0	6 (15.0)	24 (3.8)
Other cancer	19 (6.6)	0	0	0	15 (37.5)	34 (5.3)
HER2 status						
Positive ^b	187 (65.4)	249 (99.6)	4 (7.8)	12 (100)	23 (57.5)	475 (74.3)
Negative	69 (24.1)	1 (0.4)	47 (92.2)	0	14 (35.0)	131 (20.5)
Unknown/other ^c	30 (10.5)	0	0	0	3 (7.50)	33 (5.2)
Prior HER2 therapy						
Yes	201 (70.3)	250 (100)	12 (23.5)	12 (100)	24 (60.0)	499 (78.1)
No	85 (29.7)	0	39 (76.5)	0	16 (40.0)	140 (21.9)

CYP3A, cytochrome P450 gene, 3A subfamily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; 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; Lyo-DP, lyophilized powder; NSCLC, non-small-cell lung cancer; OATP1B, organic anion transporting polypeptide 1B transporter.

^a Per-study percentage for each category was computed by dividing with the study total; overall percentage per category was computed by dividing with the total number of patients included in the analysis (639).

^b HER2 positive was determined as HER2 ISH positive and/or IHC 3+.

^c HER2 unknown/other includes unknown HER2 status in breast/gastric cancer and other tumor types.

Note: OATP1B/CYP3A inhibitor use was determined only in Study A104 (not shown).

Table S4. Summary of baseline continuous covariates by study

Covariate statistic	J101 (N = 286)	U201 (N = 250)	J102 (N = 51)	A103 (N = 12)	A 104 (N = 40)	Overall (N = 639)
Age, years						
Mean (SD)	58.3 (11.4)	55.8 (11.9)	55.9 (10.5)	54.9 (8.7)	56.5 (12.0)	57.0 (11.6)
Median (range)	58.0 (23.0- 83.0)	56.0 (28.0- 96.0)	56.0 (31.0- 79.0)	54.5 (36.0- 69.0)	57.0 (31.0- 80.0)	57.0 (23.0- 96.0)
Body weight, kg						
Mean (SD)	59.8 (14.9)	61.4 (13.8)	52.7 (7.8)	60.4 (5.8)	59.2 (12.9)	59.9 (13.9)
Median (range)	58.1 (34.6- 125.4)	59.7 (37.9- 121.0)	51.5 (38.9- 75.2)	60.0 (51.0- 68.0)	55.8 (41.3- 90.7)	57.8 (34.6- 125.4)
BSA, m ²						
Mean (SD)	1.6 (0.2)	1.6 (0.2)	1.5 (0.1)	1.6 (0.1)	1.6 (0.2)	1.6 (0.2)
Median (range)	1.6 (1.2-2.3)	1.6 (1.3-2.2)	1.5 (1.2-1.8)	1.6 (1.5-1.8)	1.6 (1.3-2.0)	1.6 (1.2-2.3)
Albumin, g/L						
Mean (SD)	37.9 (4.5)	40.2 (3.7)	39.1 (4.5)	42.0 (4.2)	40.8 (3.7)	39.1 (4.3)
Median (range)	38.0 (23.0- 50.0)	41.0 (22.0- 50.0)	40.0 (28.0- 48.0)	41.5 (31.0- 47.0)	41.0 (31.0- 49.0)	40.0 (22.0- 50.0)
LDH, U/L						
Mean (SD)	336.7 (378.2)	276.8 (205.9)	271.7 (137.2)	403.6 (592.3)	254.6 (130.9)	304.2 (300.3)
Median (range)	238.0 (115.0- 3815.0)	221.5 (109.0- 1896.0)	242.0 (142.0- 891.0)	234.5 (140.0- 2262.0)	206.5 (148.0- 865.0)	227 (109.0- 3815.0)
ALT, U/L						
Mean (SD)	24.3 (20.3)	24.8 (17.1)	24.8 (15.1)	16.6 (9.8)	21.4 (16.0)	24.2 (18.3)
Median (range)	18.0 (5.0- 202.0)	19.5 (6.0- 138.0)	21.0 (6.0-88.0)	12.5 (9.0-41.0)	17.0 (7.0-87.0)	19.0 (5.0- 202.0)
AST, U/L						
Mean (SD)	37.7 (24.9)	39.7 (25.9)	35.6 (19.6)	29.3 (15.9)	28.9 (15.4)	37.6 (24.4)
Median (range)	30.0 (10.0- 170.0)	32.0 (13.0- 189.0)	28.0 (15.0- 103.0)	21.5 (16.0- 63.0)	24.5 (12.0- 82.0)	30.0 (10.0- 189.0)
Total bilirubin, μmol/L						
Mean (SD)	9.5 (4.5)	8.1 (5.2)	10.8 (4.3)	9.6 (1.8)	9.5 (3.2)	9.1 (4.7)
Median (range)	8.6 (3.4-28.2)	7.0 (3.0-56.0)	10.3 (5.1-23.9)	9.1 (6.7-12.5)	8.6 (5.1-18.8)	8.0 (3.0-56.0)
CrCL, mL/min						
Mean (SD)	89.8 (30.0)	93.0 (29.8)	91.6 (23.4)	87.9 (24.2)	94.8 (30.3)	91.5 (29.3)
Median (range)	84.8 (28.3- 188.0)	89.2 (31.8- 189.2)	87.5 (55.8- 143.8)	77.4 (61.0- 139.1)	88.1 (50.5- 188.1)	87.2 (28.3- 189.2)
Tumor size, mm						
Mean (SD)	70.4 (46.0)	66.5 (43.8)	63.4 (40.0)	73.6 (45.6)	60.9 (36.0)	67.8 (44.1)
Median (range)	57.0 (10.0- 267.0)	57.0 (11.0- 245.0)	57.0 (14.0- 230.0)	62.0 (23.0- 177.0)	55.0 (16.0- 189.0)	57.0 (10.0- 267.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CrCL, creatinine clearance, derived using Cockcroft-Gault formula; LDH, lactate dehydrogenase; U, unit.

Table S5. Summary of baseline categorical covariates by T-DXd dose level

Covariate category	Count (%) ^a							
	0.8 mg/kg (N = 3)	1.6 mg/kg (N = 3)	3.2 mg/kg (N = 3)	5.4 mg/kg (N = 313)	6.4 mg/kg (N = 290)	7.4 mg/kg (N = 21)	8.0 mg/kg (N = 6)	Overall (N = 639)
Formulation								
FL-DP1	3 (100)	3 (100)	3 (100)	91 (29.1)	159 (54.8)	0	6 (100)	265 (41.5)
FL-DP2	0	0	0	74 (23.6)	68 (23.4)	21 (100)	0	163 (25.5)
Lyo-DP	0	0	0	148 (47.3)	63 (21.7)	0	0	211 (33.0)
Sex								
Female	3 (100)	3 (100)	3 (100)	282 (90.1)	242 (83.4)	21 (100)	5 (83.3)	559 (87.5)
Male	0	0	0	31 (9.9)	48 (16.6)	0	1 (16.7)	80 (12.5)
Race								
Asian	3 (100)	3 (100)	3 (100)	155 (49.5)	215 (74.1)	12 (57.1)	3 (50.0)	394 (61.7)
White	0	0	0	137 (43.8)	64 (22.1)	8 (38.1)	3 (50.0)	212 (33.2)
Black or African American	0	0	0	8 (2.6)	4 (1.4)	1 (4.8)	0	13 (2.0)
Other	0	0	0	9 (2.9)	6 (2.1)	0	0	15 (2.3)
Unknown	0	0	0	4 (1.3)	1 (0.3)	0	0	5 (0.8)
Country								
Japan	3 (100)	3 (100)	3 (100)	99 (31.6)	190 (65.5)	11 (52.4)	3 (50.0)	312 (48.8)
Non-Japan Asia	0	0	0	58 (18.5)	25 (8.6)	1 (4.8)	0	84 (13.1)
Other	0	0	0	156 (49.8)	75 (25.9)	9 (42.9)	3 (50.0)	243 (38.0)
Hepatic function								
Normal	2 (66.7)	2 (66.7)	2 (66.7)	182 (58.1)	169 (58.3)	14 (66.7)	4 (66.7)	375 (58.7)
Mild impairment	1 (33.3)	1 (33.3)	1 (33.3)	128 (40.9)	120 (41.4)	7 (33.3)	2 (33.3)	260 (40.7)
Moderate impairment	0	0	0	1 (0.3)	0	0	0	1 (0.2)
Unknown	0	0	0	2 (0.6)	1 (0.3)	0	0	3 (0.5)
Tumor type								
Breast cancer	3 (100)	1 (33.3)	3 (100)	270 (86.3)	209 (72.1)	21 (100)	5 (83.3)	512 (80.1)
Gastric/gastroesophageal cancer	0	2 (66.7)	0	21 (6.7)	24 (8.3)	0	1 (16.7)	48 (7.5)
Colorectal cancer	0	0	0	1 (0.3)	20 (6.9)	0	0	21 (3.3)
NSCLC	0	0	0	6 (1.9)	18 (6.2)	0	0	24 (3.8)
Other cancer	0	0	0	15 (4.8)	19 (6.6)	0	0	34 (5.3)
HER2 status								
Positive ^b	2 (66.7)	3 (100)	0	273 (87.2)	174 (60.0)	21 (100)	2 (33.3)	475 (74.3)
Negative	1 (33.3)	0	2 (66.7)	37 (11.8)	87 (30.0)	0	4 (66.7)	131 (20.5)
Unknown/other ^c	0	0	1 (33.3)	3 (1.0)	29 (10.0)	0	0	33 (5.2)
Prior HER2 therapy								
Yes	2 (66.7)	3 (100)	1 (33.3)	277 (88.5)	191 (65.9)	21 (100)	4 (66.7)	499 (78.1)
No	1 (33.3)	0	2 (66.7)	36 (11.5)	99 (34.1)	0	2 (33.3)	140 (21.9)

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; Lyo-DP, lyophilized powder; NSCLC, non-small-cell lung cancer.

^a Per-study percentage for each category was computed by dividing with the study total; overall percentage per category was computed by dividing with the total number of patients included in the analysis (639).

^b HER2 positive was determined as HER2 ISH positive and/or IHC 3+.

^c HER2 unknown/other includes unknown HER2 status in breast/gastric cancer and other tumor types.

Table S6. Summary of baseline continuous covariates by T-DXd dose level

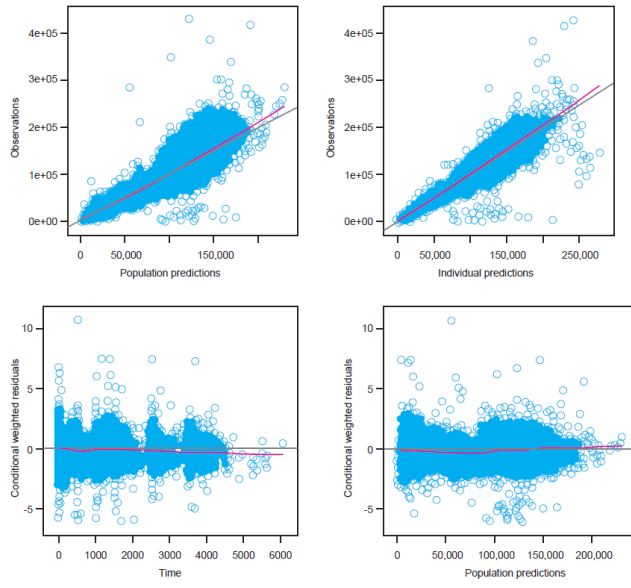
Covariate statistic	0.8 mg/kg (N = 3)	1.6 mg/kg (N = 3)	3.2 mg/kg (N = 3)	5.4 mg/kg (N = 313)	6.4 mg/kg (N = 290)	7.4 mg/kg (N = 21)	8.0 mg/kg (N = 6)	Overall (N = 639)
Age, years								
Mean (SD)	59.3 (7.10)	66.3 (4.70)	48.3 (14.6)	56.9 (11.9)	57.1 (11.2)	54.4 (10.5)	66.2 (10.7)	57 (11.6)
Median (range)	58 (53-67)	68 (61-70)	42 (38-65)	57 (28-96)	57 (23-83)	54 (32-69)	69.5 (46-74)	57 (23-96)
Body weight, kg								
Mean (SD)	57.3 (7.50)	53.8 (15.0)	52.5 (6.3)	61.7 (14.7)	58.3 (13.1)	54.6 (10.7)	64.4 (13.2)	59.9 (13.9)
Median (range)	60.6 (48.8-62.6)	49.9 (41.1-70.4)	50.5 (47.4-59.6)	59 (35.2-125.4)	57 (34.6-118.8)	54.9 (38.5-77.8)	60.8 (51.2-85.7)	57.8 (34.6-125.4)
Albumin, g/L								
Mean (SD)	40.3 (3.50)	36.7 (6.40)	38.7 (7.60)	39.7 (4.00)	38.5 (4.60)	40.0 (3.90)	40.0 (3.90)	39.1 (4.30)
Median (range)	40 (37-44)	34 (32-44)	37 (32-47)	40 (23-50)	39 (22-50)	41 (29-45)	40 (35-46)	40 (22-50)
LDH, U/L								
Mean (SD)	271.1 (149.4)	259 (49.5)	329.7 (199.3)	281.6 (192.5)	331.6 (394)	282.7 (165.2)	257.5 (85.4)	304.2 (300.3)
Median (range)	193 (178-444)	241 (221-315)	266 (170-553)	227 (109-1896)	227 (121-3815)	203 (158-764)	245 (154-355)	227 (109-3815)
ALT, U/L								
Mean (SD)	20 (6.90)	19.3 (9.60)	13.7 (12.5)	24.3 (17.6)	24.3 (19.8)	23.6 (11.8)	27 (12.9)	24.2 (18.3)
Median (range)	16 (16-28)	21 (9-28)	8 (5-28)	19 (5-138)	18 (6-202)	19 (10-50)	22.5 (15-48)	19 (5-202)
AST, U/L								
Mean (SD)	41.7 (33.2)	35.3 (14.5)	24.3 (14.5)	38.6 (25.4)	36.7 (23.8)	37.1 (21.4)	36.2 (15.5)	37.6 (24.4)
Median (range)	23 (22-80)	35 (21-50)	17 (15-41)	32 (10-189)	29 (10-157)	31 (16-99)	34 (19-56)	30 (10-189)
Total bilirubin, $\mu\text{mol/L}$								
Mean (SD)	10.8 (3.70)	9.7 (2.00)	10.9 (5.80)	8.8 (5.10)	9.5 (4.50)	6.9 (2.10)	8 (3.40)	9.1 (4.70)
Median (range)	12 (6.7-13.7)	8.7 (8.4-12)	10.3 (5.5-17.1)	8 (3-56)	8.6 (3-30)	7 (3-11)	7.7 (4.6-12)	8 (3-56)
CrCL, mL/min								
Mean (SD)	73.4 (11.1)	69.0 (24.3)	105.9 (19.7)	91.1 (29.5)	92.6 (30.0)	89 (19.8)	77.5 (20.4)	91.5 (29.3)
Median (range)	75.9 (61.2-82.9)	81.6 (40.9-84.3)	112.4 (83.8-121.4)	87.2 (28.3-188.1)	88.3 (33.5-189.2)	86.1 (50.8-118.5)	73 (56.9-116.2)	87.2 (28.3-189.2)
Tumor size, mm								
Mean (SD)	51.7 (41.0)	78.7 (49.2)	72.3 (18.2)	65.6 (42.7)	70.7 (44.7)	63.7 (56.3)	54 (53.5)	67.8 (44.1)
Median (range)	29 (27-99)	57 (44-135)	78 (52-87)	57 (11-252)	57 (10-267)	45 (11-238)	39 (13-158)	57 (10-267)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCL, creatinine clearance, derived using Cockcroft-Gault formula; LDH, lactate dehydrogenase; U, unit.

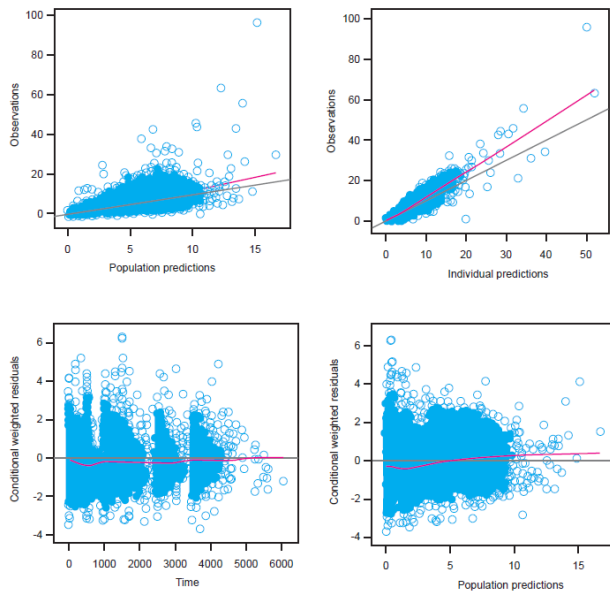
SUPPLEMENTARY FIGURES

Figure S1. Goodness of fit of the final intact trastuzumab deruxtecan model (A) and final released-drug model (B).

A

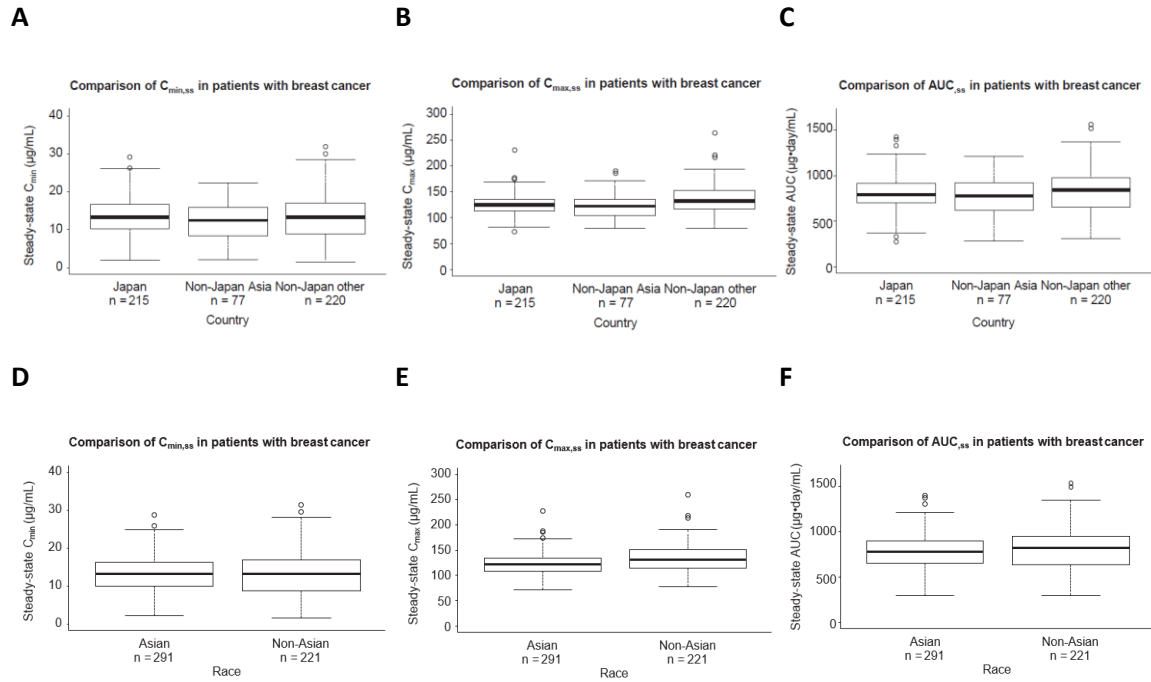


B



Note: The blue circles represent observations, the grey line represents the identity line, and the red curve represents the locally weighted scatterplot smoothers.

Figure S2. Steady-state intact trastuzumab deruxtecan (T-DXd) exposures with T-DXd 5.4 mg/kg every 3 weeks, stratified by country (A-C)^a and race (D-F)^b



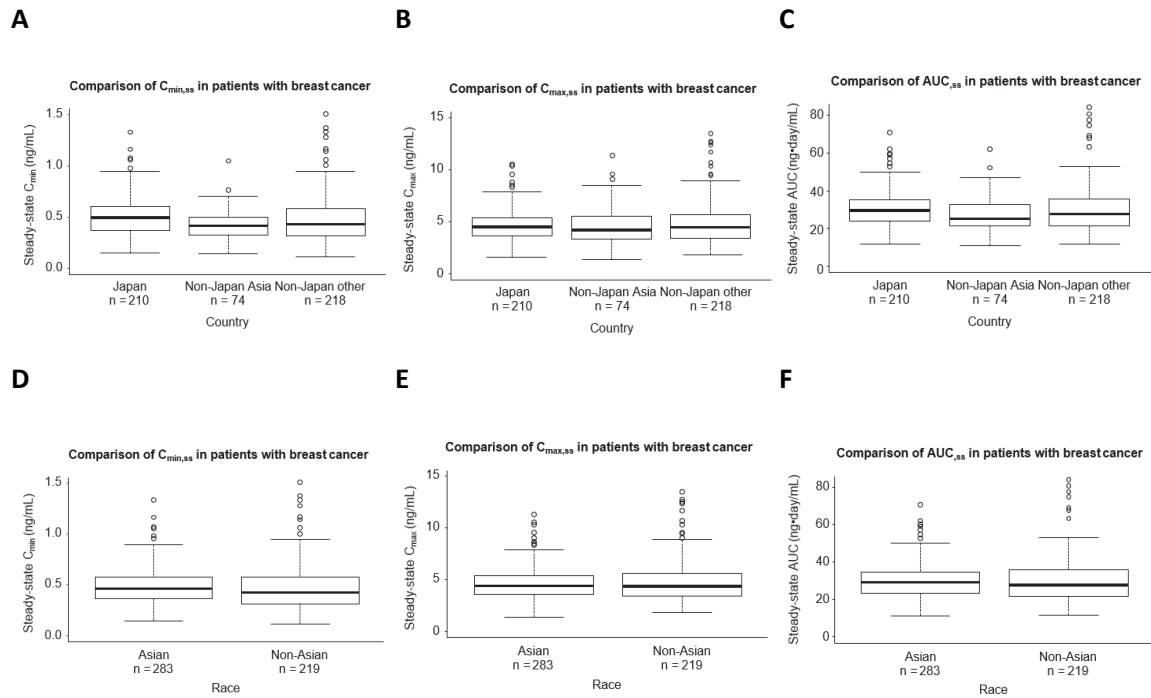
$AUC_{0-24,ss}$, area under the concentration-time curve at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state.

Note: 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.

^a The geometric mean ratios for all intact T-DXd exposure metrics ranged from 0.921 to 1.17 comparing Japanese patients with non-Japanese patients and from 0.900 to 0.916 comparing non-Japanese Asian patients with non-Asian patients.

^b The geometric mean ratios for all intact T-DXd exposure metrics ranged from 0.919 to 1.10 comparing Asian with non-Asian patients.

Figure S3. Steady-state released-drug exposures with trastuzumab deruxtecan 5.4 mg/kg every 3 weeks, stratified by country (A-C)^a and race (D-F)^b



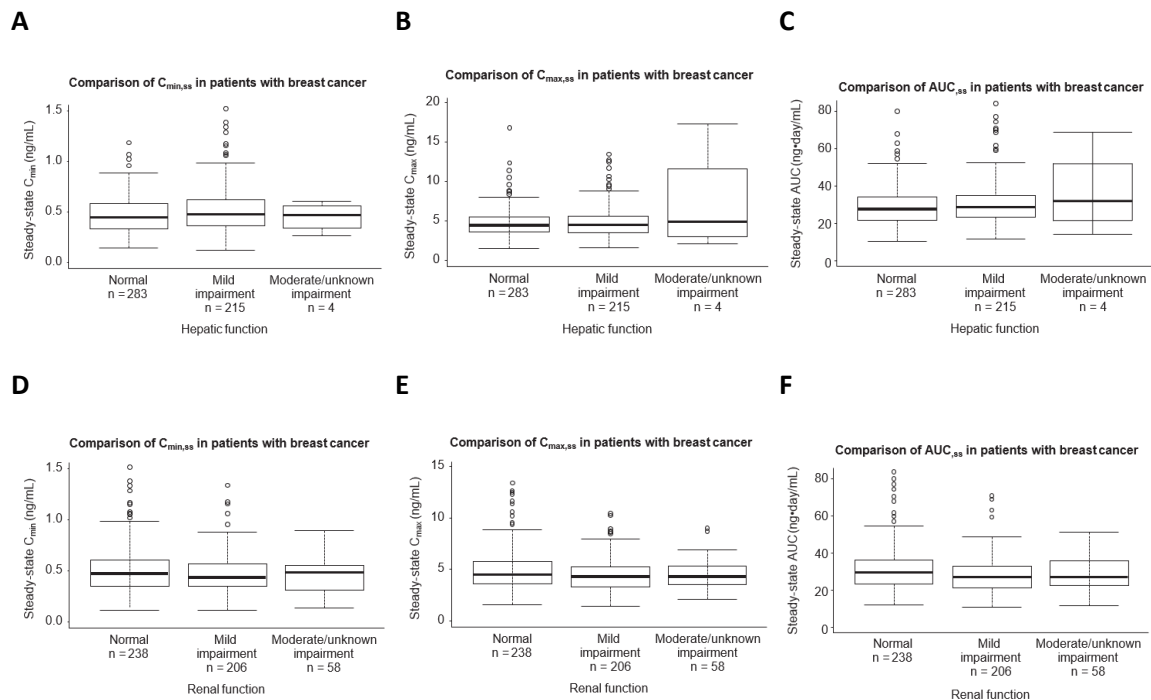
AUC_{ss} , area under the concentration-time curve at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state.

Note: 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.

^a The geometric mean ratios for all released-drug exposure metrics ranged from 0.965 to 1.19 comparing Japanese patients with non-Japanese patients and from 0.868 to 0.918 comparing non-Japanese Asian patients with all non-Japanese patients.

^b The geometric mean ratios for all released T-DXd exposure metrics ranged from 0.953 to 1.10 comparing Asian with non-Asian patients.

Figure S4. Steady-state released-drug exposures with trastuzumab deruxtecan 5.4 mg/kg every 3 weeks, stratified by hepatic function (A-C)^a and renal function (D-F)^b



AUC_{ss} , area under the concentration-time curve at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; NCI ODWG, National Cancer Institute Organ Dysfunction Working Group.

Note: 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. Hepatic impairment status was based on NCI ODWG Criteria.

^a The geometric mean ratios for all released-drug exposure metrics ranged from 1.02 to 1.11 in patients with mild hepatic impairment compared with normal hepatic function.

^b The geometric mean ratios for all released-drug exposure metrics ranged from 0.908 to 0.953 and 0.921 to 0.957 comparing exposure in patients with mild renal impairment against normal renal function and in patients with moderate/severe renal impairment against normal renal function, respectively.