Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplemental Methods

Inclusion Criteria

- Men or women aged ≥20 years in Japan and Korea, aged ≥18 years in other countries
- Pathologically documented breast cancer
    - Unresectable or metastatic
    - Centrally confirmed human epidermal growth factor receptor 2–positive expression according to the American Society of Clinical Oncology/College of American Pathologists; archival tissue was accepted
    - Resistant or refractory to ado-trastuzumab emtansine (T-DM1; discontinuation of T-DM1 for Part 2b)
    - Presence of ≥1 measurable lesion (Response Evaluation Criteria in Solid Tumors v1.1)
- Left ventricular ejection fraction ≥50%
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Absolute neutrophil count ≥1.5 × 10^9/L
- Platelet count ≥100 × 10^9/L
- Hemoglobin level ≥9.0 g/dL
- Creatinine clearance ≥30 mL/min
- Total bilirubin ≤3 × upper limit of normal (ULN) and aspartate aminotransferase/alanine aminotransferase ≤5 × ULN
- International normalized ratio and activated partial thromboplastin time ≤1.5 × ULN

Exclusion Criteria

- Myocardial infarction ≤6 months before registration, symptomatic congestive heart failure, unstable angina, or serious cardiac arrhythmia
- Corrected QT interval prolongation to >470 ms (women) or >450 ms (men)
- History of (noninfectious) interstitial lung disease (ILD)/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Brain metastases that are untreated, symptomatic, or require therapy to control symptoms
- Clinically significant corneal disease
- Prior treatment with an antibody-drug conjugate consisting of an exatecan derivative that is a topoisomerase I inhibitor

- Unresolved toxicities from previous anticancer therapy
- Current treatment with cytochrome P450 3A4 strong inhibitors (washout period of ≥3 elimination half-lives of the inhibitor is required)

Safety Assessment

The safety assessment included the analysis of treatment-emergent AEs (TEAEs), serious adverse events (AEs), treatment-related AEs, treatment-related AEs leading to discontinuations, and AEs of special interest. Additional safety assessments included the analysis of elevated troponin levels, physical examination findings, vital sign measurements, standard clinical laboratory parameters, electrocardiogram parameters, echocardiogram/multigated acquisition scan findings, and ophthalmologic findings. Left ventricular ejection fraction (LVEF) was measured by echocardiogram or multigated acquisition scans every 4 cycles. Furthermore, patients were screened for the development of antidrug antibodies during treatment with T-DXd.

Interstitial Lung Disease

Potential cases of ILD were reviewed by an international, independent, multidisciplinary ILD adjudication committee that was established to review all cases of potential ILD reported in T-DXd studies on an ongoing basis. The committee adjudicates any reported cases that are part of the ILD standardized Medical Dictionary for Regulatory Activities 42 preferred terms and the 2 preferred terms respiratory failure and acute respiratory failure.

ILD was managed per-protocol with dose interruptions, reductions or discontinuation, corticosteroids, and supportive care. A summary of ILD management (implemented as of November 2017) is included below. Please see attached protocol for further details and note that these guidelines were used during the DESTINY-Breast01; additional recommendations can be found in Supplemental Table S6.

ILD/pneumonitis should be ruled out if a patient develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high-resolution CT, pulmonologist consultation, pulmonary function tests and SpO2, arterial blood gases if clinically indicated. Other tests could be considered, as needed. As soon as

ILD/pneumonitis is suspected, treatment with study drug should be interrupted pending further evaluations and corticosteroid treatment should be started promptly as per clinical treatment guidelines. (see Kubo K, et al 2013 for guidance[1]) If the AE is confirmed to be grade 1 ILD/pneumonitis, T-DXd can be restarted only if the event is fully resolved; if resolved in ≤ 28 days from day of onset, maintain dose but if resolved in > 28 days from day of onset, reduce dose 1 level. For grade 2, 3, or 4 events, permanently discontinue study treatment.

Supplementary Tables and Figures

Supplementary Table S1. Patient Demographics and Baseline Characteristics for Both Parts 1 and 2

Demographic Variable	Patients N = 253
Age, median (range), years[a]	56.0 (28.0-96.0)
≥65 years, n (%)	64 (25.3)
Female, n (%)	253 (100)
Race, n (%)	
Asian	104 (41.1)
White	132 (52.2)
Other	12 (4.7)
Missing	5 (2.0)
Region, n (%)	
Europe	80 (31.6)
Asia	96 (37.9)
North America	77 (30.4)
ECOG performance status, n (%)	
0	146 (57.7)
1	106 (41.9)
2	1 (0.4)
Hormone receptor status, n (%)	
Positive	127 (50.2)
Negative	122 (48.2)
Unknown	4 (1.6)
HER2 expression, n (%)[b]	
IHC3+	213 (84.2)
IHC1+/2+, ISH+	38 (15.0)
Missing[c]	2 (0.8)
Sum of diameters of target lesions, median (range), cm	5.40 (1.1-24.5)

No. of prior cancer therapy regimens in the metastatic setting, median (range)	6 (2-27)
Prior cancer systemic therapy, n (%)	
Trastuzumab	253 (100)
T-DM1	253 (100)
Pertuzumab	175 (69.2)
Other anti-HER2 therapies	129 (51.0)
Hormone therapy	119 (47.0)
Other systemic therapy	252 (99.6)
Best response to T-DM1 therapy, n (%)	
Complete response/partial response/ stable disease	110 (43.5)
Progressive disease	99 (39.1)
Not evaluable	44 (17.4)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DM1, ado-trastuzumab emtansine; T-DXd, [fam-] trastuzumab deruxtecan.

[a] Median age at informed consent.

[b] HER2 expression was centrally confirmed using archival tissue.

[c] One patient sample was IHC 2+, ISH equivocal. One patient had a sample from June 2018 that was IHC 2+ and ISH not evaluable but was enrolled based on a central laboratory IHC 3+ sample from September 2017.

Supplementary Table S2. Efficacy by Independent Central Review in Patients in Part 1

	6.4 mg/kg (N = 48)	**7.4 mg/kg (N = 21)**
ORR (CR + PR), n (%)	33 (68.8) (95% CI, 53.8%-81.3%)	18 (85.7) (95% CI, 63.7 %-97.0%)
CR	2 (4.2)	1 (4.8)
PR	31 (64.6)	17 (81.0)
SD	14 (29.2)	3 (14.3)
PD	0	0
Not evaluable	1 (2.1)	0
DOR, median, months	NE (95% CI, 8.3-NE)	6.0 (95% CI, 4.8-12.0)
Events	9 (27.3)	10 (55.6)
Censored	24 (72.7)	8 (44.4)
PFS, median, months	NE (95% CI, 14.6-NE)	9.5 (95% CI, 7.4-NE)
Events	13 (27.1)	11 (52.4)
Censored	35 (72.9)	10 (47.6)
DCR (CR + PR + SD), n (%)	47 (97.9) (95% CI, 88.9%-99.9%)	21 (100) (95% CI, 83.9%-100%)

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Supplementary Table S3. Overall Safety of T-DXd in Patients Treated at the RP2D (5.4 mg/kg)

Type of Adverse Event, n (%)[a]	Patients (N = 184)
TEAEs	183 (99.5)
Drug-related TEAEs	183 (99.5)
TEAEs grade ≥3	105 (57.1)
Drug-related TEAEs grade ≥3	89 (48.4)
Serious TEAEs	42 (22.8)
Drug-related serious TEAEs	23 (12.5)
TEAEs leading to T-DXd discontinuation	28 (15.2)
Drug-related TEAEs leading to T-DXd discontinuation	27 (14.7)
TEAEs leading to dose reduction	43 (23.4)
Drug-related TEAEs leading to dose reduction	40 (21.7)
TEAEs leading to dose interruption	65 (35.3)
Drug-related TEAEs leading to dose interruption	53 (28.8)
TEAEs leading to death	9 (4.9)
Drug-related TEAEs leading to death	2 (1.1)

TEAE, treatment-emergent adverse event; T-DXd, [fam-] trastuzumab deruxtecan.

[a] TEAE relationship to study drug was determined by the treating investigator.

Supplementary Table S4. Treatment-Emergent Adverse Events in ≥10% of All Enrolled Patients

Preferred Term[a]	Patients (N = 253)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)
Patients with any TEAE	252 (99.6)	127 (50.2)	15 (5.9)
Nausea	196 (77.5)	20 (7.9)	0
Fatigue	126 (49.8)	25 (9.9)	0
Alopecia	126 (49.8)	1 (0.4)	0
Vomiting	112 (44.3)	10 (4.0)	0
Decreased neutrophil count[b]	102 (40.3)	51 (20.2)	9 (3.6)
Constipation	95 (37.5)	1 (0.4)	0
Anemia[c]	85 (33.6)	27 (10.7)	1 (0.4)
Decreased appetite	84 (33.2)	4 (1.6)	0
Diarrhea	74 (29.2)	5 (2.0)	0
Decreased white blood cell count[d]	68 (26.9)	20 (7.9)	2 (0.8)
Decreased platelet count[e]	63 (24.9)	13 (5.1)	3 (1.2)
Headache	49 (19.4)	0	0
Cough	48 (19.0)	0	0
Stomatitis[f]	45 (17.8)	2 (0.8)	0
Interstitial lung disease (ILD)[g]	39 (15.4)	2 (0.8)	0
Abdominal pain[h]	38 (15.0)	2 (0.8)	0
Increased aspartate aminotransferase	38 (15.0)	4 (1.6)	1 (0.4)
Decreased lymphocyte count[i]	33 (13.0)	14 (5.5)	2 (0.8)
Asthenia	33 (13.0)	4 (1.6)	0
Pyrexia	32 (12.6)	0	0
Dyspepsia	31 (12.3)	0	0

Increased alanine aminotransferase	31 (12.3)	4 (1.6)	1 (0.4)
Dry eye	29 (11.5)	0	1 (0.4)
Dyspnea	29 (11.5)	4 (1.6)	0
Epistaxis	28 (11.1)	0	0
Hypokalemia	28 (11.1)	10 (4.0)	0

TEAE, treatment-emergent adverse event.

[a] As reported by the investigator.

[b] Includes preferred terms “neutrophil count decreased” and “neutropenia.”

[c] Includes preferred terms “hematocrit decreased”, “hemoglobin decreased,” “red blood cell count decreased,” and “anemia.”

[d] Includes preferred terms “white blood cell count decreased” and “leukopenia.”

[e] Includes preferred terms “platelet count decreased” and “thrombocytopenia.”

[f] Includes preferred terms “stomatitis“, “aphthous ulcer“, “mouth ulceration“, “oral mucosa erosion“, and “oral mucosal blistering.”

[g] Drug-related ILD as determined by the independent ILD Adjudication Committee; includes 5 grade 5 ILD events.

[h] Includes preferred terms “abdominal discomfort“, “abdominal pain“, “abdominal pain lower“, and “abdominal pain upper.”

[i] Includes preferred terms “lymphocyte count decreased” and “lymphopenia.”

Supplementary Table S5. Treatment-Emergent Adverse Events in >10% of Patients Treated at the RP2D, Regardless of Causality

	Patients (N = 184)		
Preferred Term[a]	**Any Grade, n (%)**	**Grade 3, n (%)**	**Grade 4, n (%)**
Patients with any TEAE	183 (99.5)	89 (48.4)	7 (3.8)
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Decreased neutrophil count[b]	64 (34.8)	36 (19.6)	2 (1.1)
Decreased appetite	57 (31.0)	3 (1.6)	0
Anemia[c]	55 (29.9)	15 (8.2)	1 (0.5)
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased white blood cell count[d]	39 (21.2)	11 (6.0)	1 (0.5)
Decreased platelet count[e]	39 (21.2)	7 (3.8)	1 (0.5)
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain[f]	31 (16.8)	2 (1.1)	0

Decreased lymphocyte count[g]	26 (14.1)	11 (6.0)	1 (0.5)
Dyspnea	27 (14.7)	3 (1.6)	0
Stomatitis[h]	27 (14.7)	2 (1.1)	0
Aspartate aminotransferase increased	26 (14.1)	2 (1.1)	0
Asthenia	26 (14.1)	2 (1.1)	0
Dyspepsia	26 (14.1)	0	0
Interstitial lung disease (ILD)[i]	25 (13.6)	1 (0.5)	0
Epistaxis	24 (13.0)	0	0
Dry eye	21 (11.4)	0	1 (0.5)
Hypokalemia	21 (11.4)	6 (3.3)	0
Upper respiratory tract infection	20 (10.9)	0	0

RP2D, recommended Part 2 dose; TEAE, treatment-emergent adverse event.

[a] As reported by the investigator.

[b] Includes preferred terms “neutrophil count decreased” and “neutropenia.”

[c] Includes preferred terms “hematocrit decreased”, “hemoglobin decreased,” “red blood cell count decreased,” and “anemia.”

[d] Includes preferred terms “white blood cell count decreased” and “leukopenia.”

[e] Includes preferred terms “platelet count decreased” and “thrombocytopenia.”

[f] Includes preferred terms “abdominal discomfort“, “abdominal pain“, “abdominal pain lower“, and “abdominal pain upper.”

[g] Includes preferred terms “lymphocyte count decreased“ and “lymphopenia.”

[h] Includes preferred terms “stomatitis”, “aphthous ulcer”, “mouth ulceration”, “oral mucosa erosion”, and “oral mucosal blistering.”

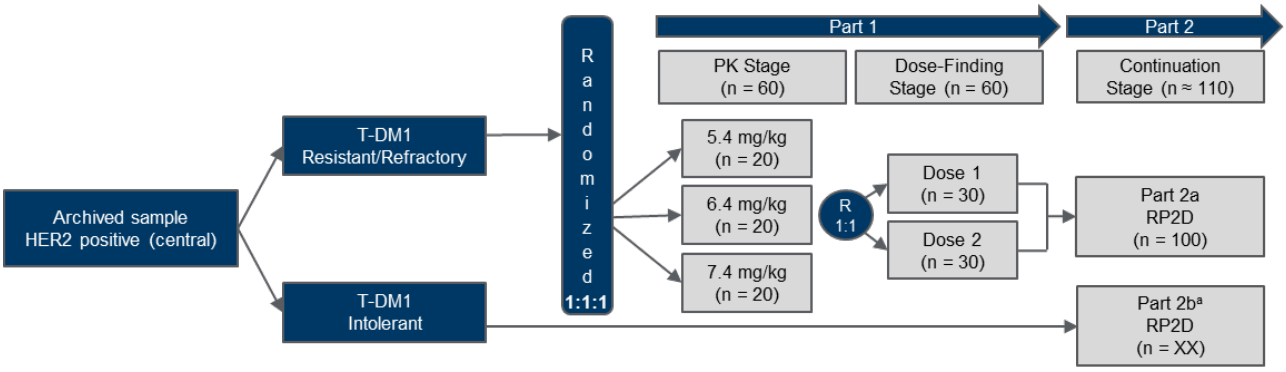
[i] Determined by the independent ILD Adjudication Committee as ILD and related to T-DXd; all grade ILD includes 4 cases of grade 5 events.

Supplementary Table S6. Recommended Guidelines for the Management of Trastuzumab Deruxtecan-Induced Interstitial Lung Disease

	Grade 1	Grade 2	Grade 3 or 4
Work-up	• If a patient develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis • Evaluations should include: – High resolution CT – Pulmonologist consultation (Infectious Disease consultation as clinically indicated) – Blood culture and CBC. Other blood tests could be considered as needed – Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible – Pulmonary function tests and pulse oximetry – Arterial blood gases if clinically indicated – One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible • If the AE is confirmed to have an etiology other than treatment-related ILD/pneumonitis, follow routine clinical practice • If another etiology for the AE cannot be identified and it could be related to trastuzumab deruxtecan, then follow the ILD/pneumonitis management guidance as outlined below • All events of ILD/pneumonitis, regardless of severity or seriousness, should be followed until resolution		
Dose modification	• The administration of trastuzumab deruxtecan must be interrupted • Trastuzumab deruxtecan can be restarted only if the event is fully resolved: – If resolved in ≤ 28 days from day of onset, maintain dose. – If resolved in > 28 days from day of onset, reduce dose by 1 level – However, if the event Grade 1 ILD occurs beyond cycle day	Permanently discontinue patient from trastuzumab deruxtecan treatment	Permanently discontinue patient from trastuzumab deruxtecan treatment

	22 and has not resolved within 49 days from the last infusion, the drug should be discontinued		
Toxicity management	• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated) • Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks • If worsening of diagnostic observations despite initiation of corticosteroids, then follow grade 2 guidelines. (If the patient is asymptomatic, then they should still be considered as grade 1 even if steroid treatment is given)	• Promptly start systemic steroids (e.g., at least 1 mg/kg/day prednisone or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks. • Monitor symptoms closely • Re-image as clinically indicated • If worsening or no improvement in clinical or diagnostic observations in 5 days, – Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone) – Re-consider additional work-up for alternative etiologies as described above – Escalate care as clinically indicated	• Hospitalization required • Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) until clinical improvement, followed by gradual taper over at least 4 weeks • Re-image as clinically indicated • If still no improvement within 3 to 5 days, – Re-consider additional work-up for alternative etiologies as described above – Consider other immuno-suppressants and/or treat per local practice

Supplementary Figure S1. Study Design

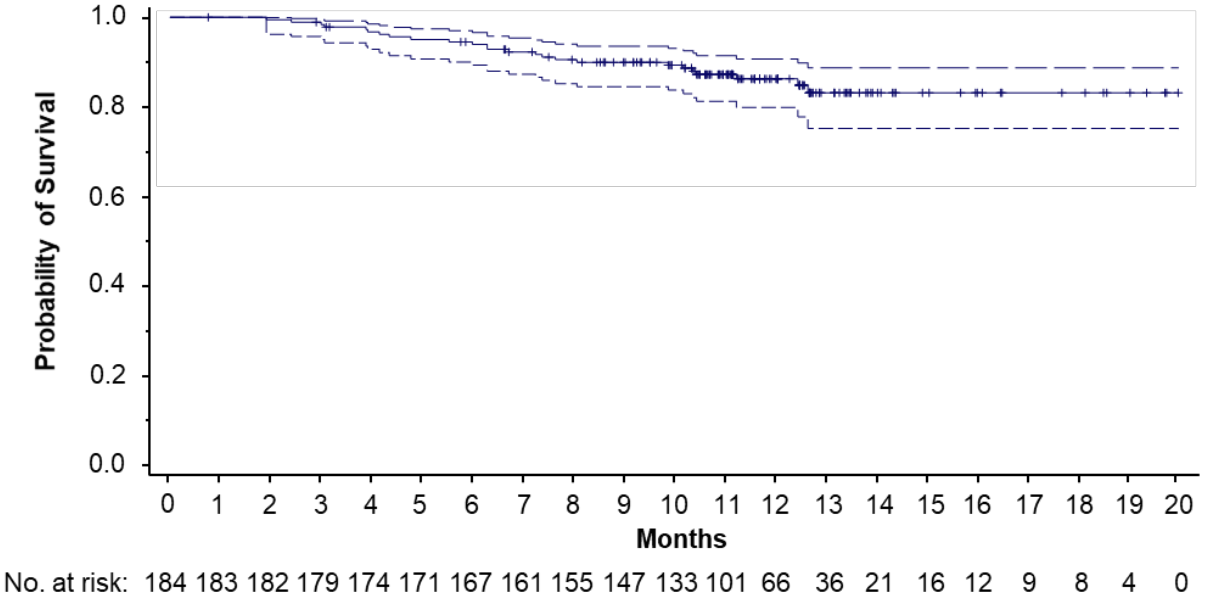


HER2, human epidermal growth factor receptor 2; PK, pharmacokinetics; RP2D, recommended Part 2 dose; T-DM1, ado-trastuzumab emtansine.

The n values shown in the figure are the planned enrollment numbers. Randomization for the dose-finding stage was based on pharmacokinetics.

[a] Approximately 10 to 15 patients were expected to enroll in Part 2b.

Supplementary Figure S2. Overall survival



As of the data cutoff, 25 of 184 patients (13.6%) had died and 159 were censored for the overall survival analysis.

Dashed lines represent 95% CIs.

References

1. Kubo K, Azuma A, Kanazawa M, et al. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. *Respir Investig*. 2013;51(4):260-277.