Supplementary Data

Supplementary Table S1. Patient baseline characteristics

Demographic variable	**BM subgroup (*n* = 24)**	**Non-BM subgroup (*n* = 160)**	**All patients (*N* = 184)**
Age, median (range), years[a]	58.0 (33.0-85.0)	55.0 (28.0-96.0)	55.0 (28.0-96.0)
≥65 years, *n* (%)	9 (37.5)	35 (21.9)	44 (23.9)
Female, *n* (%)	24 (100)	160 (100)	184 (100)
Race, *n* (%)			
Asian	9 (37.5)	61 (38.1)	70 (38.0)
White	13 (54.2)	88 (55.0)	101 (54.9)
Other	1 (4.2)	2 (1.3)	3(1.6)
Missing	1 (4.2)	3 (1.9)	4 (2.2)
Region, *n* (%)			
Europe	9 (37.5)	59 (36.9)	68 (37.0)
Asia	9 (37.5)	54 (33.8)	63 (34.2)
North America	6 (25.0)	47 (29.4)	53 (28.8)
ECOG performance status, *n* (%)			
0	15 (62.5)	87 (54.4)	102 (55.4)
1	9 (37.5)	72 (45.0)	81 (44.0)
2	0	1 (0.6)	1 (0.5)

Demographic variable	BM subgroup (*n* = 24)	Non-BM subgroup (*n* = 160)	All patients (*N* = 184)
Hormone receptor status, *n* (%)			
Positive	9 (37.5)	88 (55.0)	97 (52.7)
Negative	14 (58.3)	69 (43.1)	83 (45.1)
Unknown	1 (4.2)	3 (1.9)	4 (2.2)
HER2 expression, *n* (%)[b]			
IHC3+	19 (79.2)	135 (84.4)	154 (83.7)
IHC1+ or 2+, ISH+	5 (20.8)	23 (14.4)	28 (15.2)
Missing data	0	2 (1.3)	2 (1.1)
Sum of diameters of target lesions, median (range), cm	6.4 (1.2-15.1)	5.4 (1.4-24.5)	5.5 (1.2-24.5)
No. of prior cancer regimens in the metastatic setting, median (range)	6 (3-16)	6 (2-27)	6 (2-27)
Prior cancer systemic therapy, *n* (%)			
Trastuzumab	24 (100)	160 (100)	184 (100)
T-DM1[c]	24 (100)	160 (100)	184 (100)
Pertuzumab	15 (62.5)	106 (66.3)	121 (65.8)
Other anti-HER2 therapies	15 (62.5)	85 (53.1)	100 (54.3)
HER2 TKI	15 (62.5)	78 (48.8)	93 (50.5)
Hormone therapy	11 (45.8)	79 (49.4)	90 (48.9)
Other systemic therapy	24 (100)	159 (99.4)	183 (99.5)

Demographic variable	BM subgroup (*n* = 24)	Non-BM subgroup (*n* = 160)	All patients (*N* = 184)
Radiation therapy (any location)	20 (83.3)	110 (68.8)	130 (70.7)
Best response to T-DM1 therapy, *n* (%)			
Complete response/partial response/stable disease	10 (41.7)	69 (43.1)	79 (42.9)
Progressive disease	10 (41.7)	56 (35.0)	66 (35.9)
Not evaluable	4 (16.7)	35 (21.9)	39 (21.2)
Presence of visceral disease, *n* (%)	24 (100)	145 (90.6)	169 (91.8)
Prior CNS treatment, *n* (%)[d]			
Radiotherapy only	14 (58.3)	—	—
Surgery only	1 (4.2)	—	—
Radiotherapy plus surgery	3 (12.5)	—	—
Radiotherapy plus surgery plus capecitabine	1 (4.2)	—	—
None reported	5 (20.8)	—	—

BM, brain metastasis; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

[a]Median age at informed consent.

[b]HER2 expression was centrally confirmed prospectively on the most recent archival tissue using the American Society of Clinical Oncology/College of American Pathologists guidelines[1]

[c]56 patients (30.4%) in the overall patient population received T-DXd immediately after their initial T-DM1 therapy, 7 of whom were in the BM subgroup.

[d]Radiotherapy includes whole-brain radiotherapy, brain-directed stereotactic radiotherapy, and brain-directed radiosurgery. Surgery includes any brain-directed surgery (ie, craniotomy, metastasectomy in brain, and resection or removal of brain lesion).

References

1. Lin L, Sirohi D, Coleman JF, Gulbahce HE. American Society of Clinical Oncology/College of American Pathologists 2018 Focused Update of Breast Cancer HER2 FISH Testing Guidelines—Results From a National Reference Laboratory. Am J Clin Pathol 2019;152(4):479-85.

Supplementary Table S2. Sites of progression

Site of PD	BM subgroup[a] (*n* = 24)	Non-BM subgroup (*n* = 160)	All patients (*N* = 184)
Patients with progression on study, *n* (%)	8 (33.3)	40 (25.0)	48 (26.1)
Lung	3 (12.5)	17 (10.6)	20 (10.9)
Liver	2 (8.3)	12 (7.5)	14 (7.6)
Brain	2 (8.3)	2 (1.3)	4 (2.2)
Bone	1 (4.2)	2 (1.3)	3 (1.6)
Lymph node	1 (4.2)	11 (6.9)	12 (6.5)
Pleura	1 (4.2)	1 (0.6)	2 (1.1)
Soft tissue	1 (4.2)	0	1 (0.5)
Chest wall	0	4 (2.5)	4 (2.2)
Muscle	0	1 (0.6)	1 (0.5)
Peritoneum	0	1 (0.6)	1 (0.5)

[a]Computed tomography or magnetic resonance imaging scan of the brain was mandatory Q6W (±7 days).

Supplementary Table S3. Overall safety summary of T-DXd 5.4 mg/kg

Type of adverse event, n (%)[a]	BM subgroup (*n* = 24)	Non-BM patients (*n* = 160)	All patients (*N* = 184)
Any TEAE	24 (100)	159 (99.4)	183 (99.5)
Drug-related	24 (100)	159 (99.4)	183 (99.5)
TEAE ≥ grade 3	13 (54.2)	92 (57.5)	105 (57.1)
Drug-related	10 (41.7)	79 (49.4)	89 (48.4)
Serious TEAE	3 (12.5)	39 (24.4)	42 (22.8)
Drug-related	1 (4.2)	22 (13.8)	23 (12.5)
TEAE associated with discontinuation	2 (8.3)	26 (16.3)	28 (15.2)
Drug-related	2 (8.3)	25 (15.6)	27 (14.7)
TEAE associated with dose reduction	5 (20.8)	38 (23.4)	43 (23.4)
Drug-related	4 (16.7)	36 (22.5)	40 (21.7)
TEAE associated with dose interruption	9 (37.5)	56 (35.0)	65 (35.3)
Drug-related	8 (33.3)	45 (28.1)	53 (28.8)
TEAE associated with death[b]	2 (8.3)	7 (4.4)	9 (4.9)
Drug-related	1 (4.2)	1 (0.6)	2 (1.1)

BM, brain metastasis; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

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

[b]Each of the following TEAEs was associated with a fatal outcome: in the BM subgroup, respiratory failure and disease progression (each *n* = 1); in the non-BM subgroup, acute respiratory failure, general physical health deterioration, lymphangitis, pneumonia, pneumonitis, and shock hemorrhagic (each *n* = 1) and 1 patient had 2 TEAEs associated with death (acute kidney injury and acute hepatic failure).

Supplementary Table S4. Treatment-emergent adverse events in ≥15% of patients

Preferred term,[a] n (%)	BM subgroup (*n* = 24)		All patients (*N* = 184)	
	Grade		Grade	
	Any	≥3	Any	≥3
Any adverse event	24 (100)	13 (54.2)	183 (99.5)	105 (57.1)
Nausea	16 (66.7)	0	143 (77.7)	14 (7.6)
Fatigue	14 (58.3)	3 (12.5)	91 (49.5)	11 (6.0)
Alopecia	13 (54.2)	0	89 (48.4)	1 (0.5)
Diarrhea	10 (41.7)	2 (8.3)	54 (29.3)	5 (2.7)
Vomiting	10 (41.7)	1 (4.2)	84 (45.7)	8 (4.3)
Decreased neutrophil count[b]	10 (41.7)	6 (25.0)	64 (34.8)	38 (20.7)
Decreased white blood cell count[c]	8 (33.3)	2 (8.3)	39 (21.2)	12 (6.5)
Decreased appetite	8 (33.3)	0	57 (31.0)	3 (1.6)
Anemia[d]	7 (29.2)	1 (4.2)	55 (29.9)	16 (8.7)
Constipation	7 (29.2)	0	66 (35.9)	1 (0.5)
Cough	6 (25.0)	0	35 (19.0)	0
Stomatitis[e]	6 (25.0)	1 (4.2)	27 (14.7)	2 (1.1)
Decreased platelet count[f]	6 (25.0)	1 (4.2)	39 (21.2)	8 (4.3)
Decreased lymphocyte count[g]	5 (20.8)	4 (16.7)	26 (14.1)	12 (6.5)
Headache	5 (20.8)		36 (19.6)	0

Dizziness	4 (16.7)	0	17 (9.2)	0
Dyspepsia	4 (16.7)	0	26 (14.1)	0
Prolonged ECG QT interval	4 (16.7)	0	9 (4.9)	2 (1.1)
Hypokalemia	4 (16.7)	1 (4.2)	21 (11.4)	6 (3.3)
Mucosal inflammation	4 (16.7)	0	13 (7.1)	0
Upper respiratory tract infection	4 (16.7)	0	20 (10.9)	0
Weight decreased	4 (16.7)	0	14 (7.6)	0
Abdominal pain[h]	3 (12.5)	0	31 (16.8)	2 (1.1)

BM, brain metastasis; ECG, electrocardiogram; T-DXd, trastuzumab deruxtecan.

[a]As reported by the investigator for the safety analysis set (patients who received ≥1 dose of T-DXd 5.4 mg/kg).

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

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

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

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

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

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

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