ASCO 2023/ESMO BC 2023 Presentation Materials (vol.1)

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- **DESTINY-Breast01, -02, and -03**
  - Krop, I. et al., ASCO 2023 #1006 Oral
- **DESTINY-Breast02**
  - Fehm et al., ESMO Breast 2023 #186O Oral
- **DESTINY-Breast04**
  - Cameron et al., ESMO Breast 2023, #192MO Oral
- **DESTINY-Breast04 sub-analysis**
  - Modi et al., ASCO 2023, #1020 Poster
- **DESTINY-Breast04 safety analysis**
  - Rugo et al., ESMO Breast 2023, #185O Oral
- **DESTINY-CRC02**
  - Raghav, K. et al., ASCO 2023 #3501 Oral

An Age-Specific Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Positive Metastatic Breast Cancer (mBC) From DESTINY-Breast01, -02, and -03

Ian Krop, Yale Cancer Center, New Haven, CT, USA

Additional authors:
Hans Wildiers, Sara Hurvitz, Javier Cortes, Seock-Ah Im, Hiroji Iwata, Fabrice André, Cristina Saura, Shanu Modi, Sung-Bae Kim, Anton Egorov, Elton Mathias, Jillian Cathcart, Antonio Cagnazzo, Yingkai Cheng, Yeon Hee Park

Disclosures

Dr. Ian Krop reports:

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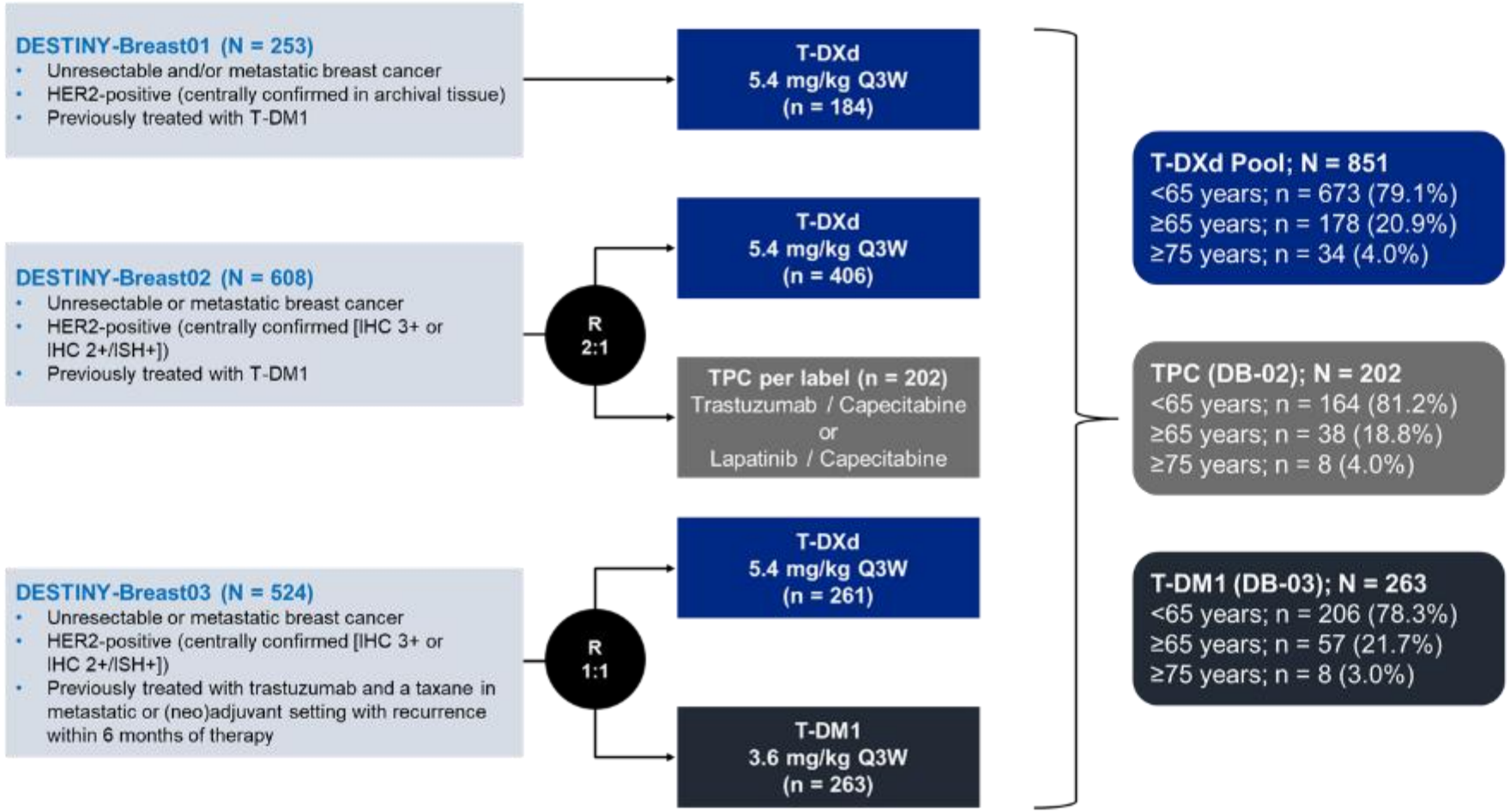
Background

- Regardless of treatment, older patients with HER2-positive mBC tend to have sub-optimal efficacy and safety outcomes[1]
- Patients ≥65 years of age are also often underrepresented in clinical trials[2]
- T-DXd is approved for use in patients with HER2-positive unresectable or mBC after a prior anti-HER2-based regimen in the metastatic or (neo)adjuvant setting, based on the randomized phase 3 DESTINY-Breast03 study[3]
- The outcomes of older patients treated with T-DXd have not been thoroughly examined
- Here we report age-specific efficacy and pooled safety analyses of T-DXd in patients aged <65 and ≥65 years, and exploratory data on patients aged ≥75 years, from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03

HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan.

1. Evans et al. *Cancer Res.* 2021; Abstract PS6-35. 2. Ou et al. *J Clin Oncol.* 2022; 40:16_suppl, 1039-1039. 3. Cortés et al. *N Engl J Med.* 2022; 386(12):1143-1154.

Study Design[1-3]



[a]Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022.
DB, DESTINY-Breast; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi et al. *N Engl J Med.* 2020; 382:610-621. 2. André et al. *The Lancet.* 2023. https://doi.org/10.1016/S0140-6736(23)00725-0. 3. Cortés et al. *N Engl J Med.* 2022; 386(12):1143-1154.

Baseline Characteristics[a]

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 673)	≥65 (n = 178)	≥75 (n = 34)	<65 (n = 164)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 206)	≥65 (n = 57)	≥75 (n = 8)
Age, median (range), years	51.5 (22.4-65.0)	69.9 (65.0-96.0)	79.0 (75.0-96.0)	52.2 (24.7-64.9)	70.8 (65.0-86.5)	78.8 (75.5-86.5)	51.1 (20.2-64.9)	68.7 (65.2-83.0)	79.2 (75.5-83.0)
Female, n (%)	670 (99.6)	177 (99.4)	34 (100.0)	164 (100.0)	36 (94.7)	7 (87.5)	206 (100.0)	56 (98.2)	7 (87.5)
Region, n (%)									
Asia	253 (37.6)	71 (39.9)	8 (23.5)	42 (25.6)	10 (26.3)	4 (50.0)	125 (60.7)	35 (61.4)	3 (37.5)
North America	82 (12.2)	29 (16.3)	8 (23.5)	16 (9.8)	7 (18.4)	1 (12.5)	13 (6.3)	4 (7.0)	0
Europe	220 (32.7)	54 (30.3)	14 (41.2)	62 (37.8)	16 (42.1)	2 (25.0)	34 (16.5)	16 (28.1)	4 (50.0)
Rest of world	118 (17.5)	24 (13.5)	4 (11.8)	44 (26.8)	5 (13.2)	1 (12.5)	34 (16.5)	2 (3.5)	1 (12.5)
Disease history, n (%)									
De novo mBC	183 (27.2)	49 (27.5)	9 (26.5)	40 (24.4)	9 (23.7)	3 (37.5)	76 (36.9)	28 (49.1)	7 (87.5)
Recurrent BC	348 (51.7)	84 (47.2)	15 (44.1)	124 (75.6)	29 (76.3)	5 (62.5)	129 (62.6)	29 (50.9)	1 (12.5)
Missing[b]	142 (21.1)	45 (25.3)	10 (29.4)	0	0	0	1 (0.5)	0	0
Time from the initial diagnosis of BC to randomization, median (range), mo	48.8 (1.5-318.1)	65.2 (6.0-431.4)	64.6 (6.2-431.4)	55.1 (11.8-303.2)	54.5 (6.9-326.0)	71.7 (11.2-198.6)	38.2 (5.1-204.5)	47.6 (5.5-325.2)	20.5 (8.0-188.6)
ECOG PS									
0	399 (59.3)	85 (47.8)	14 (41.2)	95 (57.9)	26 (68.4)	6 (75.0)	136 (66.0)	39 (68.4)	4 (50.0)
1	271 (40.3)	93 (52.2)	20 (58.8)	69 (42.1)	12 (31.6)	2 (25.0)	69 (33.5)	18 (31.6)	4 (50.0)

[a]Baseline characteristics are on the pooled analysis of patients treated with T-DXd from all 3 trials (DB-01, DB-02, and DB-03). [b]The missing data are due to the single arm, non-randomized DB-01 trial.
BC, breast cancer; DB, DESTINY-Breast; ECOG PS, Eastern Cooperative Oncology Group performance status; mBC, metastatic breast cancer; mo, months; T-DM1; trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Baseline Characteristics[a] (cont.)

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 673)	≥65 (n = 178)	≥75 (n = 34)	<65 (n = 164)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 206)	≥65 (n = 57)	≥75 (n = 8)
HER2 Status, n (%)									
3+	563 (83.7)	151 (84.8)	24 (70.6)	131 (79.9)	28 (73.7)	7 (87.5)	181 (87.9)	51 (89.5)	6 (75.0)
2+ (ISH amplified)	107 (15.9)	26 (14.6)	10 (29.4)	32 (19.5)	10 (26.3)	1 (12.5)	24 (11.7)	6 (10.5)	2 (25.0)
1+ | Not Evaluable	2 (0.3) | 1 (0.1)	1 (0.6) | 0	0 | 0	1 (0.6) | 0	0 | 0	0 | 0	0 | 1 (0.5)	0 | 0	0 | 0
Hormone receptor status[b], n (%)									
Positive	373 (55.4)	95 (53.4)	23 (67.6)	93 (56.7)	25 (65.8)	7 (87.5)	115 (55.8)	24 (42.1)	5 (62.5)
Negative	291 (43.2)	83 (46.6)	11 (32.4)	71 (43.3)	12 (31.6)	1 (12.5)	89 (43.2)	33 (57.9)	3 (37.5)
Visceral disease, n (%)									
Yes	541 (80.4)	139 (78.1)	23 (67.6)	135 (82.3)	25 (65.8)	4 (50.0)	153 (74.3)	36 (63.2)	4 (50.0)
No	132 (19.6)	39 (21.9)	11 (32.4)	29 (17.7)	13 (34.2)	4 (50.0)	53 (25.7)	21 (36.8)	4 (50.0)
Baseline brain metastases, n (%)									
Yes	168 (25.0)	35 (19.7)	6 (17.6)	52 (31.7)	5 (13.2)	0	43 (20.9)	9 (15.8)	1 (12.5)
No	505 (75.0)	143 (80.3)	28 (82.4)	112 (68.3)	33 (86.8)	8 (100.0)	163 (79.1)	48 (84.2)	7 (87.5)

[a]Baseline characteristics are on the pooled analysis of patients treated with T-DXd from all 3 trials (DB-01, DB-02, and DB-03). [b]Hormone receptor positive: estrogen receptor and/or progesterone receptor positive; hormone receptor negative: estrogen and progesterone receptor negative.
DB, DESTINY-Breast; HER2, human epidermal growth factor receptor 2; ISH, in situ hybridization; T-DM1; trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Medical History and Comorbidities[a]

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 673)	≥65 (n = 178)	≥75 (n = 34)	<65 (n = 164)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 206)	≥65 (n = 57)	≥75 (n = 8)
Disorders									
Blood and lymphatic system disorders (SOC)	73 (10.8)	26 (14.6)	5 (14.7)	12 (7.3)	6 (15.8)	1 (12.5)	14 (6.8)	6 (10.5)	1 (12.5)
Anemia	41 (6.1)	18 (10.1)	3 (8.8)	9 (5.5)	4 (10.5)	1 (12.5)	6 (2.9)	2 (3.5)	1 (12.5)
Cardiac disorders (SOC)	57 (8.5)	21 (11.8)	4 (11.8)	7 (4.3)	3 (7.9)	0	8 (3.9)	5 (8.8)	0
Diabetes mellitus	29 (4.3)	17 (9.6)	4 (11.8)	7 (4.3)	3 (7.9)	2 (25.0)	6 (2.9)	8 (14.0)	1 (12.5)
Renal and urinary disorders (SOC)	23 (3.4)	16 (9.0)	6 (17.6)	3 (1.8)	4 (10.5)	1 (12.5)	3 (1.5)	11 (19.3)	0
Vascular disorders (SOC)	174 (25.9)	109 (61.2)	28 (82.4)	43 (26.2)	24 (63.2)	5 (62.5)	52 (25.2)	31 (54.4)	6 (75.0)
Hypertension	123 (18.3)	93 (52.2)	26 (76.5)	30 (18.3)	24 (63.2)	5 (62.5)	35 (17.0)	28 (49.1)	5 (62.5)
Baseline renal function[b]									
Normal function	432 (64.2)	34 (19.1)	0	104 (63.4)	8 (21.1)	0	124 (60.2)	8 (14.0)	0
Mild renal impairment	205 (30.5)	91 (51.1)	14 (41.2)	54 (32.9)	22 (57.9)	3 (37.5)	77 (37.4)	28 (49.1)	3 (37.5)
Moderate renal impairment	35 (5.2)	53 (29.8)	20 (58.8)	6 (3.7)	8 (21.1)	5 (62.5)	4 (1.9)	21 (36.8)	5 (62.5)
Baseline hepatic function[c]									
Normal function	406 (60.3)	101 (56.7)	20 (58.8)	78 (47.6)	21 (55.3)	2 (25.0)	162 (78.6)	50 (87.7)	8 (100.0)
Mild hepatic impairment	260 (38.6)	75 (42.1)	14 (41.2)	86 (52.4)	17 (44.7)	6 (75.0)	43 (20.9)	7 (12.3)	0
Moderate hepatic impairment	2 (0.3)	2 (1.1)	0	0	0	0	0	0	0

- Comorbidities were generally low in the overall population due to selection criteria

[a]Medical history and comorbidities are on the pooled analysis of patients treated with T-DXd from all 3 trials (DB-01, DB-02, and DB-03). [b]Renal impairment status is determined by baseline creatine clearance as calculated using the Cockcroft-Gault equation. [c]Adequate hepatic function is defined as total bilirubin ≤ULN and AST≤ULN, mild hepatic dysfunction is defined as total bilirubin ≤ ULN and AST>ULN regardless of Gilbert Syndrome; moderate hepatic dysfunction is defined as total bilirubin >1.5 x ULN, ≤ 3.0 x ULN and any AST except for subjects with Gilbert syndrome.
AST, aspartate transaminase; DB, DESTINY-Breast; SOC, system organ class; T-DM1; trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; ULN, upper limit of normal.

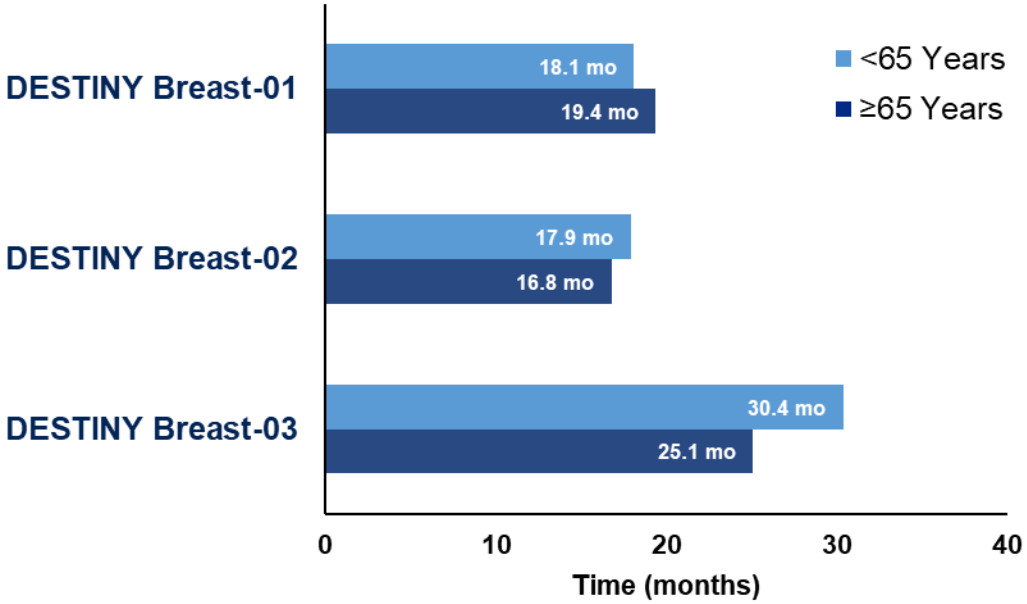
Prior Therapies[a]

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 673)	≥65 (n = 178)	≥75 (n = 34)	<65 (n = 164)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 206)	≥65 (n = 57)	≥75 (n = 8)
Prior regimens in the metastatic setting, n (%)									
0	1 (0.1)	1 (0.6)	0	0	0	0	1 (0.5)	0	0
1	102 (15.2)	22 (12.4)	5 (14.7)	9 (5.5)	2 (5.3)	0	74 (35.9)	28 (49.1)	5 (62.5)
2	188 (27.9)	45 (25.3)	6 (17.6)	59 (36.0)	14 (36.8)	1 (12.5)	50 (24.3)	14 (24.6)	3 (37.5)
3	145 (21.5)	46 (25.8)	12 (35.3)	55 (33.5)	11 (28.9)	1 (12.5)	38 (18.4)	7 (12.3)	0
4	72 (10.7)	17 (9.6)	4 (11.8)	22 (13.4)	3 (7.9)	1 (12.5)	22 (10.7)	1 (1.8)	0
≥5	165 (24.5)	47 (26.4)	7 (20.6)	19 (11.6)	8 (21.1)	5 (62.5)	21 (10.2)	7 (12.3)	0
Median prior regimens in the metastatic setting (range)	3.0 (0.0-27.0)	3.0 (0.0-16.0)	3.0 (1.0-14.0)	3.0 (1.0-7.0)	3.0 (1.0-10.0)	5.5 (2.0-10.0)	2.0 (0.0-15.0)	2.0 (1.0-12.0)	1.0 (1.0-2.0)
Prior anti-HER2 therapy, n (%)									
Trastuzumab	671 (99.7)	177 (99.4)	34 (100)	164 (100.0)	38 (100.0)	8 (100.0)	205 (99.5)	57 (100.0)	8 (100.0)
Pertuzumab	479 (71.2)	122 (68.5)	23 (67.6)	123 (75.0)	33 (86.8)	6 (75.0)	124 (60.2)	34 (59.6)	5 (62.5)
T-DM1	461 (68.5)	128 (71.9)	26 (76.5)	164 (100.0)	38 (100.0)	8 (100.0)	0	0	0
HER2 TKI	52 (7.7)	16 (9.0)	3 (8.8)	14 (8.5)	3 (7.9)	0	33 (16.0)	3 (5.3)	0

[a]Prior therapies are on the pooled analysis of patients treated with T-DXd from all 3 trials (DB-01, DB-02, and DB-03).
DB, DESTINY-Breast; HER2, human epidermal growth factor receptor 2; TKI, tyrosine kinase inhibitor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Descriptive Efficacy According to Age for T-DXd[a]

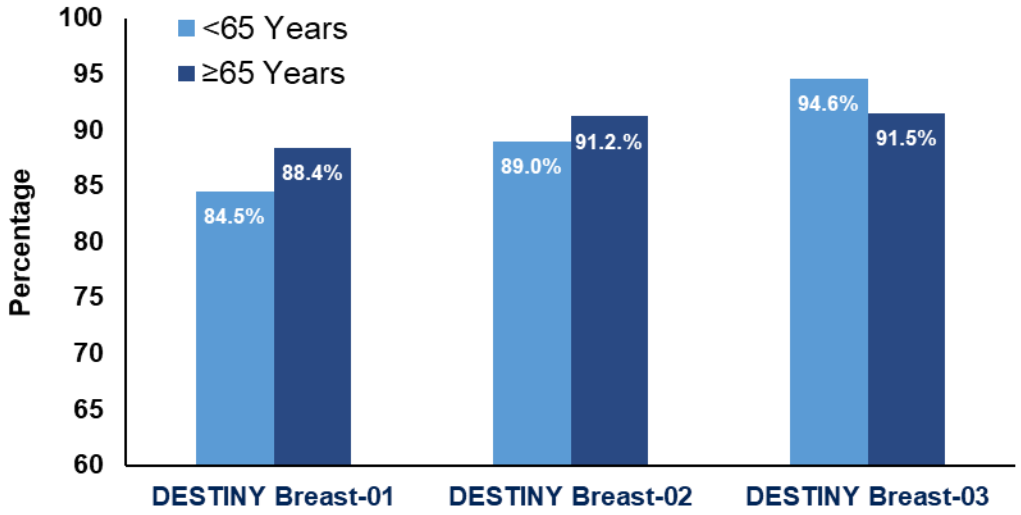
Median Progression Free Survival



Median Overall Survival

	DESTINY-Breast01		DESTINY-Breast02		DESTINY-Breast03	
	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
mOS, months (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)

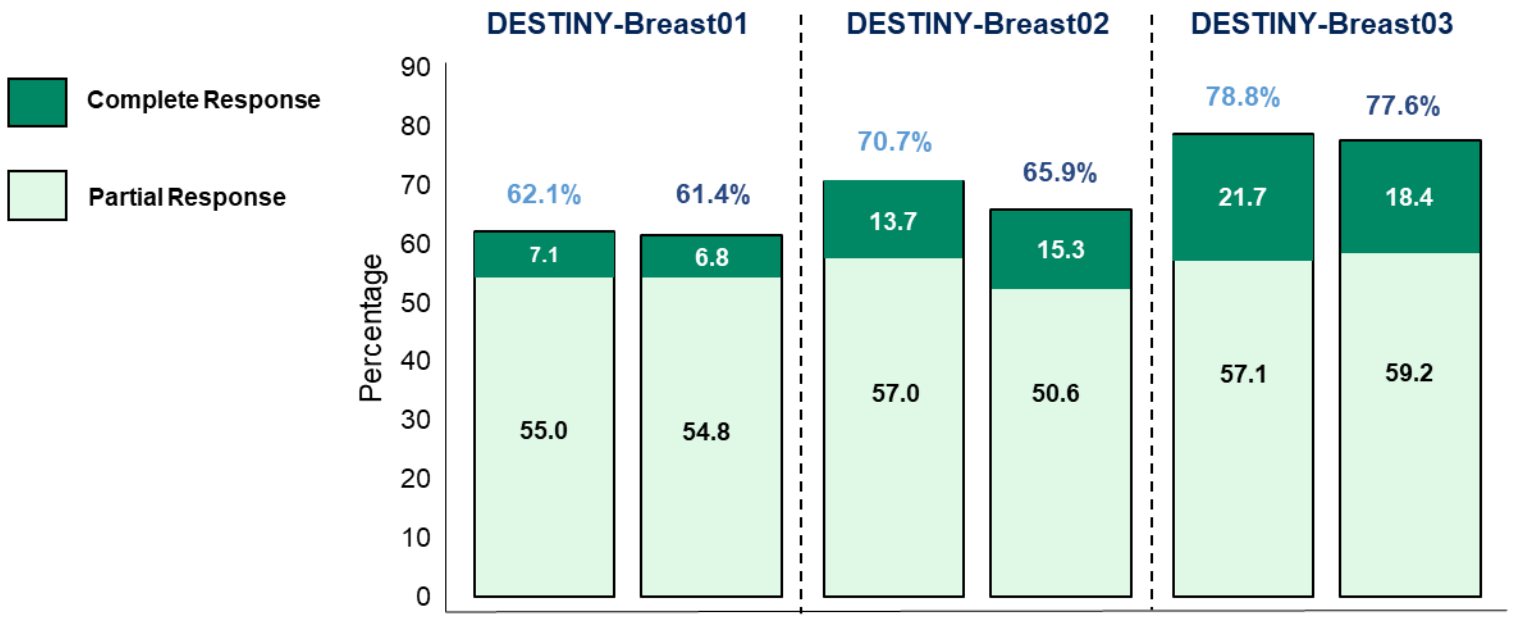
12-month Landmark Overall Survival



- Efficacy in patients aged <65 and ≥65 years treated with T-DXd was generally similar; however no formal comparison was made

[a]Efficacy data was not pooled due to bias induced by the heterogeneity of the study population. Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022.
mOS, median overall survival; NE, not estimable; NR, not reached; T-DXd, trastuzumab deruxtecan.

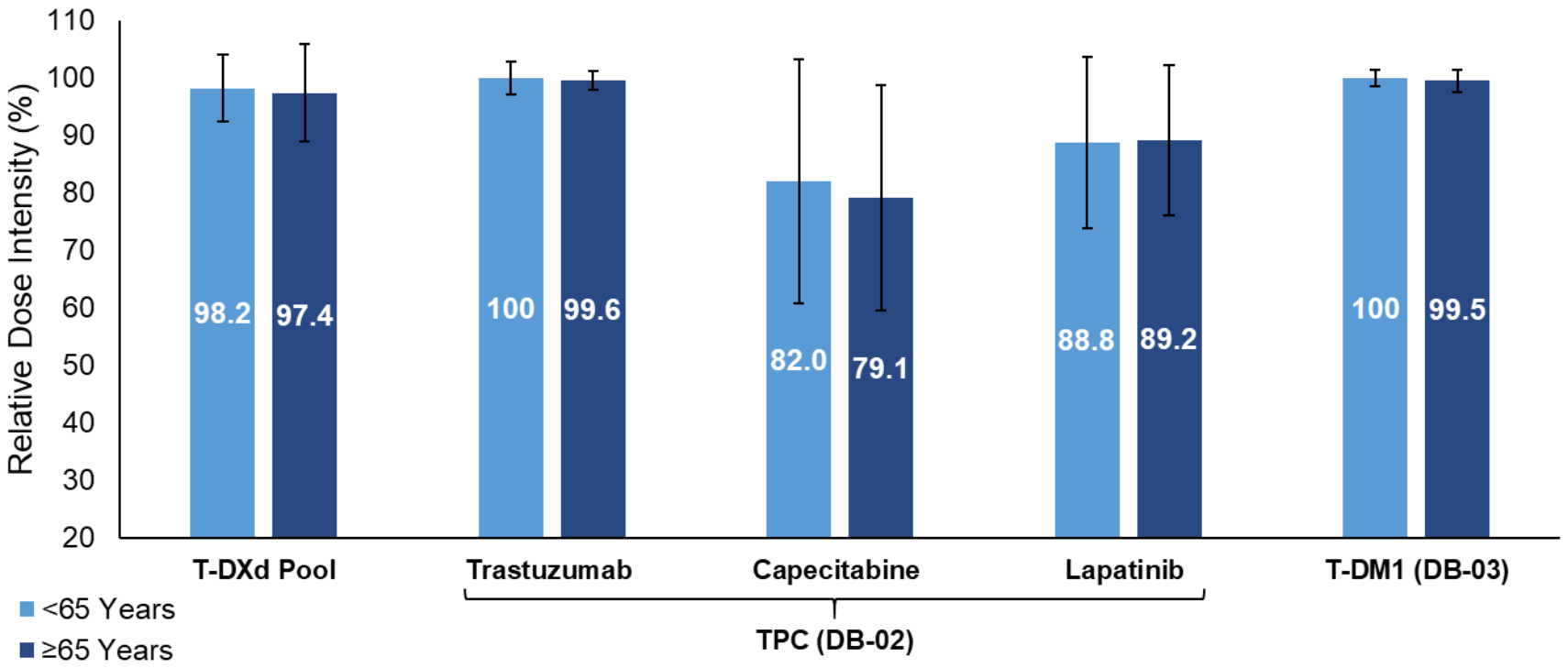
Confirmed ORR by BICR[a] with T-DXd



	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
Stable disease	49 (35.0)	16 (36.4)	69 (21.5)	26 (30.6)	38 (17.9)	9 (18.4)
Progressive disease	3 (2.1)	0	17 (5.3)	2 (2.4)	3 (1.4)	0
Not evaluable	1 (0.7)	1 (2.3)	8 (2.5)	1 (1.2)	4 (1.9)	2 (4.1)
Duration of response, months (95% CI)	20.8 (14.8-NE)	15.5 (9.7-NE)	19.6 (15.6-NE)	19.4 (12.2-NE)	36.6 (26.3-NE)	20.3 (12.5-NE)
Disease control rate, n (%)	136 (97.1)	43 (97.7)	296 (92.2)	82 (96.5)	205 (96.7)	47 (95.9)

[a]Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022.
BICR, blinded independent central review; DB, DESTINY-Breast; NE, not estimable; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

Relative Dose Intensity



- Relative dose intensity was similar between <65 and ≥65 age groups, regardless of treatment received

[a]Relative dose intensity (%) = (dose intensity/planned dose intensity) ×100.
DB, DESTINY-Breast; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Overall Safety Summary[a]

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Median treatment duration, mo (range)	**13.1 (0.7-44.0)**	**12.4 (0.7-45.1)**	**9.0 (0.7-35.6)**	**N/A[b]**	**N/A[b]**	**N/A[b]**	**6.9 (0.7-38.9)**	**8.3 (0.7-39.3)**	**7.7 (2.0-29.4)**
TEAE, n (%)	**665 (99.6)**	**177 (100.0)**	**33 (100.0)**	**148 (94.3)**	**37 (97.4)**	**8 (100.0)**	**194 (95.1)**	**55 (96.5)**	**8 (100.0)**
Drug-related	653 (97.8)	176 (99.4)	33 (100.0)	144 (91.7)	36 (94.7)	8 (100.0)	178 (87.3)	50 (87.7)	8 (100.0)
TEAEs grade ≥3, n (%)	**358 (53.6)**	**116 (65.5)**	**17 (51.5)**	**68 (43.3)**	**18 (47.4)**	**6 (75.0)**	**100 (49.0)**	**35 (61.4)**	**4 (50.0)**
Drug-related	291 (43.6)	96 (54.2)	13 (39.4)	48 (30.6)	12 (31.6)	5 (62.5)	82 (40.2)	28 (49.1)	3 (37.5)
Serious TEAEs, n (%)	**162 (24.3)**	**57 (32.2)**	**10 (30.3)**	**39 (24.8)**	**7 (18.4)**	**1 (12.5)**	**33 (16.2)**	**25 (43.9)**	**4 (50.0)**
Drug-related	77 (11.5)	29 (16.4)	5 (15.2)	13 (8.3)	2 (5.3)	1 (12.5)	11 (5.4)	9 (15.8)	2 (25.0)
TEAEs associated with drug discontinuation, n (%)	**125 (18.7)**	**45 (25.4)**	**8 (24.2)**	**15 (9.6)**	**4 (10.5)**	**1 (12.5)**	**13 (6.4)**	**11 (19.3)**	**3 (37.5)**
Drug-related	100 (15.0)	42 (23.7)	8 (24.2)	8 (5.1)	2 (5.3)	1 (12.5)	9 (4.4)	8 (14.0)	2 (25.0)
TEAEs associated with dose reduction, n (%)	**163 (24.4)**	**51 (28.8)**	**10 (30.3)**	**67 (42.7)**	**22 (57.9)**	**7 (87.5)**	**23 (11.3)**	**15 (26.3)**	**2 (25.0)**
Drug-related	156 (23.4)	47 (26.6)	8 (24.2)	67 (42.7)	22 (57.9)	7 (87.5)	23 (11.3)	15 (26.3)	2 (25.0)
TEAEs associated with dose interruption, n (%)	**302 (45.2)**	**94 (53.1)**	**15 (45.5)**	**73 (46.5)**	**17 (44.7)**	**5 (62.5)**	**53 (26.0)**	**23 (40.4)**	**3 (37.5)**
Drug-related	226 (33.8)	74 (41.8)	11 (33.3)	61 (38.9)	15 (39.5)	5 (62.5)	30 (14.7)	15 (26.3)	3 (37.5)
TEAEs associated with death, n (%)	**17 (2.5)**	**10 (5.6)**	**0**	**6 (3.8)**	**1 (2.6)**	**0**	**4 (2.0)**	**2 (3.5)**	**1 (12.5)**
Drug-related	4 (0.6)	3 (1.7)	0	0	0	0	0	0	0

[a]Trial data cutoffs; DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022. [b]Not reported for TPC as this was a combination regimen; median treatment duration, mo (range), for <65, ≥65, and ≥75 was 4.1 (0.1-43.0), 4.7 (1.4-22.7), and 13.3 (4.1-22.7) for trastuzumab; 4.5 (0.1-43.0), 4.9 (0.7-28.7), and 9.8 (2.6-22.7) for capecitabine; 4.6 (0.4-23.7), 5.2 (0.7-28.7), and 8.0 (2.6-11.5) for lapatinib.
mo, months; N/A, not applicable; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event; TPC, treatment of physician's choice.

Most Common Drug-related TEAEs in ≥20% of Patients

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Any grade[a] drug-related TEAEs, n (%)	**653 (97.8)**	**176 (99.4)**	**33 (100.0)**	**144 (91.7)**	**36 (94.7)**	**8 (100.0)**	**178 (87.3)**	**50 (87.7)**	**8 (100)**
Nausea	497 (74.4)	112 (63.3)	21 (63.6)	50 (31.8)	10 (26.3)	3 (37.5)	59 (28.9)	13 (22.8)	3 (37.5)
Fatigue[b]	344 (51.5)	98 (55.4)	21 (63.6)	45 (28.7)	16 (42.1)	7 (87.5)	56 (27.5)	20 (35.1)	2 (25.0)
Vomiting	268 (40.1)	59 (33.3)	10 (30.3)	21 (13.4)	2 (5.3)	2 (25.0)	13 (6.4)	2 (3.5)	0
Alopecia	265 (39.7)	63 (35.6)	10 (30.3)	6 (3.8)	2 (5.3)	2 (25.0)	4 (2.0)	3 (5.3)	0
Neutropenia[c]	240 (35.9)	72 (40.7)	9 (27.3)	16 (10.2)	4 (10.5)	3 (37.5)	25 (12.3)	10 (17.5)	2 (25.0)
Decreased appetite	181 (27.1)	53 (29.9)	9 (27.3)	22 (14.0)	9 (23.7)	4 (50.0)	21 (10.3)	13 (22.8)	2 (25.0)
Anemia[d]	180 (26.9)	61 (34.5)	12 (36.4)	17 (10.8)	3 (7.9)	1 (12.5)	31 (15.2)	13 (22.8)	1 (12.5)
Leukopenia[e]	156 (23.4)	49 (27.7)	6 (18.2)	10 (6.4)	1 (2.6)	0	18 (8.8)	4 (7.0)	0
Thrombocytopenia[f]	149 (22.3)	50 (28.2)	3 (9.1)	18 (11.5)	3 (7.9)	1 (12.5)	110 (53.9)	31 (54.4)	3 (37.5)
Constipation	148 (22.2)	36 (20.3)	4 (12.1)	4 (2.5)	1 (2.6)	0	18 (8.8)	7 (12.3)	2 (25.0)
Transaminases increased[g]	146 (21.9)	34 (19.2)	1 (3.0)	16 (10.2)	5 (13.2)	1 (12.5)	88 (43.1)	24 (42.1)	5 (62.5)
Diarrhea	142 (21.3)	48 (27.1)	6 (18.2)	81 (51.6)	18 (47.4)	5 (62.5)	9 (4.4)	4 (7.0)	1 (12.5)
Stomatitis[h]	82 (12.3)	35 (19.8)	2 (6.1)	28 (17.8)	10 (26.3)	1 (12.5)	7 (3.4)	5 (8.8)	0

- Any grade drug-related TEAEs were similar across age groups

[a]Any grade drug-related TEAEs present in ≥20% of patients sorted in descending order of frequency in the T-DXd pooled arm for the <65 years age group. [b]Fatigue includes preferred terms fatigue, asthenia, malaise, and lethargy. [c]Neutropenia includes preferred terms neutrophil count decreased and neutropenia. [d]Anemia includes preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [e]Leukopenia includes preferred terms white blood cell count decrease and leukopenia. [f]Thrombocytopenia includes preferred terms platelet count decreased and thrombocytopenia. [g]Transaminases increased includes preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased. [h]Stomatitis includes preferred terms stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosa blistering, and oral mucosa eruption.
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event; TPC, treatment of physician's choice.

Most Common Grade ≥3 Drug-related TEAEs in ≥5% of Patients

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Grade ≥3[a] drug-related TEAEs, n (%)	**291 (43.6)**	**96 (54.2)**	**13 (39.4)**	**48 (30.6)**	**12 (31.6)**	**5 (62.5)**	**82 (40.2)**	**28 (49.1)**	**3 (37.5)**
Neutropenia[b]	117 (17.5)	41 (23.2)	4 (12.1)	5 (3.2)	1 (2.6)	1 (12.5)	6 (2.9)	3 (5.3)	0
Fatigue[c]	52 (7.8)	20 (11.3)	5 (15.2)	1 (0.6)	1 (2.6)	1 (12.5)	2 (1.0)	0	0
Nausea	43 (6.4)	15 (8.5)	4 (12.1)	3 (1.9)	0	0	0	1 (1.8)	0
Anemia[d]	42 (6.3)	20 (11.3)	3 (9.1)	1 (0.6)	0	0	6 (2.9)	6 (10.5)	1 (12.5)
Leukopenia[e]	42 (6.3)	15 (8.5)	2 (6.1)	0	0	0	3 (1.5)	0	0
Lymphopenia[f]	28 (4.2)	11 (6.2)	1 (3.0)	2 (1.3)	0	0	2 (1.0)	1 (1.8)	0
Thrombocytopenia[g]	28 (4.2)	9 (5.1)	0	2 (1.3)	0	0	47 (23.0)	19 (33.3)	2 (25.0)
Transaminases increased[h]	18 (2.7)	1 (0.6)	0	1 (0.6)	1 (2.6)	0	16 (7.8)	4 (7.0)	0
Diarrhea	9 (1.3)	4 (2.3)	0	10 (6.4)	2 (5.3)	1 (12.5)	2 (1.0)	0	0

- Patients ≥65 years of age experienced more grade ≥3 TEAEs across all trials

[a]Grade ≥3 drug-related TEAEs present in ≥5% of patients, sorted in descending order of frequency in the T-DXd pooled arm for the <65 years age group. Grade ≥3 drug-related TEAEs calculated in all patients in the analysis set. [b]Neutropenia includes the preferred terms neutrophil count decreased and neutropenia. [c]Fatigue includes the preferred terms fatigue, asthenia, malaise, and lethargy. [d]Anemia includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [e]Leukopenia includes the preferred terms white blood cell count decrease and leukopenia. [f]Lymphopenia includes the preferred terms lymphocute count decreased and lymphopenia. [g]Thrombocytopenia includes the preferred terms platelet count decreased and thrombocytopenia. [h]Transaminases increased includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased.
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event; TPC, treatment of physician's choice.

Adjudicated Drug-related ILD/Pneumonitis[a]

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Any grade, n (%)	**79 (11.8)**	**31 (17.5)**	**5 (15.2)**	**0**	**1 (2.6)**	**0**	**6 (2.9)**	**2 (3.5)**	**1 (12.5)**
1	21 (3.1)	7 (4.0)	0	0	0	0	3 (1.5)	1 (1.8)	0
2	48 (7.2)	20 (11.3)	5 (15.2)	0	0	0	2 (1.0)	1 (1.8)	1 (12.5)
3	4 (0.6)	3 (1.7)	0	0	1 (2.6)	0	1 (0.5)	0	0
4	0	0	0	0	0	0	0	0	0
5	6 (0.9)	1 (0.6)	0	0	0	0	0	0	0

- Rates of adjudicated ILD/pneumonitis were generally higher in patients ≥65 years of age across all trials compared to patients <65 years of age
- Most drug-related ILD/pneumonitis cases were of low grade

[a]No ILD/pneumonitis cases were pending adjudication at the respective data cutoff dates (DESTINY-Breast01: March 26, 2021; DESTINY-Breast02: June 30, 2022; DESTINY-Breast03: July 25, 2022).
ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Conclusion

- Results of this pooled analysis indicate that T-DXd remains an effective treatment option for patients ≥65 years of age
  - mPFS and confirmed ORR by BICR were similar with T-DXd in patients <65 and ≥65 years of age within each trial
- The safety profile of T-DXd was acceptable across all age subgroups
  - Patients ≥65 years of age experienced more TEAEs and grade ≥3 TEAEs across all trials
- Further research/real-world evidence studies for older patients, also addressing aspects of comorbidities and frailty, would be informative

T-DXd may be considered as an effective option for patients across all age subgroups with an acceptable safety profile

BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mPFS, median progression free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event.

PATIENT-REPORTED OUTCOMES FROM DESTINY-BREAST02, A RANDOMIZED PHASE 3 STUDY OF TRASTUZUMAB DERUXTECAN (T-DXd) VS TREATMENT OF PHYSICIAN'S CHOICE (TPC) IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

Tanja Fehm, Gynecology and Obstetrics, Universitaetsklinikum Düsseldorf AöR, Düsseldorf, Germany

Additional authors:

Francesco Cottone, Kyle Dunton, Fabrice André, Ian Krop, Yeon Hee Park, Michelino De Laurentiis, Yasuo Miyoshi, Anne Armstrong, Manuel Ruiz Borrego, Rinat Yerushalmi, Francois P. Duhoux, Toshimi Takano, Wenjing Lu, Christopher Livings, Anton Egorov, Sung-Bae Kim

Declaration of Interests

- Prof Fehm reports advisory board compensation from Daiichi Sankyo, Novartis, Roche, Pfizer, MSD, and Teva Pharmaceuticals

DESTINY-Breast02 study design

Randomized, open-label, multicenter, phase 3 study (NCT03523585)

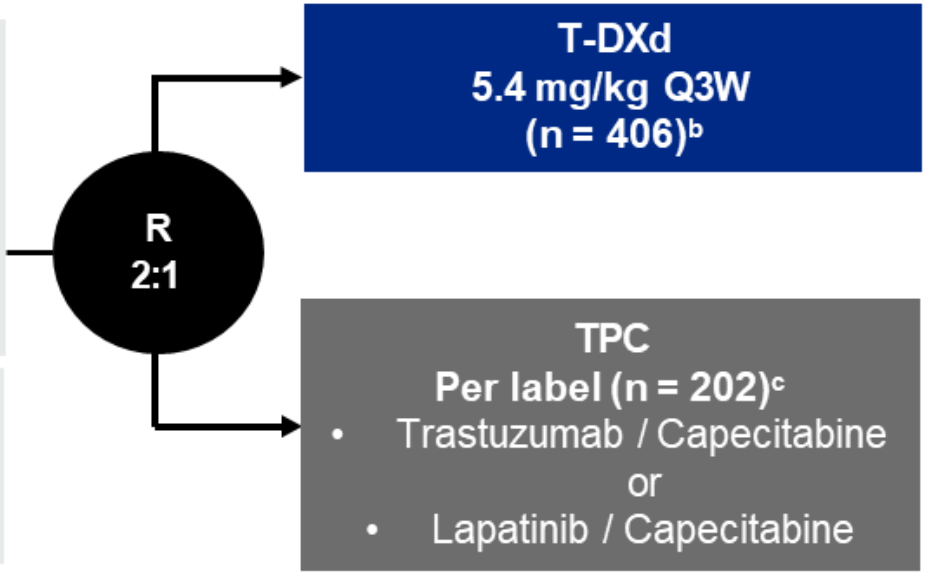
Daiichi-Sankyo

Key eligibility criteria[a]

- Centrally confirmed HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable or metastatic breast cancer
- Documented radiographic progression after most recent treatment
- Previously treated with T-DM1

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR[d])

Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR[d])
- DoR (BICR[d])
- PFS (investigator)
- Safety
- HEOR endpoints (PROs, hospitalization)

Data cutoff: June 30, 2022

PRO assessment schedule[e]

Cycle 1	Cycle 2	Cycle 3	Every 2 cycles (cycle 5, 7, 9, etc)	EOT	40-day follow-up visit	3-month follow-up visit

BICR, blinded independent central review; DoR, duration of response; EOT, end of treatment; HEOR, health economics outcomes research; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

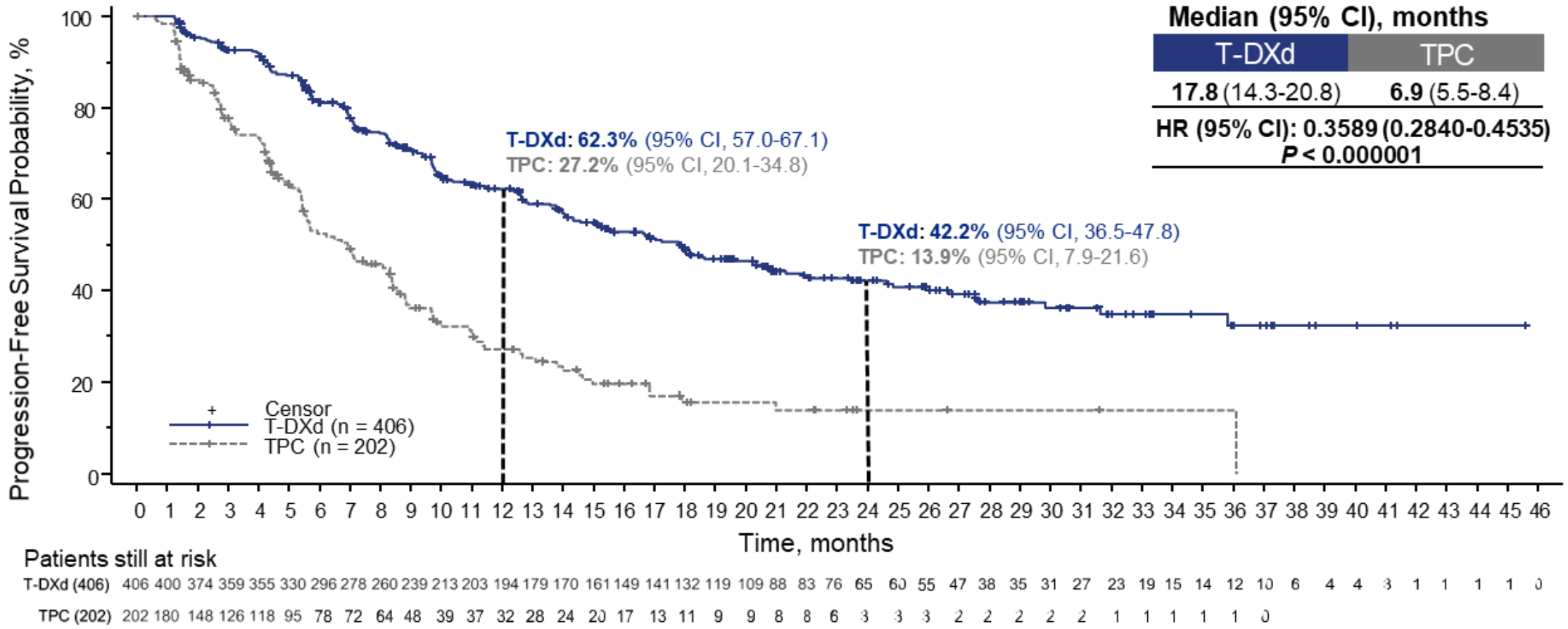
[a]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [b]2 patients were randomly assigned but not treated. [c]7 patients were randomly assigned but not treated. [d]BICR assessed per modified Response Evaluation Criteria in Solid Tumours version 1.1. [e]1 cycle = 21 days; T-DXd or TPC were administered on day 1 of each cycle; questionnaires completed before treatment on day 1 of cycles indicated.

Baseline characteristics

Baseline Characteristics	T-DXd n = 406	TPC n = 202
Age, median (range), years	54.2 (22.4-88.5)	54.7 (24.7-86.5)
Region, n (%)		
Asia	112 (27.6)	52 (25.7)
Europe	152 (37.4)	78 (38.6)
North America	41 (10.1)	23 (11.4)
Rest of world	101 (24.9)	49 (24.3)
HER2 status (IHC),[a] n (%)		
3+ | 2+ (ISH+)	326 (80.3) | 79 (19.5)	159 (78.7) | 41 (20.3)
2+ (ISH- or non-evaluable) | 1+ (ISH+)	1 (0.2) | 0	1 (0.5) | 1 (0.5)
ECOG PS, n (%)		
0 | 1 | 2	228 (56.2) | 177 (43.6) | 1 (0.2)	121 (59.9) | 81 (40.1) | 0
Hormone-receptor status,[b] n (%)		
Positive | Negative	238 (58.6) | 165 (40.6)	118 (58.4) | 83 (41.1)
Brain metastases at baseline,[c] n (%)		
Yes | No	74 (18.2) | 332 (81.8)	36 (17.8) | 166 (82.2)
Visceral disease, n (%)		
Yes | No	316 (77.8) | 90 (22.2)	160 (79.2) | 42 (20.8)
Median number of prior lines of systemic therapy in the metastatic setting,[d] (range)	2 (0-10)	2 (1-8)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice. [a]HER2 status as evaluated by central laboratory testing. [b]3 (0.7%) patients in the T-DXd arm and 1 (0.5%) patient in the TPC arm had indeterminate hormone receptor status (neither estrogen receptors nor progesterone receptors positive and estrogen receptors indeterminate or progesterone receptors indeterminate) based on factors reported from electronic data capture. [c]Patients with clinically inactive brain metastases and patients with treated brain metastases that were no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants could be included. [d]Includes regimens indicated for advanced/metastatic disease or rapid progression within 6 months of (neo)adjuvant (12 months for pertuzumab) therapy. Line of therapy does not include hormone therapy. 1. Krop et al. Presented at: San Antonio Breast Cancer Symposium; December 6-10, 2022; San Antonio, TX. Presentation GS2-01.

Progression-free survival by blinded independent central review



Median duration of follow up[a]: T-DXd, 21.5 months (range, 0.1-45.6 months); **TPC**, 18.6 months (range, 0-45.7 months)

HR, hazard ratio; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Defined as study duration equal to the date last known alive minus the date of randomization plus 1.
1. Krop et al. Presented at SABCS 2022. Presentation GS2-01.

DESTINY-Breast02: safety summary

Type of Adverse Event, n (%)	T-DXd n = 404[a]	TPC n = 195[a]
Any-grade drug-related TEAE	394 (97.5)	180 (92.3)
Drug-related Grade ≥3 TEAEs	167 (41.3)	60 (30.8)
Serious drug-related TEAEs	46 (11.4)	15 (7.7)
Drug-related TEAEs associated with drug discontinuations	58 (14.4)	10 (5.1)
Drug-related TEAEs associated with drug interruptions	132 (32.7)	76 (39.0)
Drug-related TEAEs associated with dose reductions	95 (23.5)	89 (45.6)
Drug-related TEAEs associated with an outcome of death	4 (1.0)[b]	0

Median treatment duration

- T-DXd, 11.3 months
- TPC, ~4.5 months[c]

Most common drug-related TEAEs associated with drug discontinuation

- T-DXd, pneumonitis (6.2%) and ILD (3.2%)
- TPC, palmar-plantar erythrodysesthesia (1.5%)

Most common drug-related TEAEs associated with dose reduction

- T-DXd, nausea (5.4%)
- TPC, palmar-plantar erythrodysesthesia (23.6%)

ILD, interstitial lung disease. TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The safety analysis set includes all randomized patients who received at least 1 dose of study treatment. [b]Drug-related TEAEs associated with an outcome of death included pneumonitis (n = 2), acute myeloid leukemia (n = 1), and pneumonia (n = 1). [c]Median treatment duration was 4.4 months with trastuzumab, 4.6 months with capecitabine, and 4.5 months with lapatinib.
1. Krop et al. Presented at: San Antonio Breast Cancer Symposium; December 6-10, 2022; San Antonio, TX. Presentation GS2-01. 2. André et al. *The Lancet* 2023 [in press].

HEOR endpoints

Questionnaire	Description	Measures of interest	Main analyses
EORTC QLQ-C30	Oncology-specific questionnaire	• Global health status (GHS)/quality of life (QoL)[a] • Physical, emotional, and social functioning • Pain symptoms	• Change from baseline • Time to definitive deterioration (TDD)[b]
EORTC QLQ-BR45[c]	Breast cancer–specific questionnaire	• Breast and arm symptoms	• TDD[b]
EQ-5D-5L	Generic questionnaire	• Self-rated health status (visual analogue scale [VAS])	• TDD[b]

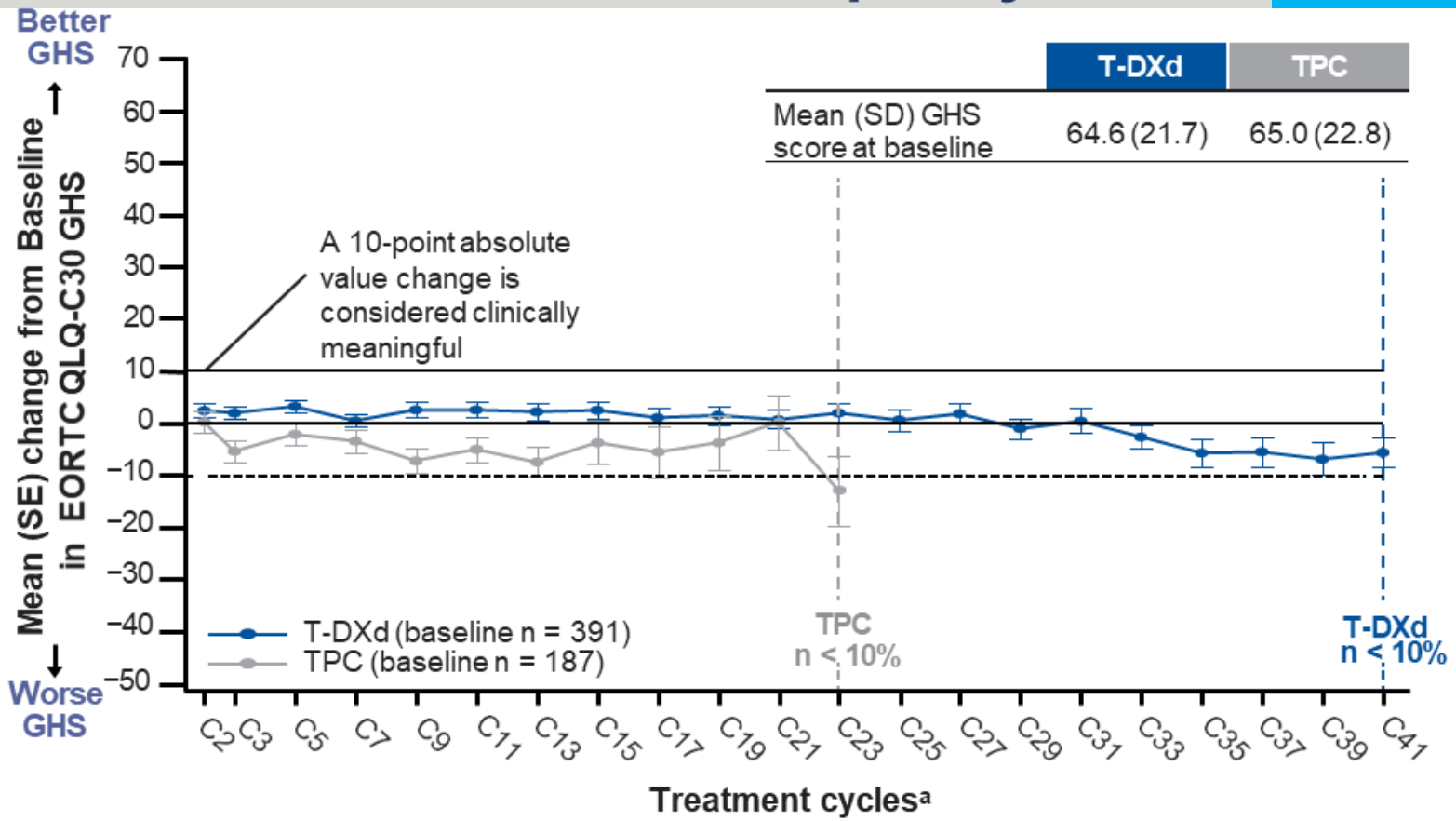
PRO assessment schedule[d]

Cycle 1	Cycle 2	Cycle 3	Every 2 cycles (cycle 5, 7, 9, etc)	EOT	40-day follow-up visit	3-month follow-up visit

In general, **compliance** for health-related patient questionnaires was **>92% at baseline** and **>80% at cycles 3-39,** after which n was < 10% and results were no longer informative

EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Primary PRO variable of interest. [b]A clinically meaningful definitive deterioration event was defined as a ≥10-point increase (compared to baseline) at ≥2 timepoints on symptom scales and a ≥10-point decrease at ≥2 timepoints on GHS/QoL, functional, or EQ-5D-5L VAS scales (unless it was the last assessment). TDD was defined as the time between the date of randomization and the date of the assessment at which the definitive deterioration event was first seen. [c]Scored as EORTC QLQ-BR23. [d]1 cycle = 21 days; T-DXd or TPC were administered on day 1 of each cycle; questionnaires completed before treatment on day 1 of cycles indicated.

Global health status and health-related quality of life



Global health status was maintained in the T-DXd and TPC arms until cycle 39 and 21, respectively[b]

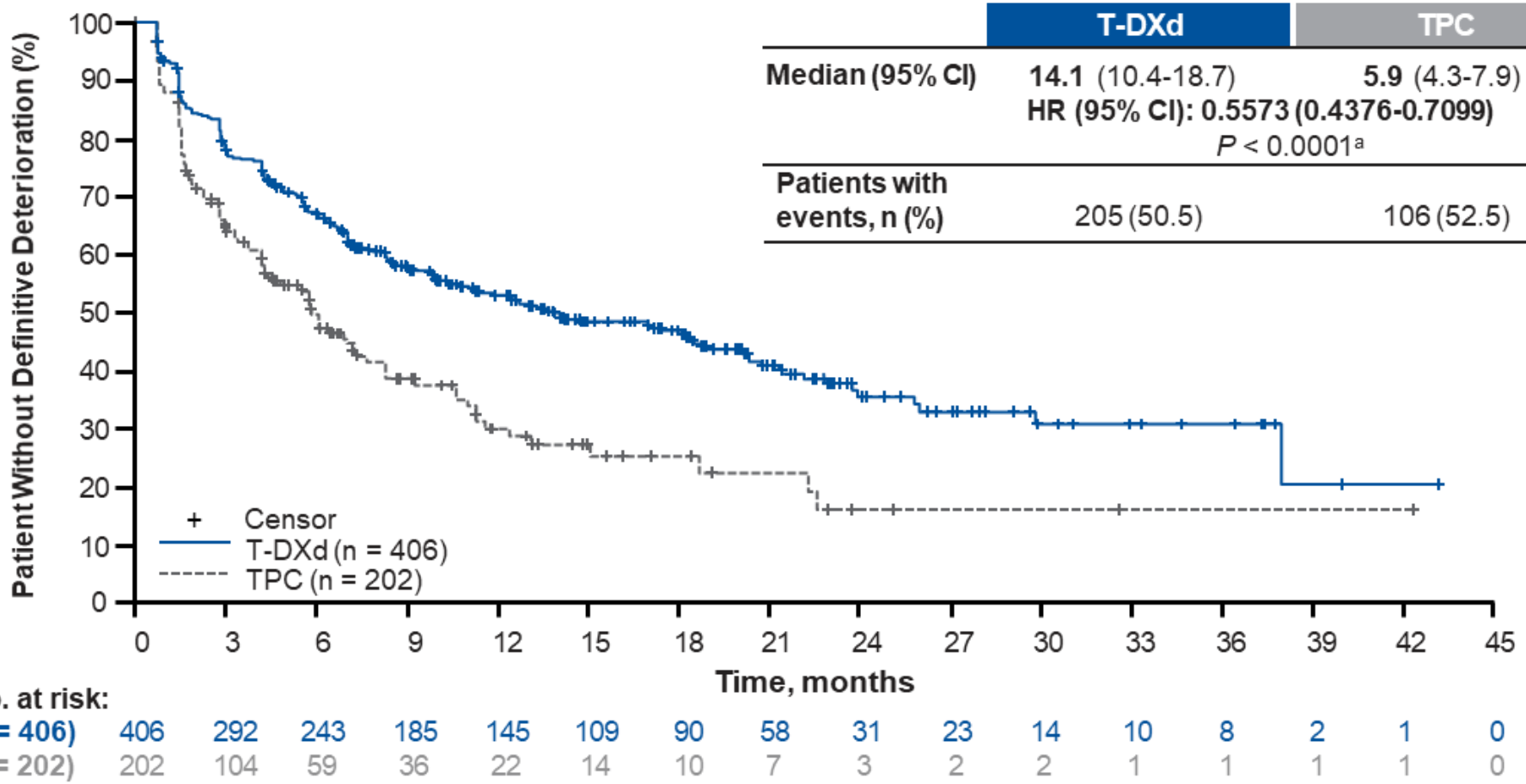
Results should be considered in conjunction with median treatment duration (T-DXd, 11.3 months; TPC, ~4.5 months)

C, cycle; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; GHS, global health status; QoL, quality of life; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Scores range from 0 to 100; a higher score represents a higher ("better") GHS/overall QoL. [a]On day 1 of cycle [b]After these cycles, n < 10% (T-DXd, n = 39; TPC, n = 17) and results were no longer informative (indicated by vertical dashed lines).

Time to definitive deterioration of EORTC QLQ-C30 GHS/overall QoL

	T-DXd	TPC
Median (95% CI)	**14.1** (10.4-18.7)	**5.9** (4.3-7.9)
	HR (95% CI): 0.5573 (0.4376-0.7099)	
	P < 0.0001[a]	
Patients with events, n (%)	205 (50.5)	106 (52.5)



No. at risk:																
T-DXd (n = 406)	406	292	243	185	145	109	90	58	31	23	14	10	8	2	1	0
TPC (n = 202)	202	104	59	36	22	14	10	7	3	2	2	1	1	1	1	0

Patients in the T-DXd arm experienced longer median TDD of GHS/QoL

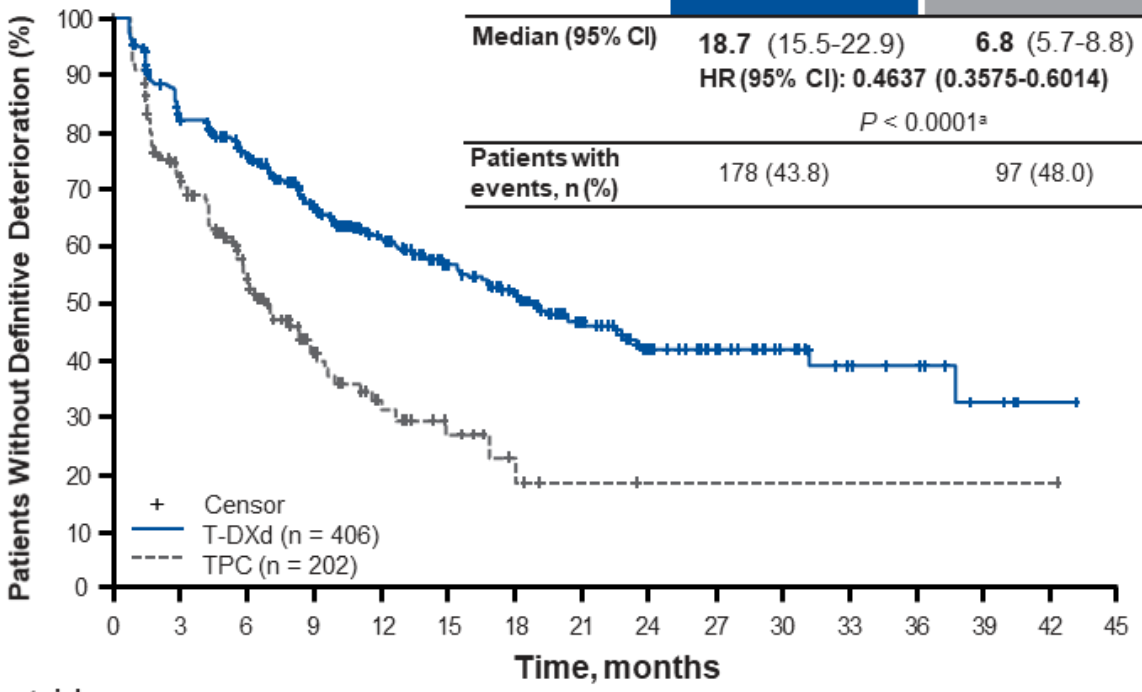
European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; GHS, global health status; HR, hazard ratio; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]*P* values are two-sided and based on a stratified log-rank test. EORTC QLQ-C30,

Time to definitive deterioration of EORTC QLQ-C30 physical functioning and pain symptoms

Physical Functioning

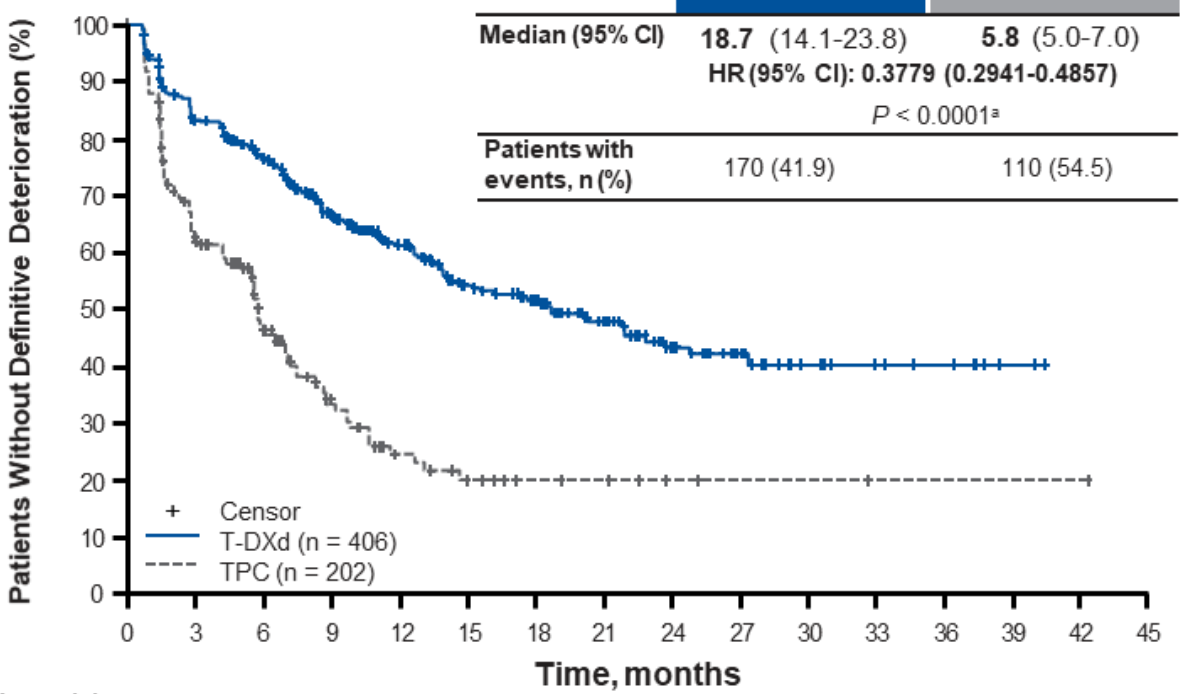
	T-DXd	TPC
Median (95% CI)	**18.7** (15.5-22.9)	**6.8** (5.7-8.8)
	HR (95% CI): 0.4637 (0.3575-0.6014)	
	P < 0.0001[a]	
Patients with events, n (%)	178 (43.8)	97 (48.0)



No. at risk:																
T-DXd (n = 406)	406	310	270	214	166	129	103	66	41	31	20	12	10	4	1	0
TPC (n = 202)	202	115	65	33	18	10	5	2	1	1	1	1	1	1	1	0

Pain Symptoms

	T-DXd	TPC
Median (95% CI)	**18.7** (14.1-23.8)	**5.8** (5.0-7.0)
	HR (95% CI): 0.3779 (0.2941-0.4857)	
	P < 0.0001[a]	
Patients with events, n (%)	170 (41.9)	110 (54.5)

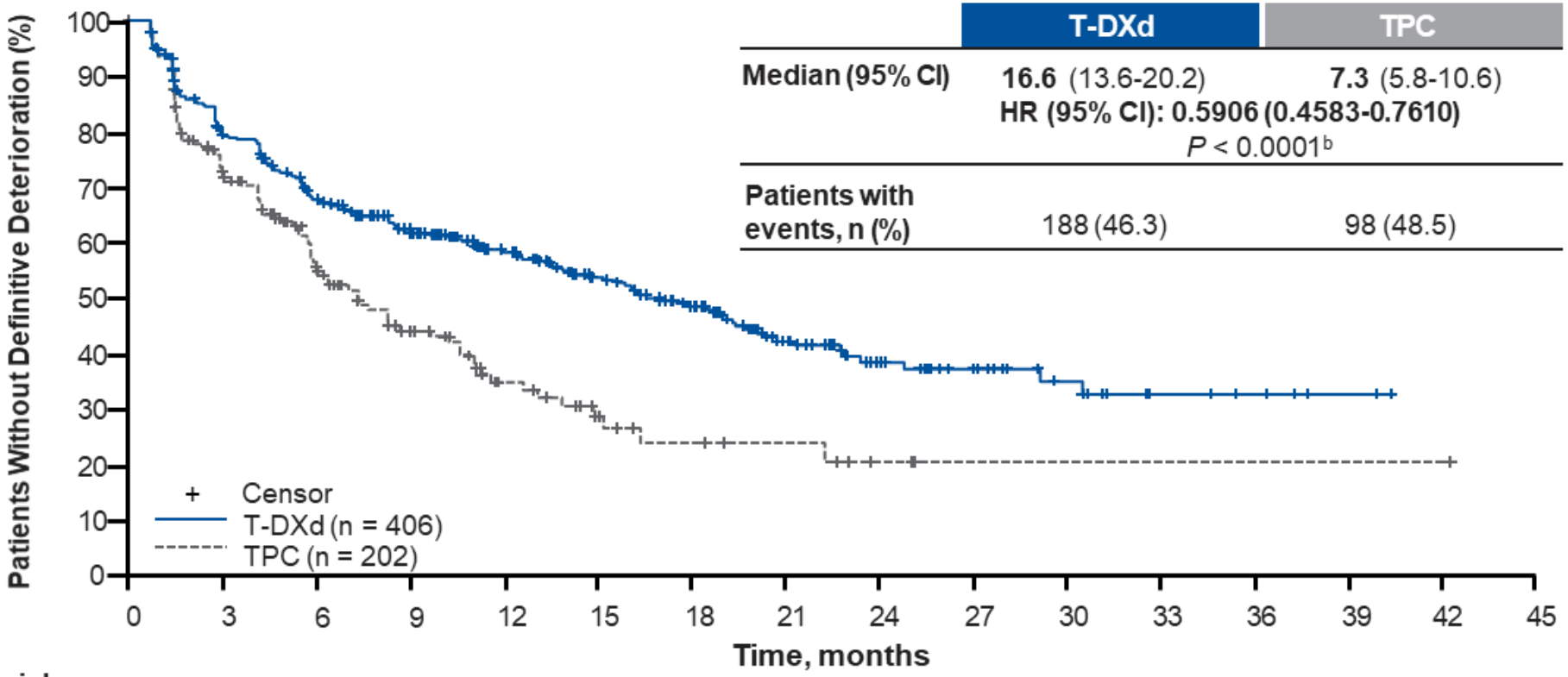


No. at risk:																
T-DXd (n = 406)	406	311	269	206	149	110	92	63	37	25	14	9	7	2	0	0
TPC (n = 202)	202	99	58	34	17	11	7	6	3	2	2	1	1	1	1	0

Patients in the T-DXd arm experienced longer median TDD of pain symptoms and physical functioning

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; HR, hazard ratio; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]*P* values are two-sided and based on a stratified log-rank test.

Time to definitive deterioration of EQ-5D-5L VAS[a]



	T-DXd	TPC
Median (95% CI)	**16.6** (13.6-20.2)	**7.3** (5.8-10.6)
	HR (95% CI): 0.5906 (0.4583-0.7610)	
	P < 0.0001[b]	
Patients with events, n (%)	188 (46.3)	98 (48.5)

No. at risk:																
T-DXd (n = 406)	406	291	237	193	149	118	91	56	33	24	15	8	6	2	0	0
TPC (n = 202)	202	117	70	44	25	14	9	7	3	1	1	1	1	1	1	0

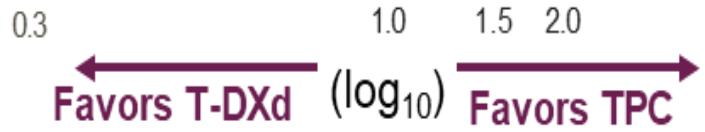
TDD was prolonged among patients in the T-DXd arm versus the TPC arm for the EQ-5D-5L VAS, further supporting the delay in HRQoL deterioration with T-DXd

EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; HR, hazard ratio; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan; TPC. Treatment of physician's choice; VAS, visual analogue scale.

[a]VAS of self-rated overall health and quality of life, measured on a scale from 0 to 100. [b]*P* values are two-sided and based on a stratified log-rank test.

Time to definitive deterioration in PRO measures

QLQ-C30	Physical functioning[c]	18.7 (15.5-22.9)	6.8 (5.7-8.8)	0.46 (0.36-0.60)	<0.0001
	Emotional functioning[c]	21.4 (16.9-NE)	10.7 (6.9-15.4)	0.67 (0.51-0.88)	0.0041
	Social functioning[c]	18.7 (13.9-28.8)	6.3 (4.9-8.8)	0.54 (0.42-0.70)	<0.0001
	Pain[c]	18.7 (14.1-23.8)	5.8 (5.0-7.0)	0.38 (0.29-0.49)	<0.0001
EORTC QLQ-BR45[d]	Arm symptoms[c]	18.3 (13.9-21.2)	8.8 (6.1-11.6)	0.57 (0.44-0.75)	<0.0001
	Breast symptoms[c]	NE (30.3-NE)	18.1 (12.5-NE)	0.42 (0.29-0.59)	<0.0001
EQ-5D-5L	VAS[c]	16.6 (13.6-20.2)	7.3 (5.8-10.6)	0.59 (0.46-0.76)	<0.0001

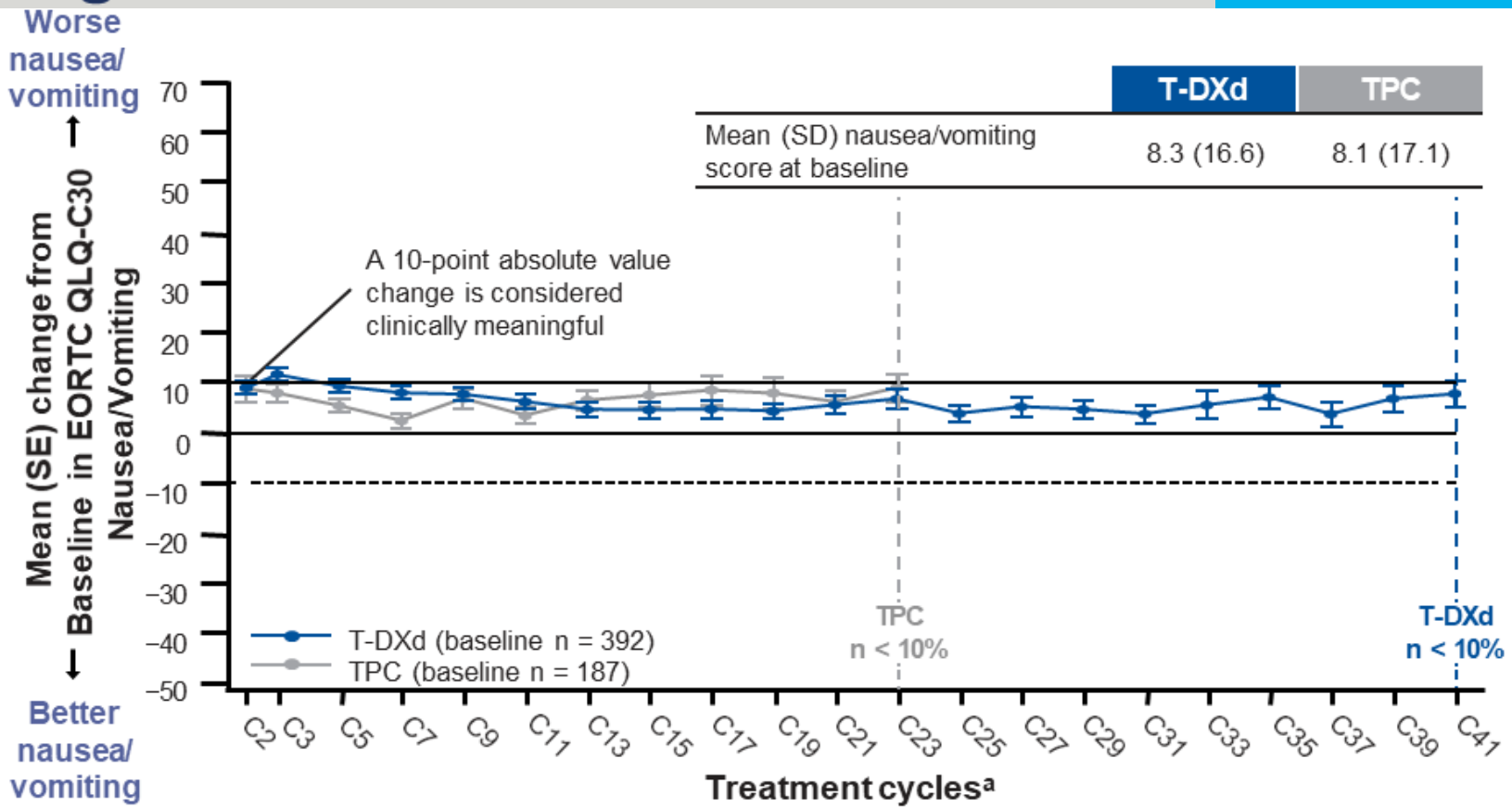


TDD was delayed among patients in the T-DXd arm vs the TPC arm for all prespecified scales

EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HR, hazard ratio; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; VAS, visual analogue scale.

[a]*P* values are two-sided and based on a stratified log-rank test. [b]Primary PRO variable of interest. [c]Secondary PRO variable of interest. [d]Scored as QLQ-BR23.

Mean change from baseline in EORTC QLQ-C30 nausea/vomiting score



In the T-DXd arm, an increase in nausea/vomiting scores was only clinically relevant in early cycles, after which scores decreased and remained stable over time (within 10 points of baseline)

C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]On day 1 of cycle

Conclusions

- **Overall HRQoL was maintained longer with T-DXd than with TPC**, as suggested by mean change from baseline data
- **Definitive deterioration of HRQoL was delayed for patients in the T-DXd arm**, as indicated by the hazard ratios for TDD which favored T-DXd over TPC for all evaluable prespecified scales
    - **Patients in the T-DXd arm experienced longer time until definitive deterioration in GHS/overall QoL, physical functioning, and pain symptoms** compared with patients in the TPC arm, which is of particular interest given the profound impact of pain on QoL[1]
- PRO results of this study are **consistent with** those reported in **DESTINY-Breast03**,[2,3] demonstrating that HRQoL is sustained in T-DXd-treated patients with HER2-positive mBC

These PRO data, together with previous efficacy and safety data from DESTINY-Breast02, **support the benefit of T-DXd in patients with T-DM1–resistant HER2-positive mBC**

EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; HR, hazard ratio; mBC, metastatic breast cancer; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Dams L et al. *Support Care Cancer*. 2022;30(5):4465-75. 2.Curigliano et al. Presented at ESMO Breast; May 3-5, 2022, Berlin, Germany. Presentation 163O. 3. Cortés et al. *N Eng J Med*. 2022;386:12.

DESTINY-BREAST04 SUBGROUP ANALYSES OF TRASTUZUMAB DERUXTECAN VS TREATMENT OF PHYSICIAN'S CHOICE IN PATIENTS WITH HER2-LOW, ESTROGEN- RECEPTOR EXPRESSION IMMUNOHISTOCHEMISTRY 0-10% METASTATIC BREAST CANCER

David A. Cameron, Institute of Genomics and Cancer, University of Edinburgh, Edinburgh, United Kingdom

Additional authors:

William Jacot, Toshinari Yamashita, Maria Vidal, Peter Schmid, Keun Seok Lee, Michelino De Laurentiis, Flora Zagouri, Naoto T. Ueno, Aleix Prat, Nadia Harbeck, Rinat Yerushalmi, Yen-Shen Lu, Andrea Gombos, Cecilia Orbegoso Aguilar, Fu-Chih Cheng, Lotus Yung, Rachana Rajagopalan, Junji Tsurutani, Shanu Modi

Declaration of Interests

- Dr. David Cameron has previously received consulting fees from Lilly, Novartis, and Sanofi, as well as payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Lilly, Novartis, and Pfizer. Dr. Cameron has also participated on a data safety monitoring board or advisory board for Roche, Grail, Novartis, Astra-Zeneca, and Syntheon

Background

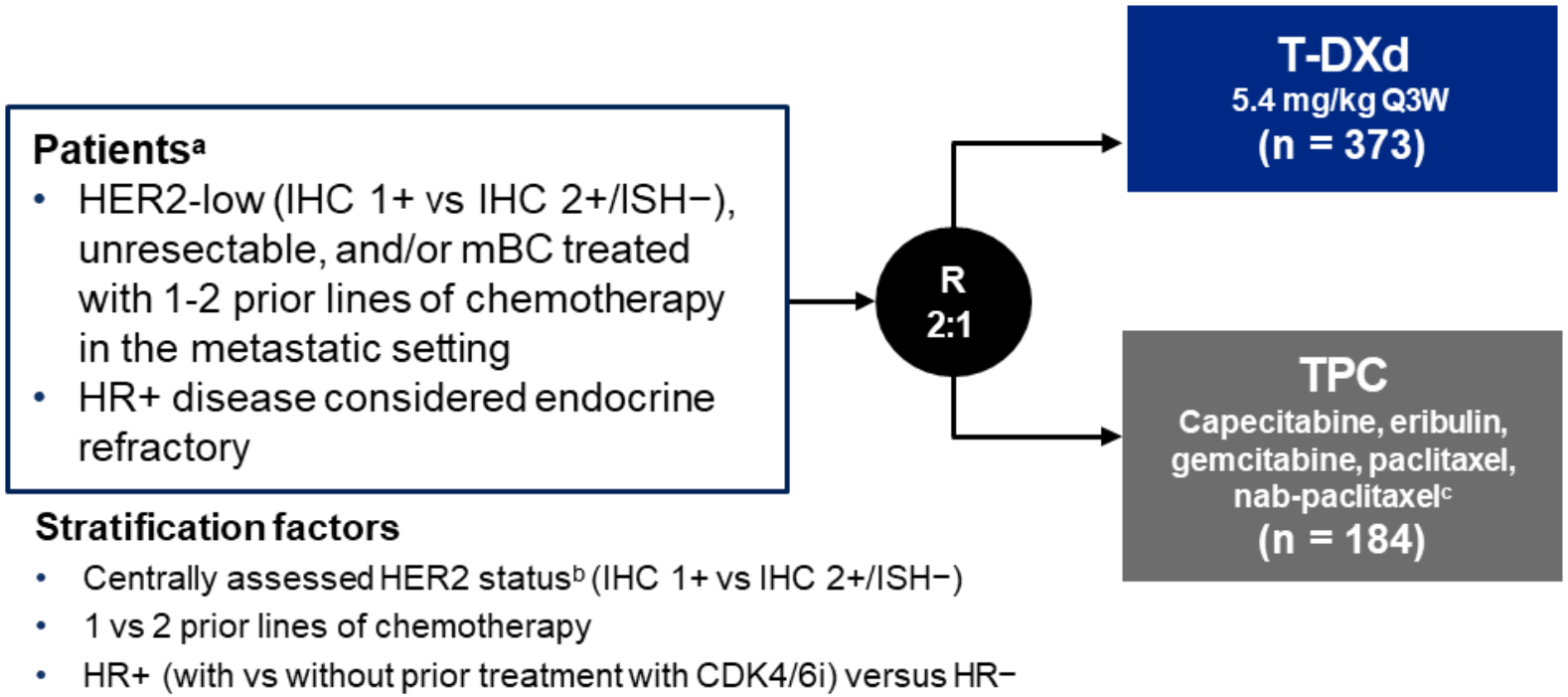
- A small but clinically significant proportion (~2-3%) of breast cancer tumors are considered HER2-low (IHC 1+ or IHC 2+/ISH−) with low ER expression (IHC 1-10%)[1,2] and less sensitivity to endocrine therapies
- Rather than behaving like tumors with high ER expression (IHC >10%), HER2-low, ER-low (IHC 1-10%) breast cancers tend to mimic TNBC, which accounts for 10-15% of breast cancers[1,2]
- ASCO/CAP guidelines recommend an IHC ER expression cutoff of ≥1% for ER positive tumors, however, endocrine therapy studies are increasingly using a higher cut-off of 10%[2,3]
- Potential for 3 classifications of ER expression: negative (IHC 0%), low (IHC 1-10%), and positive (IHC >10%)
- This subgroup analysis explored efficacy and safety outcomes for T-DXd versus TPC in the subset of patients from the DESTINY-Breast04 study[4] with low ER expression (IHC 1-10%)

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TNBC, triple-negative breast cancer.

1. Kim MC et al. *J Breast Cancer*. 2022;25:318-26. 2. Yoder R et al. *NPJ Breast Cancer*. 2022;8:80. 3. Tarantino P et al. *J Clin Oncol*. 2020;38:1951-62. 4. Modi S et al. *NEJM*. 2022;387:9-20.

DESTINY-Breast04 Study Design

An open-label, multicenter study (NCT03734029)[1-3]



Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Other secondary endpoints
- PFS (investigator)
- ORR (BICR and investigator)
- DOR (BICR)
- Safety
- Patient-reported outcomes (HR+)[e]

ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ISH, in situ hybridization; IUO, investigational use only; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) IUO Assay system. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

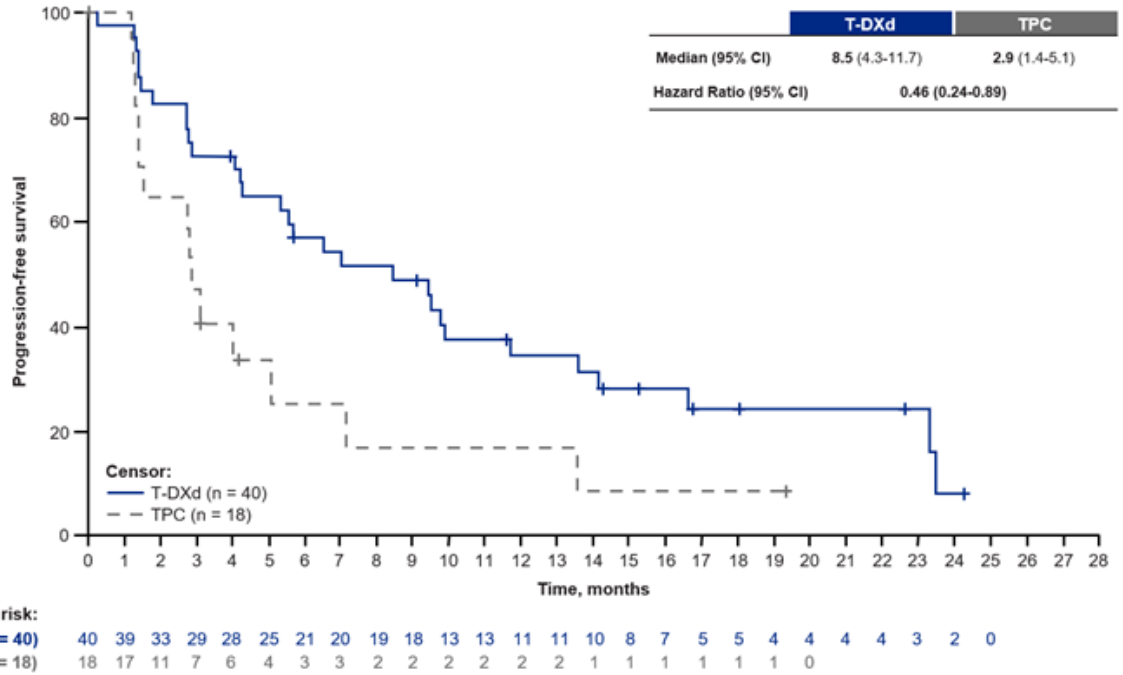
Baseline Demographic Characteristics of ER Subgroups

	ER-negative (IHC 0%)		ER-low (IHC 1-10%)	
Baseline Characteristic[a]	**T-DXd (n = 40)**	**TPC (n = 18)**	**T-DXd (n = 35)**	**TPC (n = 17)**
Age				
Median (range), years	58.9 (36.6-78.9)	55.9 (32.6-80.5)	57.6 (31.5-76.4)	50.6 (32.6-69.7)
Age < 65 years, n, (%)	30 (75.0)	13 (72.2)	31 (88.6)	16 (94.1)
Age ≥ 65 years, n, (%)	10 (25.0)	5 (27.8)	4 (11.4)	1 (5.9)
Race, n (%)				
White	19 (47.5)	11 (61.1)	15 (42.9)	10 (58.8)
Black or African American	0	1 (5.6)	1 (2.9)	1 (5.9)
Asian	20 (50.0)	6 (33.3)	14 (40.0)	5 (29.4)
Other	1 (2.5)	0	5 (14.3)	1 (5.9)
Previous CDK4/6i, n (%)				
Yes	2 (5.0)	0	22 (62.9)	9 (52.9)
No	38 (95.0)	18 (100)	12 (34.3)	8 (47.1)
Missing	0	0	1 (2.9)	0
Number of prior lines of chemotherapy, n (%)				
1	16 (40.0)	5 (27.8)	21 (60.0)	8 (47.1)
2	24 (60.0)	13 (72.2)	14 (40.0)	9 (52.9)
HER2 IHC/ISH status, n (%)				
HER2 1+	22 (55.0)	10 (55.6)	17 (48.6)	12 (70.6)
HER2 2+/ISH-	18 (45.0)	8 (44.4)	18 (51.4)	5 (29.4)
PR expression, n (%)[b]				
PR staining 1-10% of cells positive	0	0	20 (57.1)	4 (23.5)
PR staining > 10% of cells positive	0	0	4 (11.4)	3 (17.6)
PR staining unknown	0	0	0	0
Negative	40 (100.0)	18 (100.0)	11 (31.4)	10 (58.8)
Baseline liver metastases, n (%)	19 (47.5)	5 (27.8)	23 (65.7)	8 (47.1)
Baseline CNS metastases, n (%)	5 (12.5)	1 (5.6)	1 (2.9)	2 (11.8)
Pretreated anthracycline status, n (%)	30 (75.0)	9 (50.0)	25 (71.4)	12 (70.6)

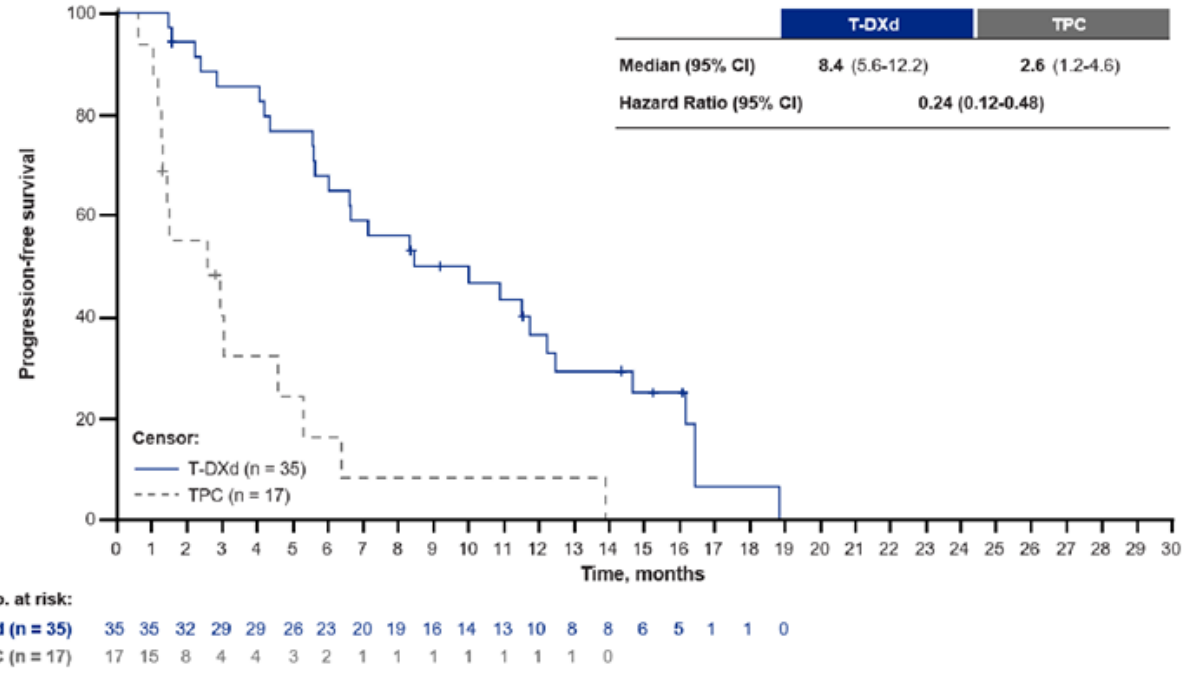
CNS, central nervous system; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PR, progesterone receptor; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]All patients (100%) in each subgroup were female. [b]No patients in either subgroup had indeterminate PR expression.

PFS in Patients by ER Expression

Patients with ER-negative (IHC 0%)



Patients with ER-low (IHC 1-10%)

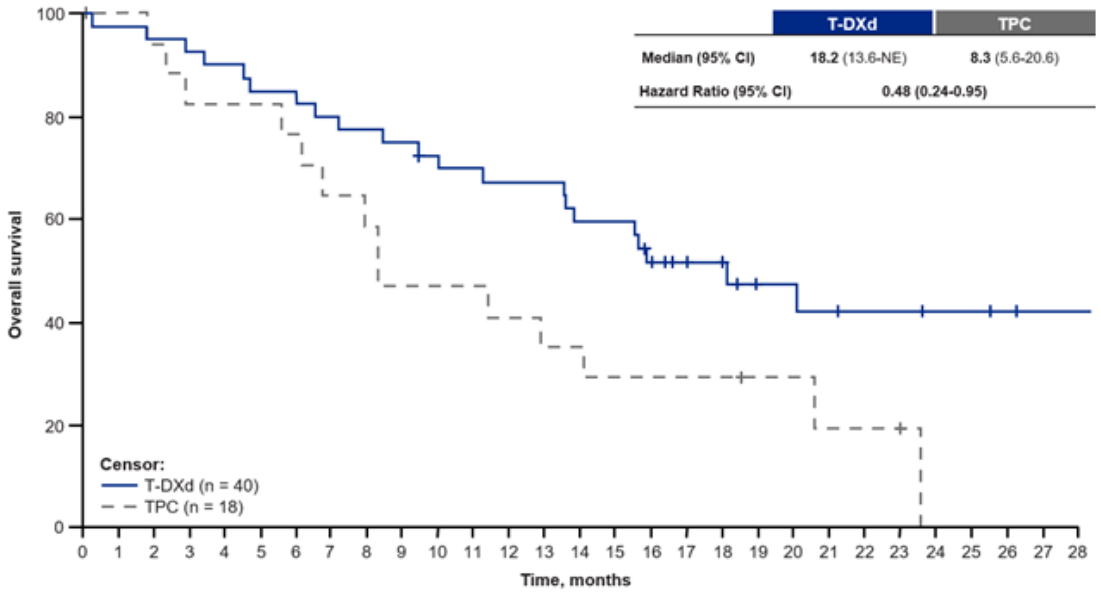


- T-DXd achieved better PFS outcomes compared with TPC

CI, confidence interval; ER, estrogen receptor; IHC, immunohistochemistry; NE, not estimable; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Cutoff date: January 11, 2022.
[a]Analysis conducted in the full analysis set.

OS in Patients by ER Expression

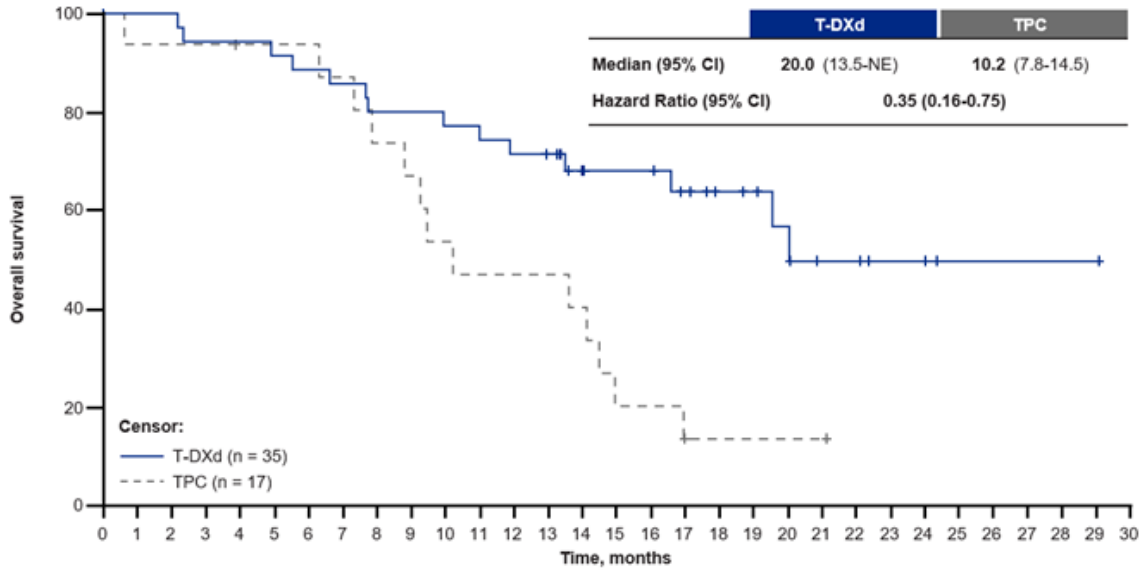
Patients with ER-negative (IHC 0%)



No. at risk:

T-DXd (n = 40)	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18)	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

Patients with ER-low (IHC 1-10%)



No. at risk:

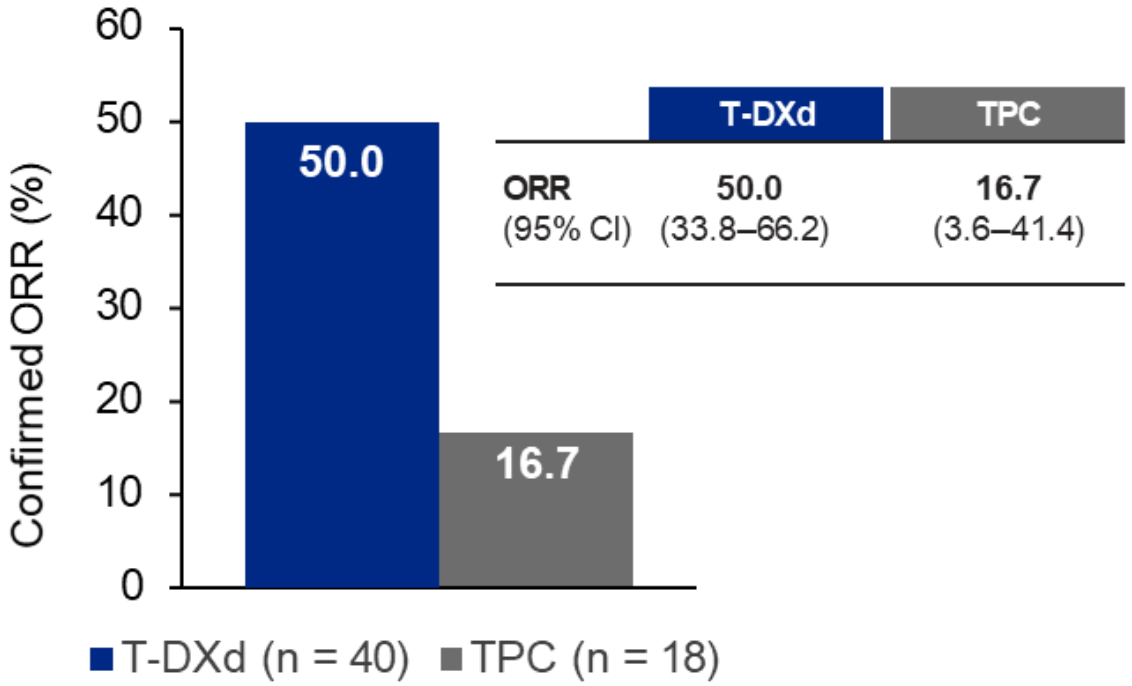
T-DXd (n = 35)	35	35	35	33	33	32	31	30	28	28	27	27	25	24	18	17	17	14	11	10	8	5	5	3	3	1	1	1	1	1	0
TPC (n = 17)	17	15	15	15	14	14	14	13	11	10	8	7	7	7	6	3	3	1	1	1	1	1	0								

- T-DXd achieved better OS outcomes compared with TPC

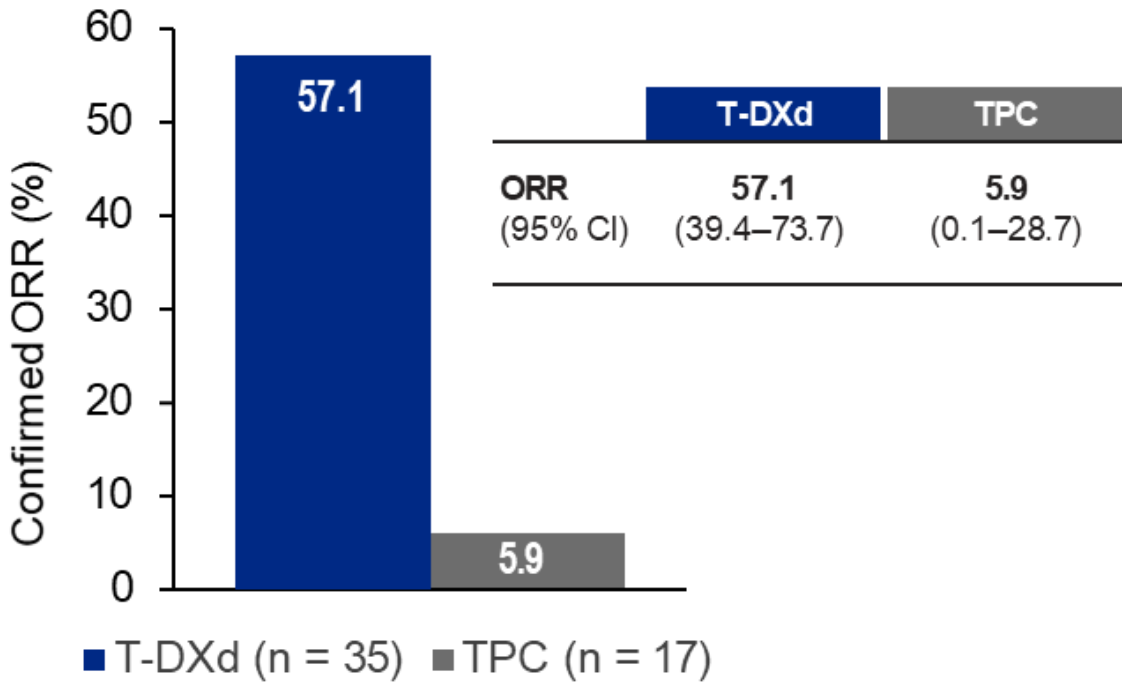
CI, confidence interval; ER, estrogen receptor; IHC, immunohistochemistry; NE, not estimable; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Cutoff date: January 11, 2022.
[a]Analysis conducted in the full analysis set.

ORR in Patients by ER Expression

Patients with ER-negative (IHC 0%)



Patients with ER-low (IHC 1-10%)



- Confirmed ORR is higher with T-DXd versus TPC, regardless of ER expression

ER, estrogen receptor; IHC, immunohistochemistry; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Reported as hormone receptor-negative cohort in Modi S et al.
Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

Most common TEAEs in ≥20% Patients with ER IHC 0-10%

Preferred Term, %	T-DXd (N = 75)		TPC (N = 32)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any		53.3		75.0
Nausea	77.3	4.0	34.4	0
Vomiting	40.0	1.3	21.9	0
Fatigue	37.3	8.0	40.6	9.4
Decreased appetite	34.7	1.3	25.0	3.1
Alopecia	33.3	0	31.3	0
Constipation	33.3	0	21.9	0
Anemia	30.7	10.7	34.4	3.1
Diarrhea	29.3	2.7	21.9	3.1
Aspartate aminotransferase increased	26.7	5.3	28.1	0
Alanine aminotransferase increased	18.7	4.0	21.9	0
White blood cell count decreased	18.7	5.3	31.3	25.0
Neutrophil count decreased	14.7	2.7	31.3	25.0
Median duration of treatment, months (range)	**8.2 (0.2 to 33.3)**		**3.5 (0.3 to 17.6)**	

- Safety outcomes are consistent with results observed in the primary analysis

ER, estrogen receptor; IHC, immunohistochemistry; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events; TPC, treatment of physician's choice.
Modi S et al. N Engl J Med. 2022;387(1):9-20.

Conclusions

- In this analysis, T-DXd showed better efficacy compared to TPC in terms of PFS, OS, and ORR in patients with HER2-low, ER-low (IHC 1-10%) mBC
  - These results are comparable with those seen for patients with HER2-low, ER-negative (IHC 0%) mBC
- Consistent with the primary analysis of DESTINY-Breast04, T-DXd also demonstrated an acceptable and manageable safety profile in patients with ER IHC 0-10%

This analysis provides evidence that patients with ER-low mBC have similar outcomes to patients with ER-negative mBC with T-DXd achieving better outcomes than TPC in patients with HER2-low, ER-low mBC

ER, estrogen receptor; IHC, immunohistochemistry; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TNBC, triple-negative breast cancer.

1020

Trastuzumab Deruxtecan Versus Treatment of Physician's Choice in Patients With HER2-Low, Hormone Receptor-Positive Unresectable and/or Metastatic Breast Cancer: Exploratory Biomarker Analysis of DESTINY-Breast04

Shanu Modi,[1] Naoki Nikkuni,[2] Toshinari Yamashita,[3] William Jacot,[4] Joo Hyuk Sohn,[5] Eriko Tokunaga,[6] Maria Vidal,[7] Yoon Hee Park,[8] Kaun Seok Lee,[9] Yee Soo Chae,[10] Naoto Ueno,[11] Alex Prat,[12] Fumitaka Suto,[13] Yosuke Kuwahara,[13] Robert McEwen,[13] Wenjin Feng,[13] Hiroki Goto,[13] Cecilia Orbegoso Aguilar,[13] David Cameron,[14] Junji Tsurutani[15]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Gifu University Hospital, Gifu, Japan; [3]Kanagawa Cancer Center, Yokohama, Japan; [4]Institut du Cancer de Montpellier, Montpellier University, Montpellier, France; [5]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [6]NHO Kyushu Cancer Center, Fukuoka, Japan; [7]Hospital Clínic de Barcelona, Barcelona, Spain; [8]Samsung Medical Center, Seoul, Republic of Korea; [9]National Cancer Center, Goyang-si, Republic of Korea; [10]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [11]University of Hawai'i Cancer Center, Honolulu, HI, USA; [12]Clínic Barcelona, Barcelona, Spain; [13]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [14]Daiichi Sankyo, Edinburgh, UK; [15]Daiichi Sankyo Co., Ltd., Tokyo, Japan; [16]Edinburgh Cancer Centre, Edinburgh, Scotland; [17]Nihon University Hospital, Tokyo, Japan

Background

- Around 60% of metastatic breast cancers (mBC) are considered human epidermal growth factor receptor 2 (HER2)–negative and express HER2 at low levels (HER2 low: immunohistochemistry [IHC] score of 1+ or an IHC score of 2+ with negative results on in situ hybridization [ISH])[1,2]
- Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody drug conjugate that can target tumor cells with low levels of HER2 expression. It can also deliver its payload to neighboring tumor cells regardless of HER2 protein expression through the bystander antitumor effect[3,4]
- DESTINY-Breast04, a randomized, open-label, phase 3 trial in patients with HER2-low (IHC 1+ or IHC 2+/ISH−), unresectable and/or mBC treated with 1–2 prior lines of chemotherapy in the metastatic setting demonstrated that patients with metastatic HER2-low breast cancer (BC) treated with T-DXd experienced significantly longer progression-free survival (PFS) and overall survival than the physician's choice of chemotherapy.[5] Benefit with T-DXd was observed across subgroups regardless of HER2 IHC status or prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) use.[6] These results confirmed HER2-low mBC as a targetable patient population with T-DXd as the standard of care
- *ESR1* mutations, *PIK3CA* mutations, and CDK4/6i resistance markers are common in hormone-receptor positive (HR+) breast cancer and can impact treatment response[7–9]; *ESR1* mutations may be associated with poor prognosis,[7] *PIK3CA* mutations have been associated with endocrine resistance and poorer outcomes,[8] and biomarkers associated with CDK4/6i resistance are important when attempting to optimize treatment strategies[10]

Conclusion

- Greater clinical benefit was consistently observed with T-DXd versus physician's choice of chemotherapy independent of intrinsic subtype, *ESR1* mutation, *PIK3CA* mutation, or known CDK4/6i resistance marker status

Plain Language Summary

Why did we perform this research?

Breast cancer can be categorized by the amount of a protein called human epidermal growth factor receptor 2 (HER2) expressed on the surface of tumor cells. However, tumors categorized as HER2-negative can still express low levels of HER2.[1,2] The antibody-drug conjugate, T-DXd, targets the HER2 protein to deliver chemotherapy to tumor cells. In the DESTINY-Breast04 clinical trial, T-DXd treatment resulted in better outcomes than physician's choice of chemotherapy for patients with HER2-low metastatic breast cancer. This led to the approval of T-DXd for the treatment of patients with HER2 low metastatic breast cancer. Development of tumor mutations and other resistance mechanisms is a common problem in hormone receptor positive breast cancer. This analysis investigated whether the benefit of T-DXd differed based on the presence or absence of common biomarkers of prognosis or resistance to other approved therapies, using data from patients with hormone-receptor-positive metastatic breast cancer enrolled in the DESTINY-Breast04 trial.

How did we perform this research?

Most tumor tissue and all blood samples were collected after prior treatment but before T-DXd or physician's choice of chemotherapy treatment in patients with hormone receptor–positive HER2-low metastatic breast cancer who participated in the DESTINY-Breast04 trial. Clinical benefits of T-DXd were analyzed according to tumor receptor positive breast cancer molecular subtype, mutations of *ESR1* and/or *PIK3CA* genes, and biomarkers associated with CDK4/6 inhibitor resistance.

What were the findings of this research and what are the implications?

Greater clinical benefit was consistently observed with T-DXd compared with physician's choice of chemotherapy regardless of the molecular subtype of the tumor, *ESR1* mutation, *PIK3CA* mutation, or markers of CDK4/6i resistance. These results provide evidence that T-DXd is effective for the treatment of HER2-low metastatic breast cancer across patients with common markers of resistance mechanisms.

Where can I access more information?

DESTINY-Breast04: ClinicalTrial.gov: Trastuzumab Deruxtecan (DS-8201a) Versus Investigator's Choice for HER2-Low Breast Cancer That Has Spread or Cannot Be Surgically Removed. https://www.clinicaltrials.gov/ct2/show/NCT03734029

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 2–6, 2023

Objective

- To investigate associations between clinically relevant biomarkers at baseline and clinical treatment outcomes in patients with HER2-low, HR+ mBC in an exploratory analysis of DESTINY-Breast04

Methods

- Tumor tissue and plasma samples were collected from patients with HER2-low mBC who participated in the DESTINY-Breast04 trial (cutoff: January 11, 2022)
  - Almost all tumor tissues for RNA-seq analysis were collected after prior treatment but before T-DXd or TPC treatment
  - Plasma samples for ctDNA analysis were collected just prior to T-DXd or TPC treatment
- The biomarker-derived subgroups investigated in this analysis include
  - *PIK3CA* mutation status (patients with activating mutations categorized as mutant [Mut] vs patients without activating mutations categorized as wild type [WT]; selected according to the EMILIA study)[11]
  - *ESR1* mutation status (Mut vs WT; selected by OncoKB annotation)[12]
  - Intrinsic subtypes (Luminal A, Luminal B, HER2 enriched)[13]

  Exploratory CDK4/6i resistance marker signatures derived from the compilation of published CDK4/6i resistance mutations.[14] These mutations can be either intrinsic or acquired during treatment. Although the signature is not yet clinically validated, demonstrating T-DXd activity in patients with or without prior CDK4/6i exposure and with or without inherent and/or acquired CDK4/6i resistance may have clinical relevance
- Intrinsic subtypes were estimated by PAM50 gene expression[15] derived from sequencing of mRNA isolated from tumor tissue samples collected after prior treatment
- The status of *PIK3CA* and *ESR1* mutations and CDK4/6i resistance markers was based on baseline ctDNA analysis performed on baseline blood samples, using the Guardant OMNI panel, which can detect alterations in approximately 500 genes. Known gene alterations associated with resistance to CDK4/6i included *CCND1*, *CDK6*, and *FGFR1/2* amplification and *RB1*, *PTEN*, *TP53*, *AKT1*, *ZNF217*, and *FAT1* mutations
- Association between biomarker status and the objective response rate (ORR) and PFS was assessed

Results

Baseline Characteristics for ctDNA and RNA-seq Datasets

- Baseline characteristics of patients with samples that underwent ctDNA and RNA-seq analysis were generally similar across treatment groups; most patients had HR+ breast cancer (primary [pr.] 74%) in the T-DXd arm and 132/156 (97.8%) in the TPC arm in the ctDNA dataset and 223/256 (87.5%) and 103/119 (86.6%), respectively, in the RNA-seq dataset) and approximately two-thirds had prior CDK4/6i treatment
  - Among HR+ patients in the ctDNA dataset, 51.3% in the T-DXd arm and 54.0% in the TPC arm had *ESR1* mutations at baseline, 38.1% and 41.6%, respectively, had *PIK3CA* mutations at baseline, and, among patients with prior CDK4/6i treatment, 71.0% and 70.2%, respectively, had at least 1 CDK4/6i resistance marker

Efficacy According to Biomarker Subgroups

- Clinical outcomes (ORR and PFS) in the RNA-seq and ctDNA populations were generally comparable with the overall study population (**Table 1**)[5]
- Improved ORR for T-DXd over TPC was observed in this population of patients with HER2-low, HR+ mBC regardless of intrinsic molecular subtype, *ESR1* or *PIK3CA* mutation status, and CDK4/6i resistant markers (**Figure 1**)
- Longer median PFS was observed in the T-DXd arm compared to the TPC arm regardless of intrinsic molecular subtypes, *ESR1* or *PIK3CA* mutation status (**Figure 2**)
- CDK4/6i resistance markers were examined in patients with or without prior CDK4/6i therapy (**Figure 3**). Longer median PFS was observed in the T-DXd arm compared to the TPC arm regardless of the presence of these markers

Table 1. Clinical Outcomes in Patients With HER2-low HR+ mBC

Population	Treatment Arm	Confirmed ORR, % (n/N, 95% CI)	n	mPFS, months (95% CI)	PFS Hazard Ratio (95% CI)
Overall HR+ mBC[a]	T-DXd	59.8 (179/333, 47.0-65.0)	381	10.1 (9.0-11.6)	0.51 (0.40-0.64)
	TPC	16.3 (27/166, 11.0-23.6)	163	5.4 (4.4-7.1)	
RNA-seq	T-DXd	54.7 (122/223, 47.9-61.4)	223	10.9 (9.0-12.8)	0.52 (0.39-0.68)
	TPC	18.4 (19/103, 11.5-27.3)	103	6.8 (5.0-7.6)	
ctDNA	T-DXd	59.7 (149/277, 49.9-65.7)	277	10.0 (8.3-11.4)	0.54 (0.42-0.70)
	TPC	16.5 (23/137, 11.0-24.1)	137	5.9 (4.5-7.9)	

Figure 1. ORR According to Baseline Biomarker Status

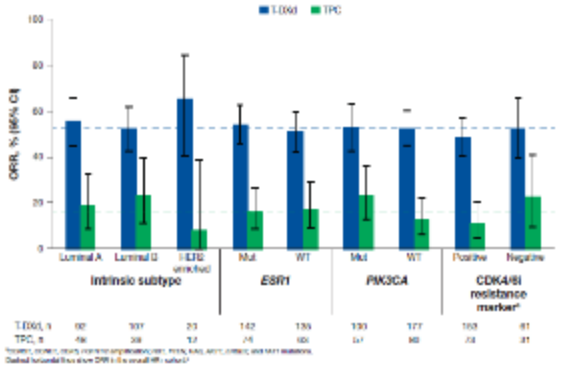


Figure 2. PFS According to (A) *PIK3CA* Mutation Status, (B) *ESR1* Mutation Status, and (C) Intrinsic Subtype

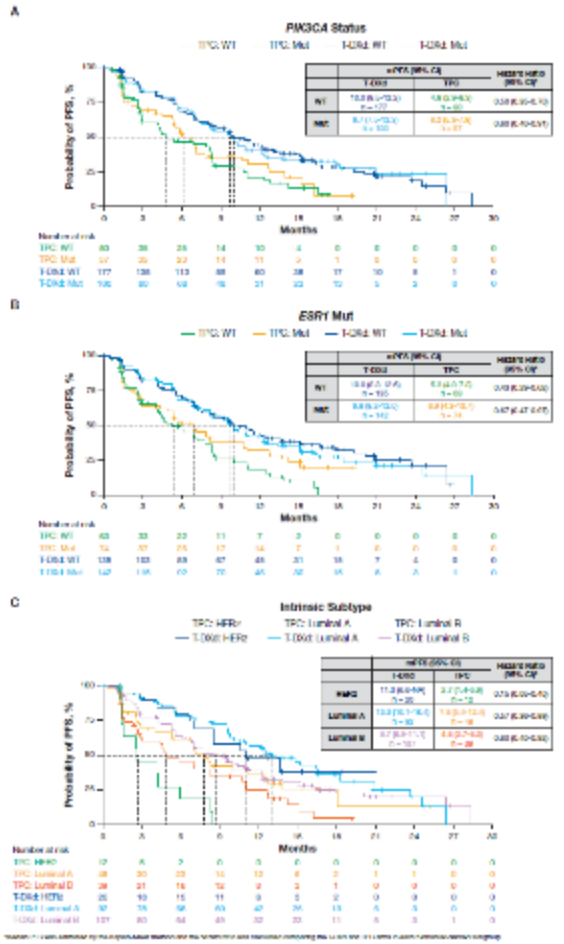
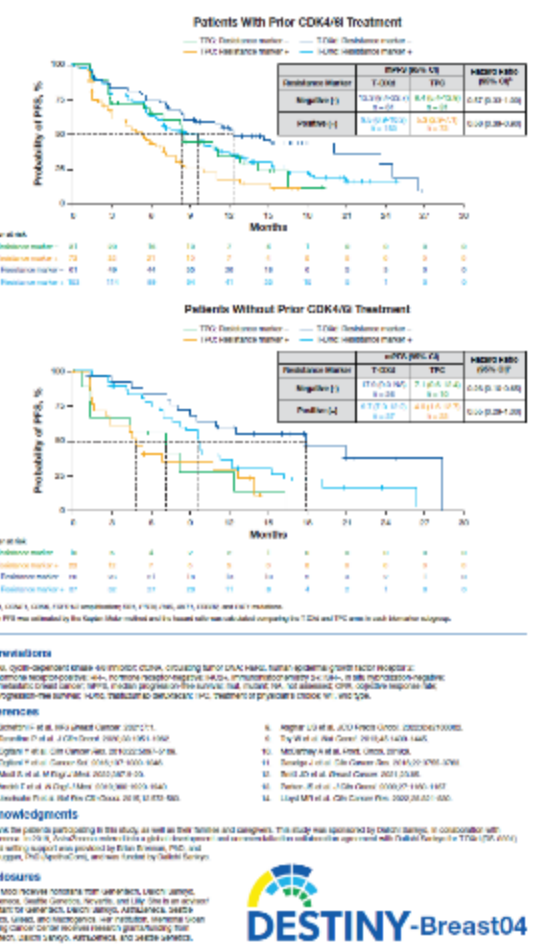


Figure 3. PFS According to CDK4/6i Resistance Markers[c] (A) in Patients With Prior CDK4/6i Treatment and (B) in Patients Without Prior CDK4/6i Treatment



Abbreviations

References

Acknowledgments

Disclosures

DESTINY-Breast04

ASCO 2023 #1020 Poster

TRASTUZUMAB DERUXTECAN (T-DXD) VS TREATMENT OF PHYSICIAN'S CHOICE (TPC) IN PATIENTS WITH HER2-LOW UNRESECTABLE AND/OR METASTATIC BREAST CANCER: A DETAILED SAFETY ANALYSIS OF THE RANDOMIZED, PHASE 3 DESTINY-BREAST04 TRIAL

Hope S. Rugo, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

Additional authors:

William Jacot, Eriko Tokunaga, Joohyuk Sohn, Fatima Cardoso, Binghe Xu, Maria Vidal, Miguel Gil-Gil, Naoto Ueno, Aleix Prat, Halle C.F. Moore, Ursula Hasler-Strub, David Cameron, Henrik Lindman, Klara Mezei, Rachana Rajagopalan, Cecilia Orbegoso Aguilar, Fu-Chih Cheng, Aashima Puri,

Shanu Modi

Declaration of Interests

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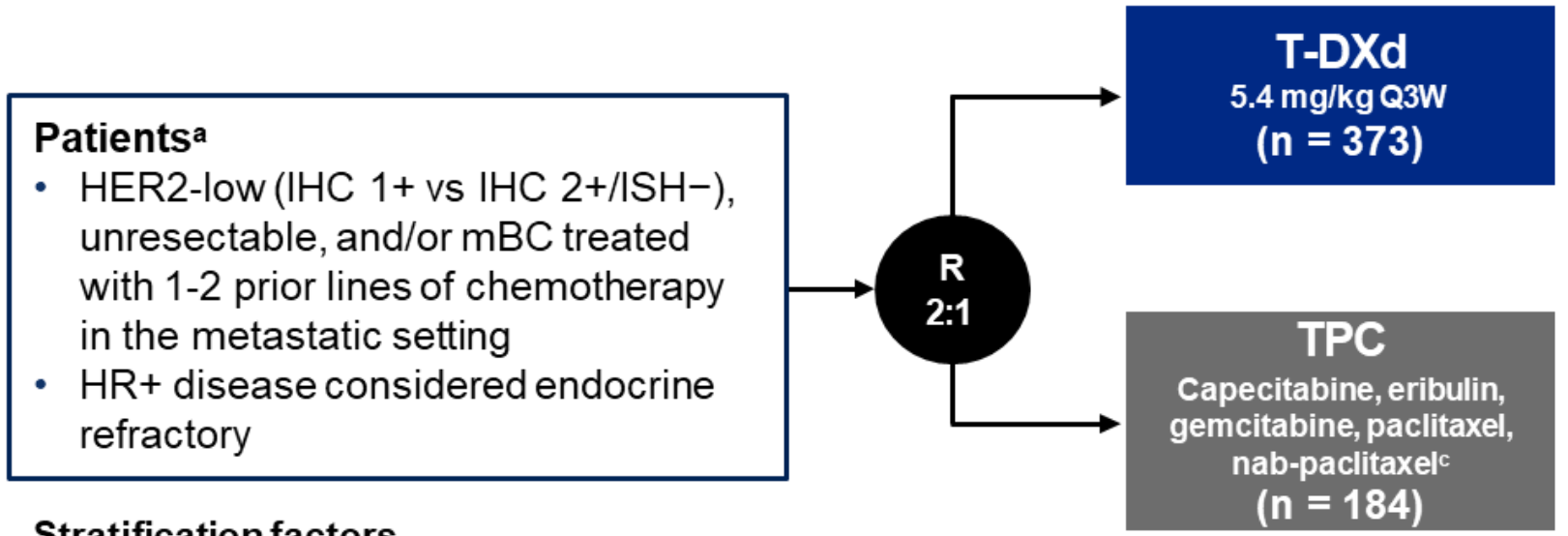
DESTINY-Breast04 Study Design

An open-label, multicenter study (NCT03734029)[1-3]



Stratification factors

- Centrally assessed HER2 status[b] (IHC 1+ vs IHC 2+/ISH−)
- 1 vs 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6i) versus HR−

DCO: January 11, 2022

Primary endpoint

- PFS by BICR (HR+)

Key secondary endpoints[d]

- PFS by BICR (all patients)
- OS (HR+ and all patients)

Secondary endpoints[d]

- PFS (investigator)
- ORR (BICR and investigator)
- DOR (BICR)
- Safety
- Patient-reported outcomes (HR+)[e]

ASCO, American Society of Clinical Oncology; BICR, blinded independent central review; CAP, College of American Pathologists; CDKi, cyclin-dependent kinase 4/6 inhibitors; DCO, data cutoff; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

DESTINY-Breast04 Background

Efficacy in All Patients[1]
(HR+ and HR−)

Progression-Free Survival (by BICR)

Hazard ratio: 0.50, *P* <0.0001

Overall Survival

Hazard ratio: 0.64, *P* = 0.001

- T-DXd is the first HER2-directed therapy to demonstrate statistically significant and clinically meaningful improvement in PFS and OS versus TPC[1]
- Similar magnitudes of benefit were reported across all subgroups, including HER2 IHC status and prior CDK4/6i use[1]
- Treatment with T-DXd also delayed deterioration of global health score/quality of life[2]
- DESTINY-Breast04 established HER2-low (IHC 1+, IHC 2+/ISH−) mBC as a new targetable patient population, with T-DXd as a new standard of care[1]

BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; mo, month; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. Ueno N et al. Presented at: ESMO 2022; September 9-13, 2022.

Exposure-Adjusted Incidence Rates[a] Overview

	T-DXd n = 373	TPC n = 184
Safety analysis set[b], n (%)	**371 (99.5%)**	**172 (93.5%)**
Treatment duration, median (range), mo	**8.2 (0.2-33.3)**	**3.5 (0.3-17.6)**
Exposure, patient-years[c]	283.55	63.59
EAIR, any-grade TEAE	1.30	2.66
EAIR, grade ≥3 TEAE	0.69	1.82
EAIR, any-grade serious TEAE	0.36	0.68
EAIR, grade ≥3 serious TEAE	0.28	0.49
EAIR, TEAE associated with drug discontinuation	0.21	0.22
EAIR, TEAE associated with dose reduction	0.30	1.04
EAIR, TEAE associated with dose interruption	0.50	1.13

- EAIRs were measured to account for differences in treatment duration exposure between T-DXd and TPC and provide a more meaningful comparison
- EAIRs per patient-year were lower in the T-DXd arm than in the TPC arm for all overall parameters of TEAEs

EAIR, exposure-adjusted incidence rate; mo, month; TEAE, treatment emergent adverse events; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]EAIR is the number of patients with at least 1 adverse event incidence divided by the sum of patient-years of exposure over patients in the safety analysis set (total patient-years of exposure). [b]Data cutoff: January 11, 2022. [c]Patient-years of exposure were the treatment duration with year as unit.
Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

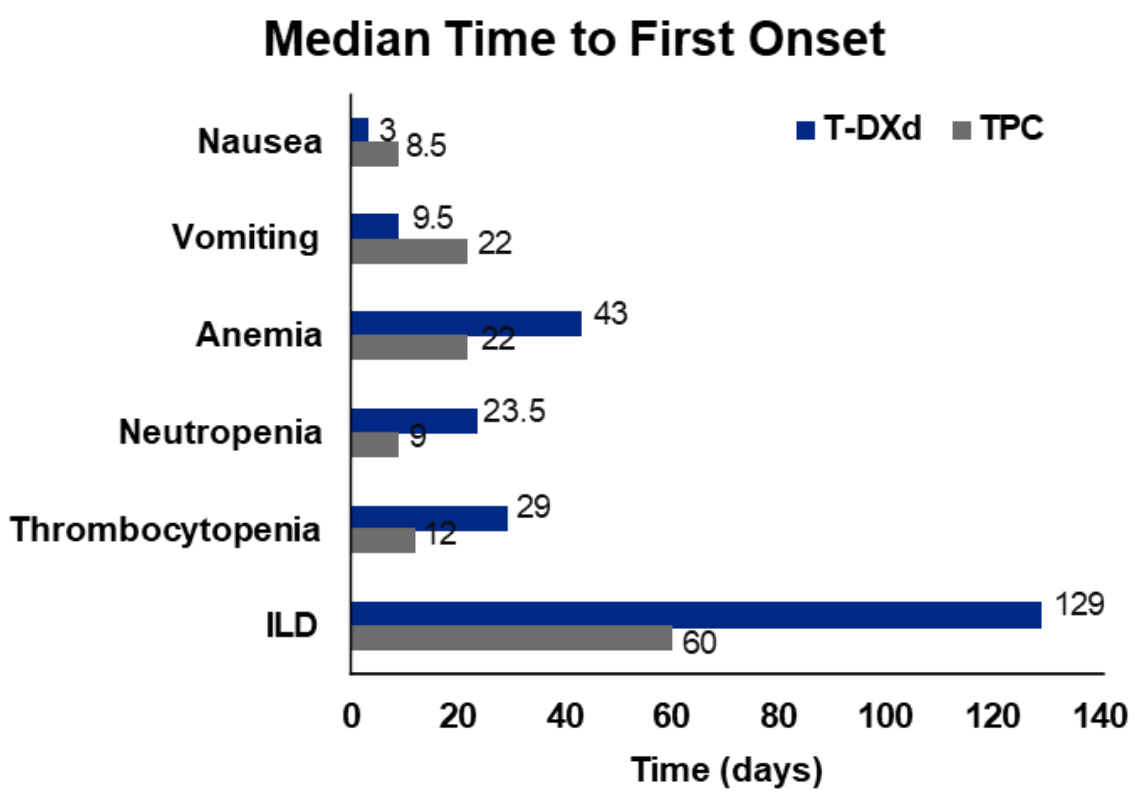
Exposure-Adjusted Incidence Rates for Selected TEAEs in ≥10% of Patients[a]

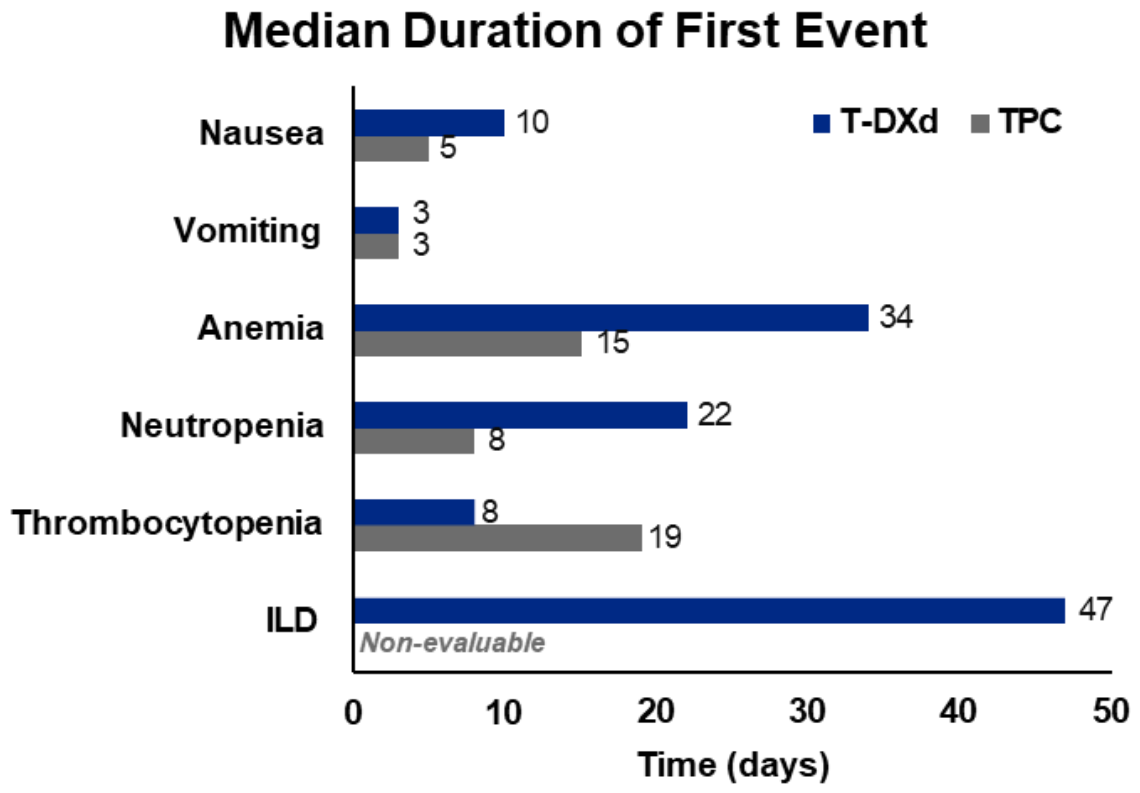
n (%)	T-DXd n = 371		TPC n = 172	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Total patient-years of exposure	**283.5**		**63.6**	
Nausea	282 (76.0)	17 (4.6)	52 (30.2)	0
EAIR per patient-year	0.99	0.06	0.82	0
Vomiting	150 (40.4)	6 (1.6)	23 (13.4)	0
EAIR per patient-year	0.53	0.02	0.36	0
Anemia	143 (38.5)	38 (10.2)	47 (27.3)	9 (5.2)
EAIR per patient-year	0.50	0.13	0.74	0.14
Neutropenia	126 (34.0)	52 (14.0)	90 (52.3)	71 (41.3)
EAIR per patient-year	0.44	0.18	1.42	1.12
Thrombocytopenia	95 (25.6)	22 (5.9)	16 (9.3)	1 (0.6)
EAIR per patient-year	0.34	0.08	0.25	0.02
Alopecia	147 (39.6)	0	57 (33.1)	0
EAIR per patient-year	0.52	0	0.90	0
Fatigue	199 (53.6)	32 (8.6)	83 (48.3)	8 (4.7)
EAIR per patient-year	0.70	0.11	1.31	0.13
ILD	45 (12.1)	8 (2.2)	1 (0.6)	0
EAIR per patient-year	0.16	0.03	0.02	0

- EAIRs per patient-year for anemia, neutropenia, alopecia, and fatigue were higher in the TPC arm than the T-DXd arm
- EAIRs per patient-year for nausea, vomiting, thrombocytopenia, and ILD were higher in the T-DXd arm than the TPC arm

EAIR, exposure-adjusted incidence rate; ILD, interstitial lung disease; mo, month; TEAE, treatment emergent adverse events; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Based on any grade events in the T-DXd arm; data cutoff: January 11, 2022.

Selected TEAEs[a] for ≥10% of Patients





- Median TTO of gastrointestinal and hematological TEAEs was generally within the first month of treatment
- Median DUR for gastrointestinal TEAEs was a median of 3 up to 10 days whereas for hematological TEAEs was a median of 8 up to 34 days

DUR, duration of first event; ILD, interstitial lung disease; mo, month; TEAE, treatment emergent adverse events; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice; TTO, time to first onset.
[a]Includes the most common TEAEs and ILD that was identified as a TEAE of special interest; data cutoff: January 11, 2022

ESMO BC 2023 #185O Oral

Incidence of Selected TEAEs by Cycle[a]

%	T-DXd			TPC		
	Cycle 1 n = 371	Cycle 2 n = 357	Cycle 3 n = 330	Cycle 1 n = 172	Cycle 2 n = 162	Cycle 3 n = 131
Nausea	63.3	24.6	17.3	19.8	4.9	4.6
Vomiting	22.6	10.6	10.6	6.4	4.3	0.8
Anemia	15.4	4.8	4.2	12.8	7.4	5.3
Neutropenia	13.5	8.4	6.7	44.8	16.0	15.3
Thrombocytopenia	12.7	1.7	1.5	5.8	3.7	0.8
Fatigue	31.5	12.9	5.5	30.8	8.6	8.4
Diarrhea	15.4	4.2	6.1	14.5	5.6	1.5
Decreased Appetite	18.1	7.0	4.5	10.5	5.6	3.8

Shading cutoffs	T-DXd	TPC
≤10%		
>10 - ≤20%		
>20 - ≤30%		
>30 - ≤40%		
>40 - ≤50%		
>50 - ≤60%		
>60 - ≤70%		

- The incidence of selected TEAEs in both arms was higher in cycle 1 and decreased thereafter

TEAE, treatment emergent adverse events; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]TEAEs observed in ≥20% of patients at any given cycle; data cutoff: January 11, 2022.

Nausea and Vomiting

- 189/371 patients (50.9%) in the T-DXd arm and 64/172 patients (37.2%) in the TPC arm received antiemetic prophylaxis[a]

	Nausea		Vomiting	
n (%)	T-DXd n = 371	TPC n = 172	T-DXd n = 371	TPC n = 172
Dose reduction associated with N/V	17 (4.6)	4 (2.3)	3 (0.8)	1 (0.6)
Drug interruption associated with N/V	5 (1.3)	4 (2.3)	0	0
Drug discontinuation associated with N/V	1 (0.3)	0	1 (0.3)	0

Use of prophylaxis was not mandatory per the study protocol but was recommended and administered in accordance with local institutional guidelines

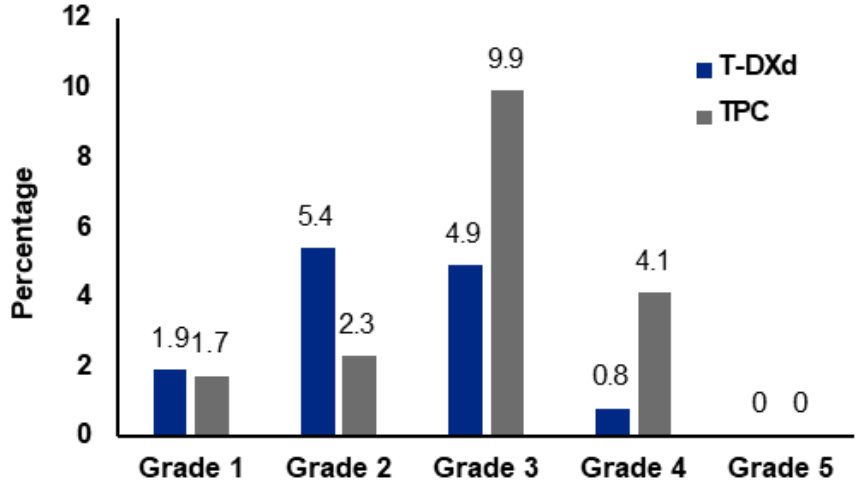
N/V, nausea or vomiting; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Prophylaxis included antiemetics and antinauseants, corticosteroids for systemic use, drugs for functional gastrointestinal disorders, or other.

Neutropenia and Febrile Neutropenia

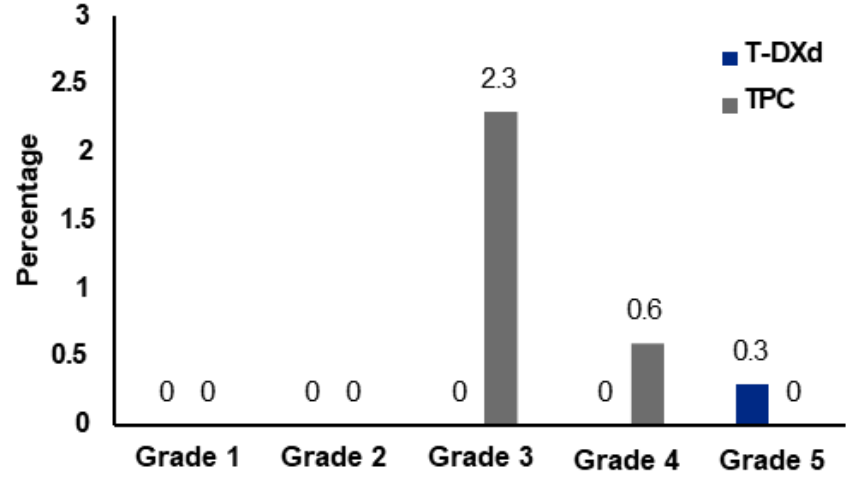
- Treatment-related neutropenia and febrile neutropenia of any grade were less frequent in the T-DXd arm than the TPC arm (12.9% vs 18.0% and 0.3% vs 2.9%, respectively)
- Neutropenia and febrile neutropenia were associated with fewer drug interruptions and dose reductions in the T-DXd arm, than in the TPC arm

n (%)	Neutropenia		Febrile neutropenia	
	T-DXd n = 371	TPC n = 172	T-DXd n = 371	TPC n = 172
Associated with dose reduction	11 (3.0)	24 (14.0)	1 (0.3)	3 (1.7)
Associated with drug interruption	34 (9.2)	39 (22.7)	0	2 (1.2)
Associated with drug discontinuation	0	0	1 (0.3)	0

Treatment-related Neutropenia Per Grade



Treatment-related Febrile Neutropenia Per Grade



DCO, data cutoff; TEAE, treatment emergent adverse events; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

G-CSF Use for Neutropenia and Febrile Neutropenia

n (%)	T-DXd n = 371	TPC n = 172
Patients treated with G-CSF within 28 days of onset	**25 (6.7)**	**34 (19.8)**
G-CSF use for neutropenia	24 (6.5)	33 (19.2)
G-CSF use for febrile neutropenia	1 (0.3)	2 (1.2)

- Patients treated with G-CSF within 28 days of neutropenia/febrile neutropenia onset was less frequent in the T-DXd arm than the TPC arm
- This suggests that T-DXd-induced neutropenia was likely manageable with routine clinical practice, dose modifications, and the use of supportive medication

G-CSF, granulocyte colony-stimulating factor; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice..

Drug-Related TEAEs Based on Age

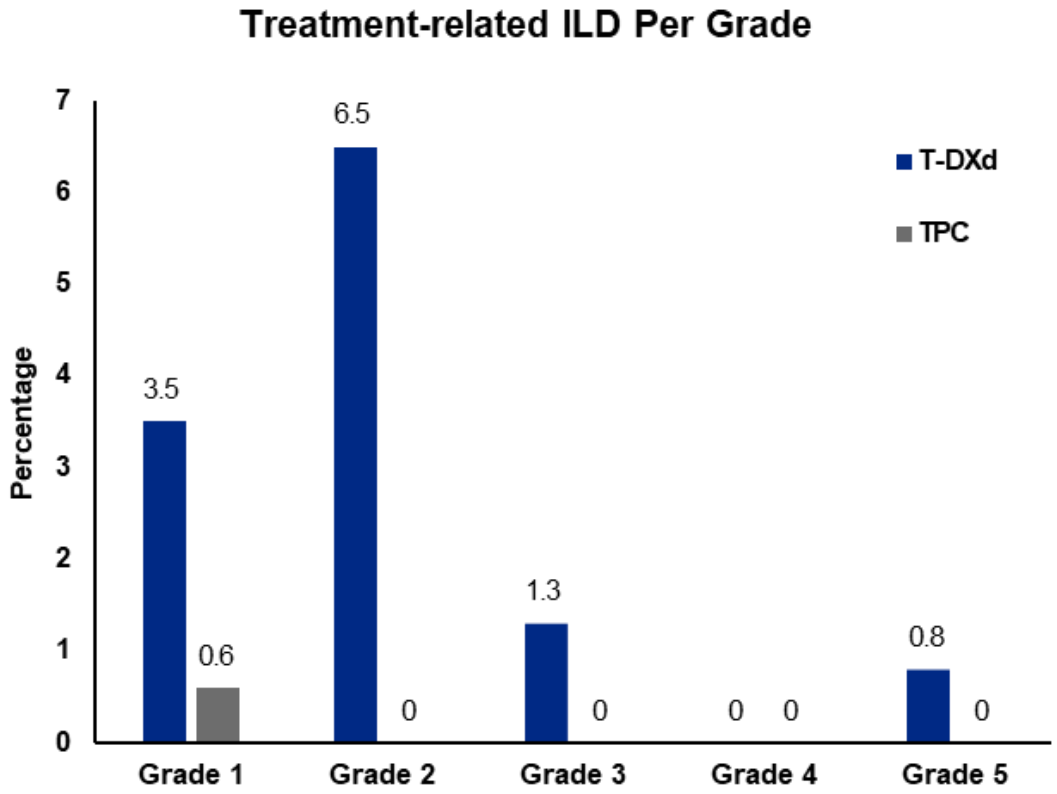
n (%)	<65 years		≥65 years	
	T-DXd (n = 289)	TPC (n = 126)	T-DXd (n = 82)	TPC (n = 46)
Any grade drug-related TEAEs[a]	258 (89.3)	92 (73.0)	67 (81.7)	38 (82.6)
Grade ≥3 drug-related TEAEs	115 (39.8)	71 (56.3)	39 (47.6)	28 (60.9)
Most prevalent drug-related TEAEs (all grades)[a]				
Nausea	213 (73.7)	27 (21.4)	58 (70.7)	14 (30.4)
Vomiting	102 (35.3)	11 (8.1)	24 (29.3)	6 (13.0)
Neutropenia	97 (33.6)	65 (51.6)	26 (31.7)	23 (50.0)
Anemia	93 (32.2)	26 (20.6)	30 (36.6)	13 (28.3)
Thrombocytopenia	74 (25.6)	9 (7.1)	14 (17.1)	7 (15.2)
ILD	29 (10.0)	1 (0.8)	14 (17.1)	0
TEAEs associated with drug discontinuation	40 (13.8)	12 (9.5)	20 (24.4)	2 (4.3)
ILD/Pneumonitis	25 (8.7)	0	12 (14.6)	0

- The toxicity profile for T-DXd was consistent regardless of age
- mPFS also favored T-DXd over TPC in all patients, regardless of age[1]
  - Patients <65 years had an mPFS of 9.8 months (95% CI, 8.4-11.3 months) in the T-DXd arm and 4.6 months (95% CI, 2.9-5.9 months) in the TPC arm; hazard ratio was 0.47 (95% CI, 0.37-0.61)
  - Patients ≥65 years had a mPFS of 11.4 months (95% CI, 8.3-13.3 months) in the T-DXd arm and 6.2 months (95% CI, 4.3-10.8 months) in the TPC arm; hazard ratio was 0.57 (95% CI, 0.36-0.89)

ILD, interstitial lung disease; mPFS, median progression-free survival; TEAE, treatment emergent adverse events; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Drug-related TEAEs reported in 10% of patients in either treatment arm.
1. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3.

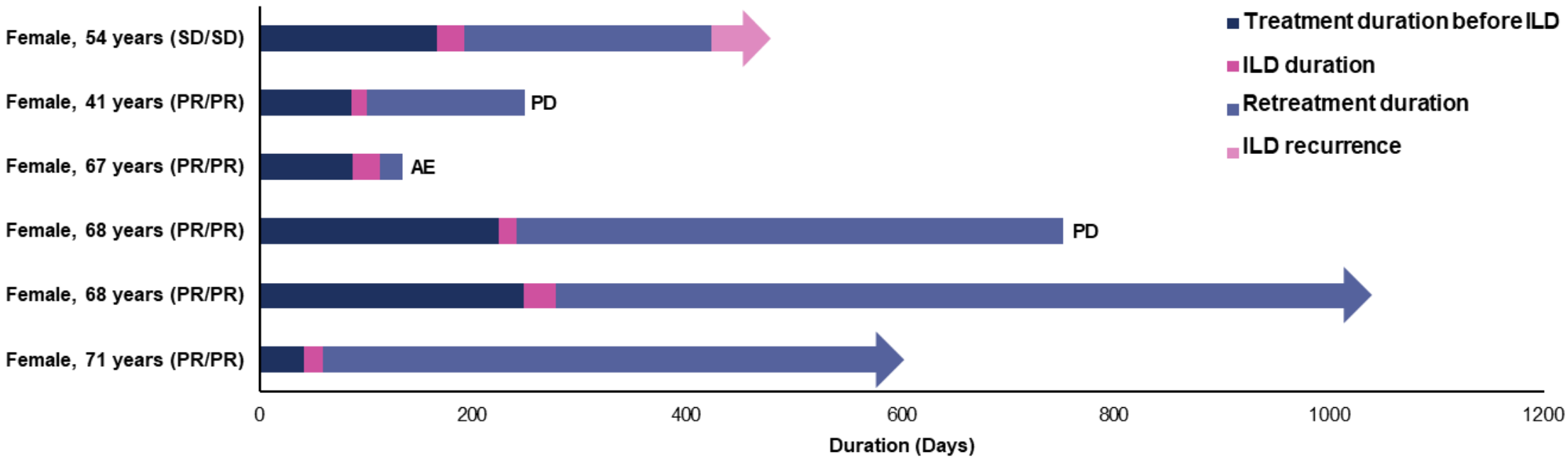
Adjudicated Drug-Related ILD

- Adjudicated ILD occurred in 45 patients (12.1%) in the T-DXd arm versus in 1 patient (0.6%) in the TPC arm
- Most ILD events were low in grade; 3 patients (0.8%) had grade 5 ILD in the T-DXd arm
- At DCO, 31 patients (68.9%) in the T-DXd arm recovered, were recovering, or recovered with sequalae and 10 patients (22.2%) in the T-DXd arm had not yet recovered



DCO, data cutoff; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Re-Treatment in Patients After Occurrence of Grade 1 ILD



- 6 patients with grade 1 ILD (as assessed by investigator) were re-treated after resolution; 1 of these patients had a second ILD event that was adjudicated as grade 2 by the adjudication committee at re-occurrence
  - At DCO, 1 patient discontinued due to an AE; 2 patients discontinued due to PD; 3 patients remained on T-DXd

AE, adverse event; DCO, data cutoff; ILD, interstitial lung disease; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

Conclusions

- EAIRs for anemia, neutropenia, alopecia and fatigue were lower for T-DXd, whereas nausea, vomiting, thrombocytopenia and ILD were higher, compared to TPC
- Treatment-related neutropenia and febrile neutropenia occurred more often in patients treated with TPC, compared to T-DXd
- The incidence of any-grade drug-related TEAEs was similar for patients aged <65 and ≥65 years
  - For T-DXd, the incidence of grade ≥3 TEAEs and TEAEs associated with drug discontinuations was higher in patients aged ≥65 years compared with patients aged <65 years
- Most ILD/pneumonitis events associated with T-DXd were low in grade and resolved over time
  - Of the 6 patients with grade 1 ILD who were re-treated with T-DXd, 1 patient discontinued due to an AE; 2 patients discontinued due to PD; 3 patients remained on T-DXd at DCO
  - ILD/pneumonitis remains an important identified risk and an adverse event of interest and proper adherence to management guidelines is highly recommended

T-DXd demonstrated a manageable safety profile consistent with prior reports and results from this safety analysis continue to support its use as the new standard of care in patients with HER2-low mBC

AE, adverse event; DCO, data cutoff; EAIR, exposure-adjusted incidence rate; ILD, interstitial lung disease; PD, progressive disease; TEAE, treatment emergent adverse events; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

T-DXd in Patients With HER2-Overexpressing/Amplified (HER2+) Metastatic Colorectal Cancer (mCRC): Primary Results From the Multicenter, Randomized, Phase 2 DESTINY-CRC02 Study

Kanwal Raghav, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Additional authors:
Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Christina Gravalos Castro, John Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino

Disclosures

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- **Honoraria:** Bayer, Daiichi Sankyo, Seagen
- **Advisory Board:** Daiichi Sankyo, Eisai/Merck, SAGA Diagnostics, Bayer, Seagen, Pfizer, AstraZeneca

Background and Objective

- HER2+ mCRC
  - HER2+ (IHC 3+ or IHC 2+/ISH+) mCRC represents about 2%-3% of mCRC[1,2], and is associated with resistance to EGFR-targeted therapy[3-5]
  - Ongoing research has shown HER2-targeted therapies to be a promising strategy for patients with HER2+ mCRC, an area of unmet need[6]
- T-DXd is designed to deliver an optimal antitumor effect
  - T-DXd is an antibody-drug conjugate made up of 3 components: a humanized anti-HER2 IgG1 monoclonal antibody, a topoisomerase I inhibitor payload, and a tetrapeptide-based cleavable linker[7,8]
  - T-DXd 6.4 mg/kg Q3W showed antitumor activity in patients with HER2+ mCRC in DESTINY-CRC01[9]

Here we present the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with HER2+, *RAS* wild-type or mutant, *BRAF* wild-type mCRC who have received prior standard of care chemotherapy, in order to further characterize the benefit-risk profile of T-DXd in this patient population

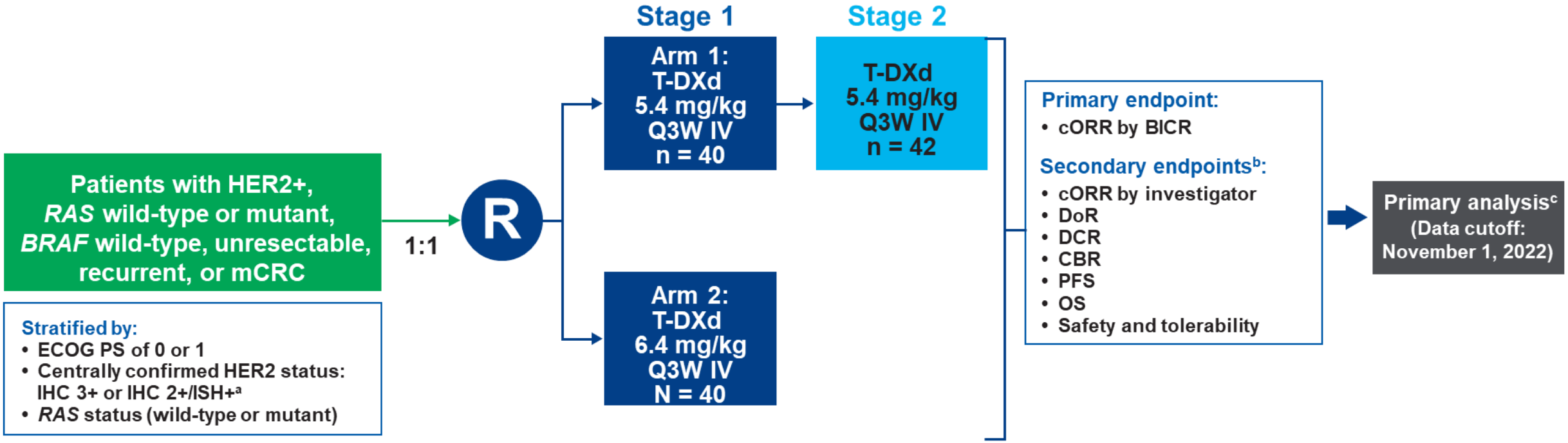
BRAF, v-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.

1. Ross JS et al. *Cancer*. 2018;124:1358-1373. 2. Siena S et al. *Ann Oncol*. 2018;29:1108-1119. 3. Bertotti A et al. *Nature*. 2015;526:263-267. 4. Leto SM, Trusolino L. *J Mol Med (Berl)*. 2014;92:709-722. 5. Yonesaka K et al. *Sci Transl Med*. 2011;3:99ra86. 6. Yoshikawa A et al. *Cancers*. 2023;15(1):183. 7. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 8.Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108. 9. Siena S et al. *Lancet Oncol*. 2021;22:779-789.

DESTINY-CRC02 Study Design

A randomized, blinded, 2-stage, 2-arm, multicenter, global, phase 2 study (NCT04744831)

- Stage 1 (randomized) was followed by Stage 2 (nonrandomized), which enrolled an additional 42 patients



This study was not powered to statistically compare the two arms.

BICR, blinded independent central review; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Both investigators and patients were blind to treatments.
[a]HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (IUO). [b]Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. [c]Primary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

Baseline Characteristics

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median age, years (range)	58.2 (26-78)	60.6 (30-84)	59.1 (26-84)	62.3 (35-81)
Sex, n (%)				
Male	21 (52.5)	24 (57.1)	45 (54.9)	19 (47.5)
Region, n (%)				
Asia-Pacific	25 (62.5)	22 (52.4)	47 (57.3)	24 (60.0)
US	5 (12.5)	1 (2.4)	6 (7.3)	2 (5.0)
Europe	10 (25.0)	19 (45.2)	29 (35.4)	14 (35.0)
HER2 status, n (%)				
IHC 3+	32 (80.0)	32 (76.2)	64 (78.0)	34 (85.0)
IHC 2+/ISH+	8 (20.0)	10 (23.8)	18 (22.0)	6 (15.0)
ECOG PS, n (%)				
0	22 (55.0)	24 (57.1)	46 (56.1)	22 (55.0)
1	18 (45.0)	18 (42.9)	36 (43.9)	18 (45.0)
***RAS* status, n (%)**				
Wild-type	34 (85.0)	34 (81.0)	68 (82.9)	34 (85.0)
Mutant	6 (15.0)	8 (19.0)	14 (17.1)	6 (15.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.

Baseline Characteristics (cont.)

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
HER2/*RAS* status, n (%)				
IHC 2+ ISH+/wild-type	7 (17.5)	5 (11.9)	12 (14.6)	6 (15.0)
IHC 2+ ISH+/mutant	1 (2.5)	5 (11.9)	6 (7.3)	0
IHC 3+/wild-type	27 (67.5)	29 (69.0)	56 (68.3)	28 (70.0)
IHC 3+/mutant	5 (12.5)	3 (7.1)	8 (9.8)	6 (15.0)
Liver metastases at baseline, n (%)	29 (72.5)	30 (71.4)	59 (72.0)	26 (65.0)
CNS metastases at baseline, n (%)	3 (7.5)	0	3 (3.7)	1 (2.5)
Primary tumor site, n (%)				
Left colon[a]	32 (80.0)	29 (69.0)	61 (74.4)	34 (85.0)
Rectum	15 (37.5)	12 (28.6)	27 (32.9)	19 (47.5)
Right colon[b]	8 (20.0)	13 (31.0)	21 (25.6)	6 (15.0)

CNS, central nervous system; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
[a]Includes rectum, sigmoid, and descending. [b]Includes cecum, ascending, and transverse.

Prior Treatment

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median prior lines of systemic therapy, n (range)	4 (1-12)	3 (1-7)	3 (1-12)	4 (1-8)
Systemic chemotherapy, n (%)	**40 (100)**	**42 (100)**	**82 (100)**	**40 (100)**
Irinotecan	39 (97.5)	40 (95.2)	79 (96.3)	40 (100)
Fluoropyrimidines[a]	40 (100)	42 (100)	82 (100)	40 (100)
Oxaliplatin	40 (100)	41 (97.6)	81 (98.8)	40 (100)
Anti-EGFR, n (%)	29 (72.5)	28 (66.7)	57 (69.5)	31 (77.5)
Anti-HER2, n (%)	**11 (27.5)**	**6 (14.3)**	**17 (20.7)**	**10 (25.0)**
HER2 TKI[b]	6 (15.0)	4 (9.5)	10 (12.2)	7 (17.5)
Anti-HER2 antibodies[c]	10 (25.0)	6 (14.3)	16 (19.5)	10 (25.0)
Anti-VEGF, n (%)	36 (90.0)	38 (90.5)	74 (90.2)	38 (95.0)
Regorafenib and tipiracil/trifluridine, n (%)	20 (50.0)	14 (33.3)	34 (41.5)	13 (32.5)
Other systemic therapy, n (%)	5 (12.5)	6 (14.3)	11 (13.4)	10 (25.0)

5FU, fluorouracil; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
[a]Includes 5FU, capecitabine, S1, or tegafur. [b]Includes tucatinib and lapatinib. [c]Includes trastuzumab, trastuzumab duocarmazine, trastuzumab emtansine, pertuzumab, and zanidatamab (ZW25).

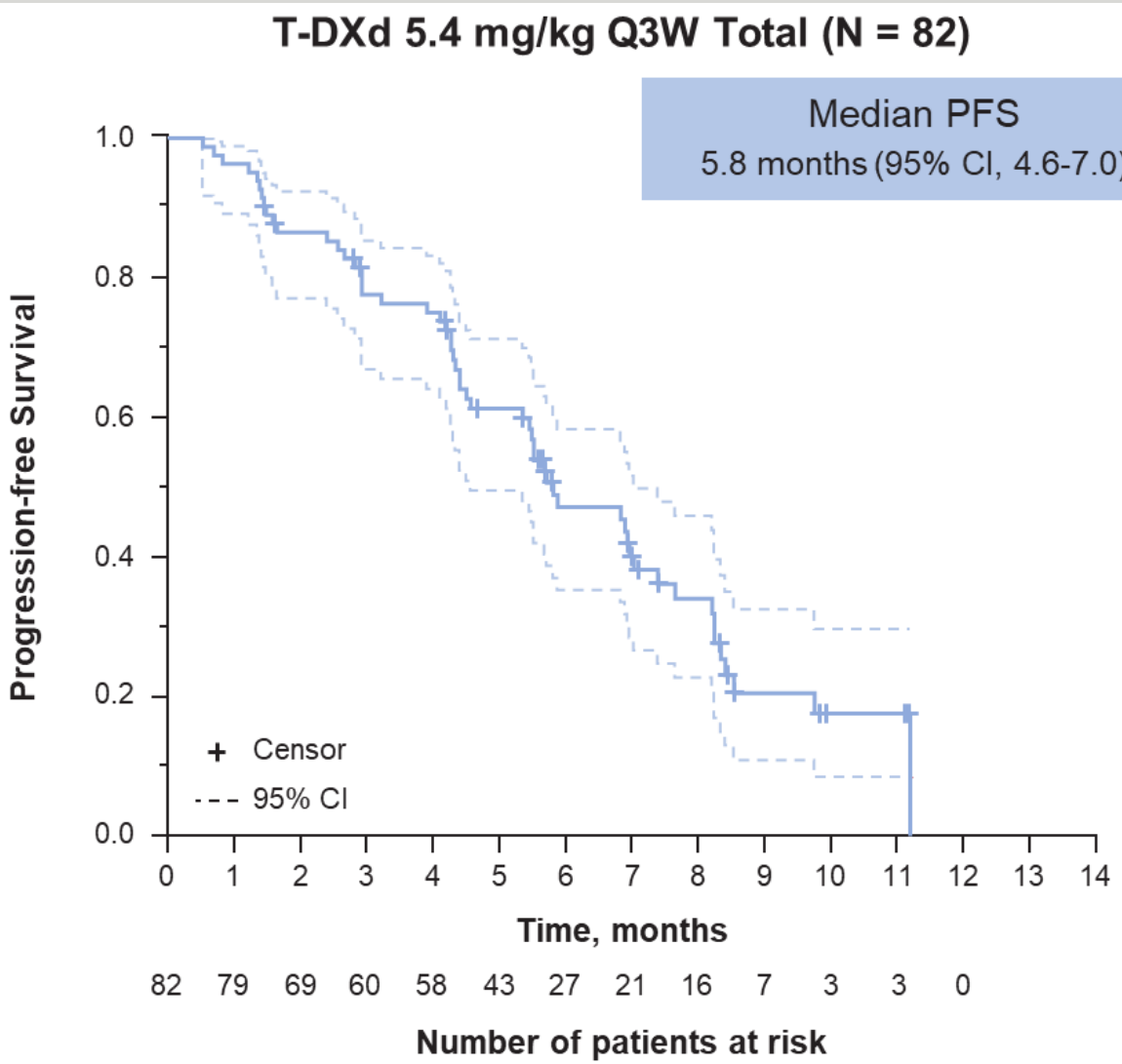
Efficacy Results

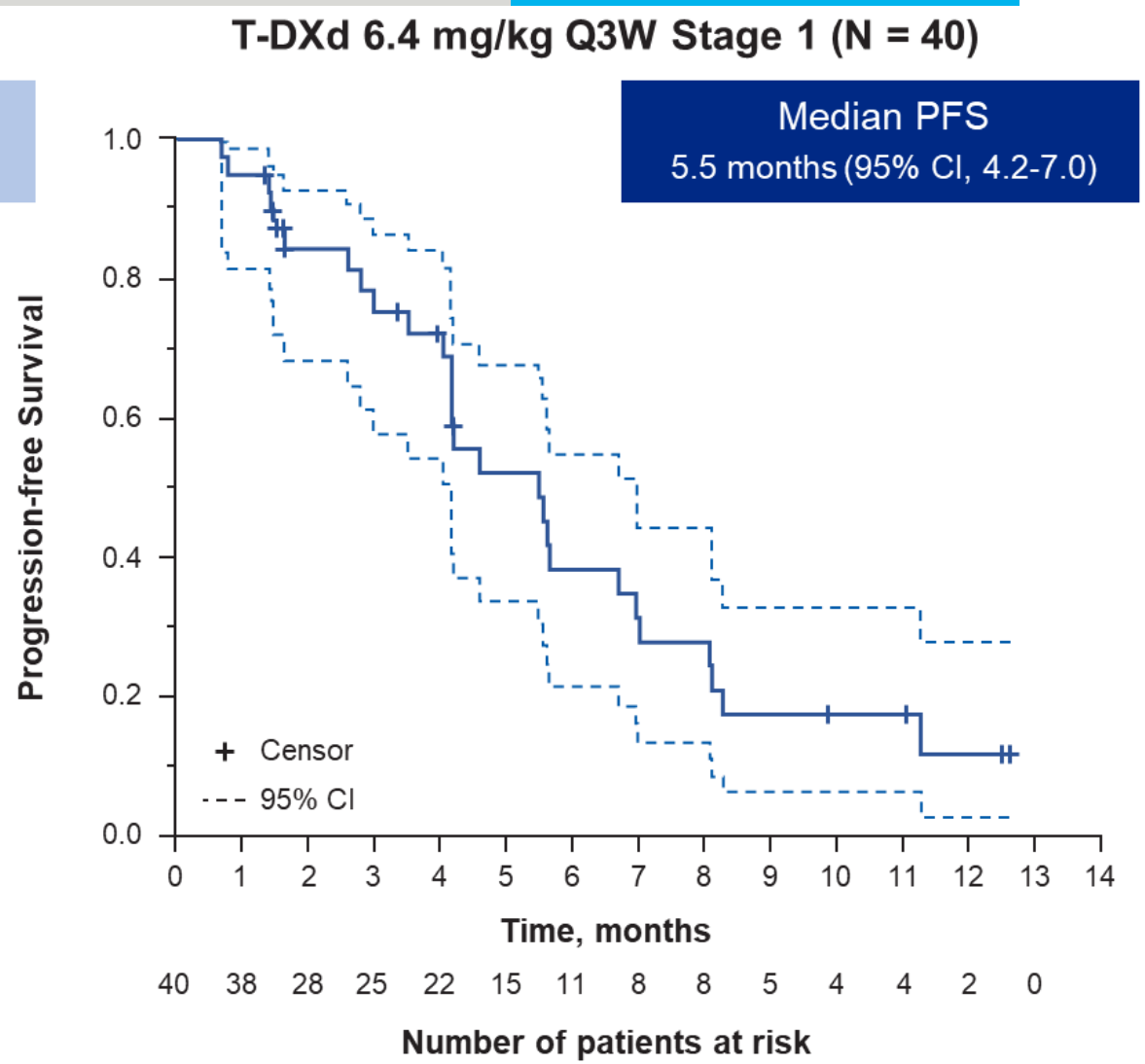
	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, month; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; T-DXd, trastuzumab deruxtecan.

ASCO 2023 #3501 Oral

Median Progression-Free Survival by BICR





BICR, blinded independent central review; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

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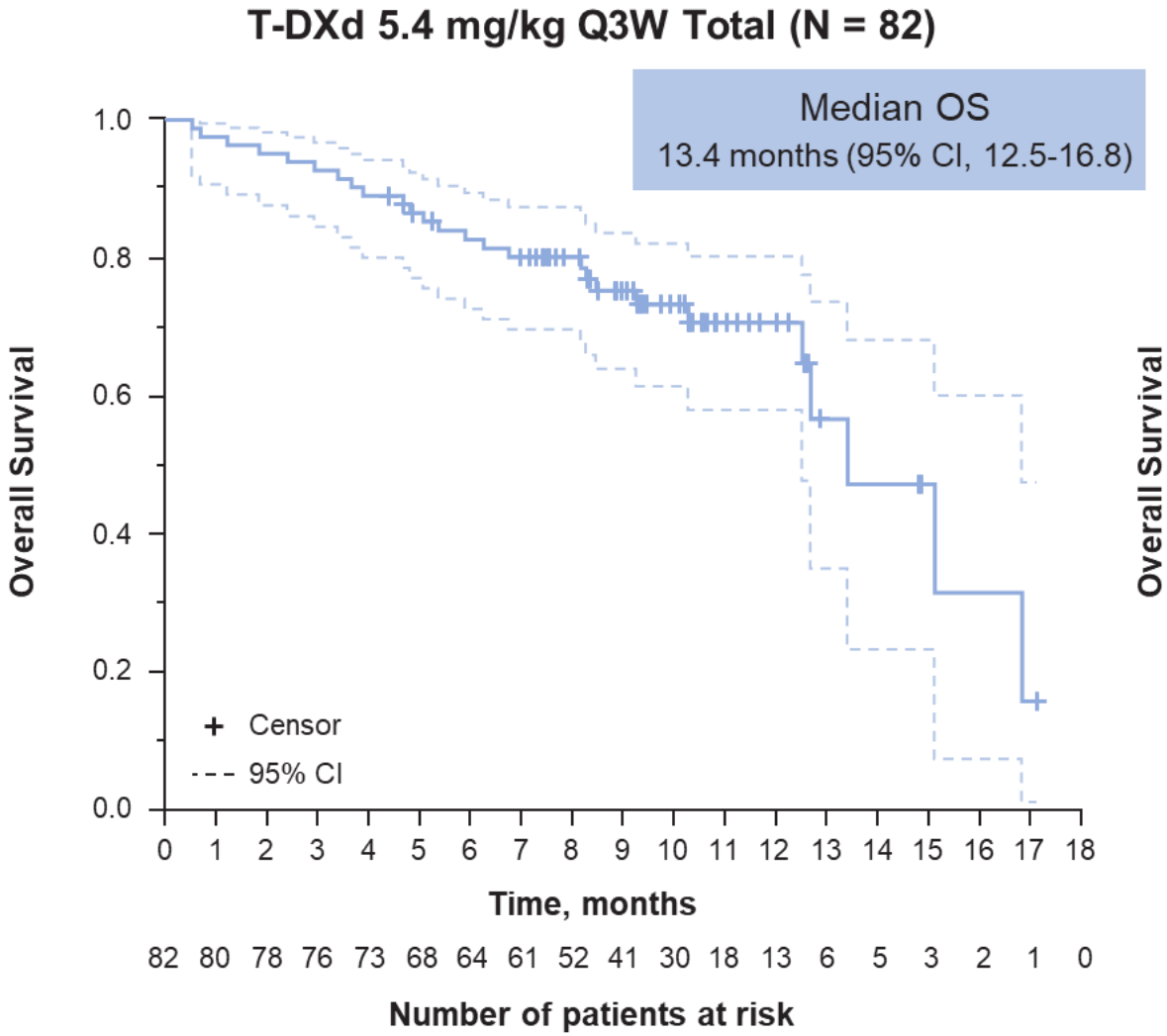
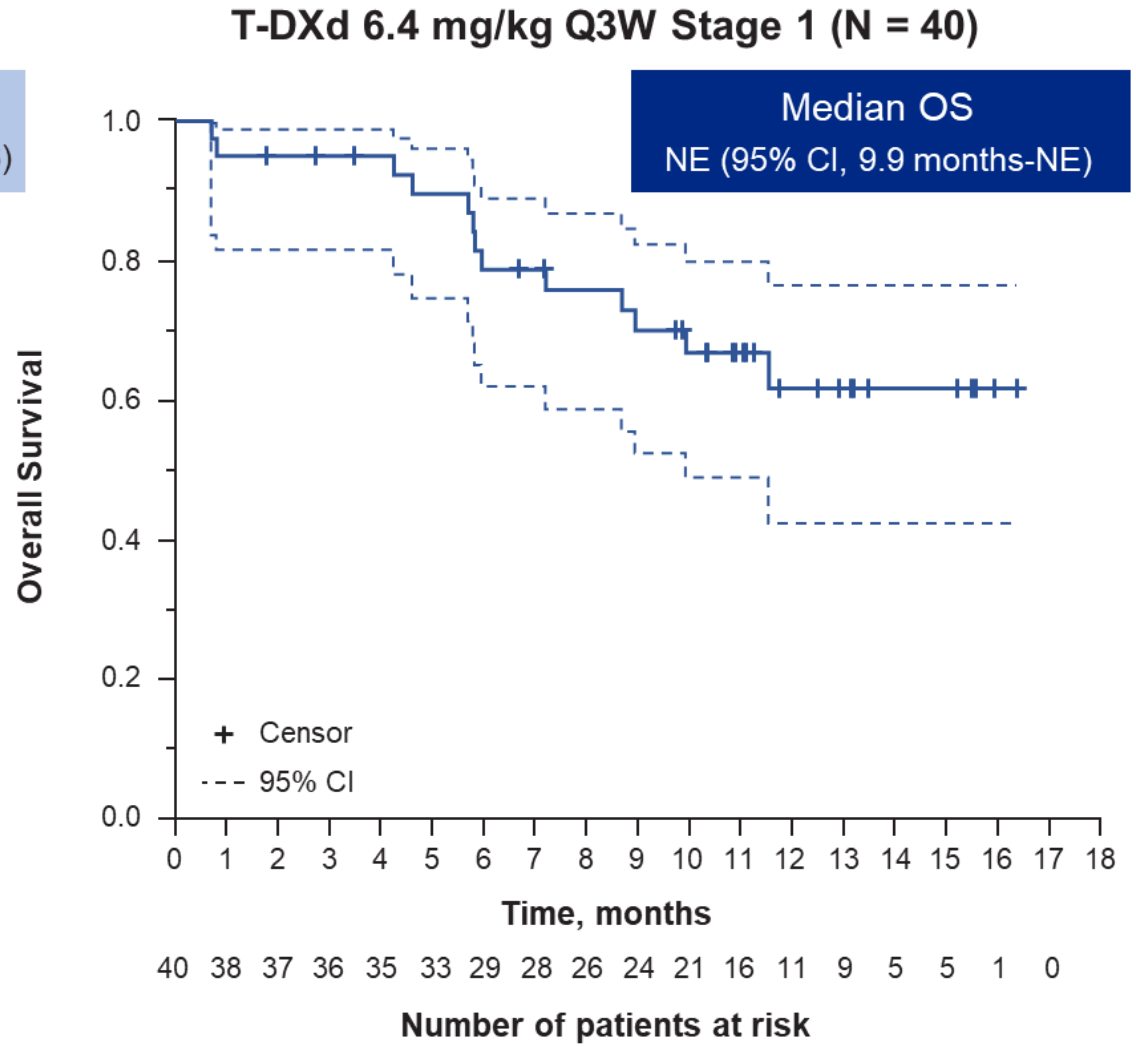
Median Overall Survival

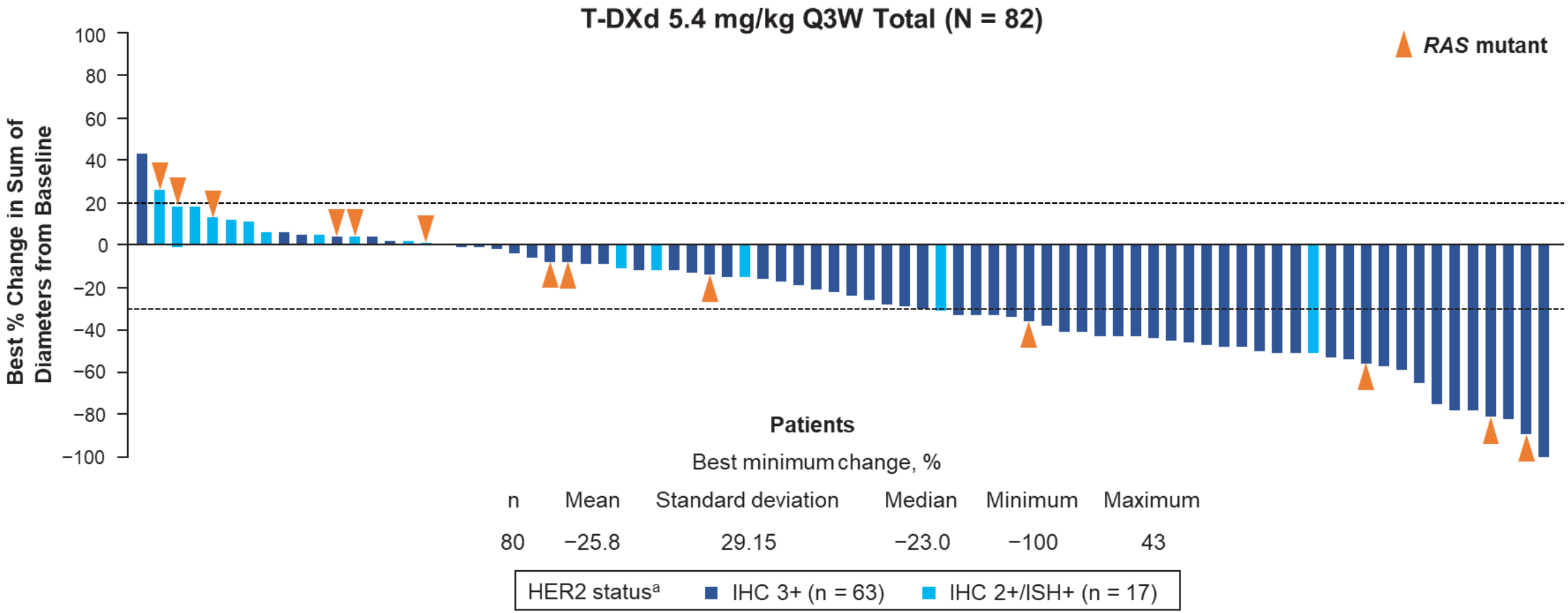




NE, not evaluable; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

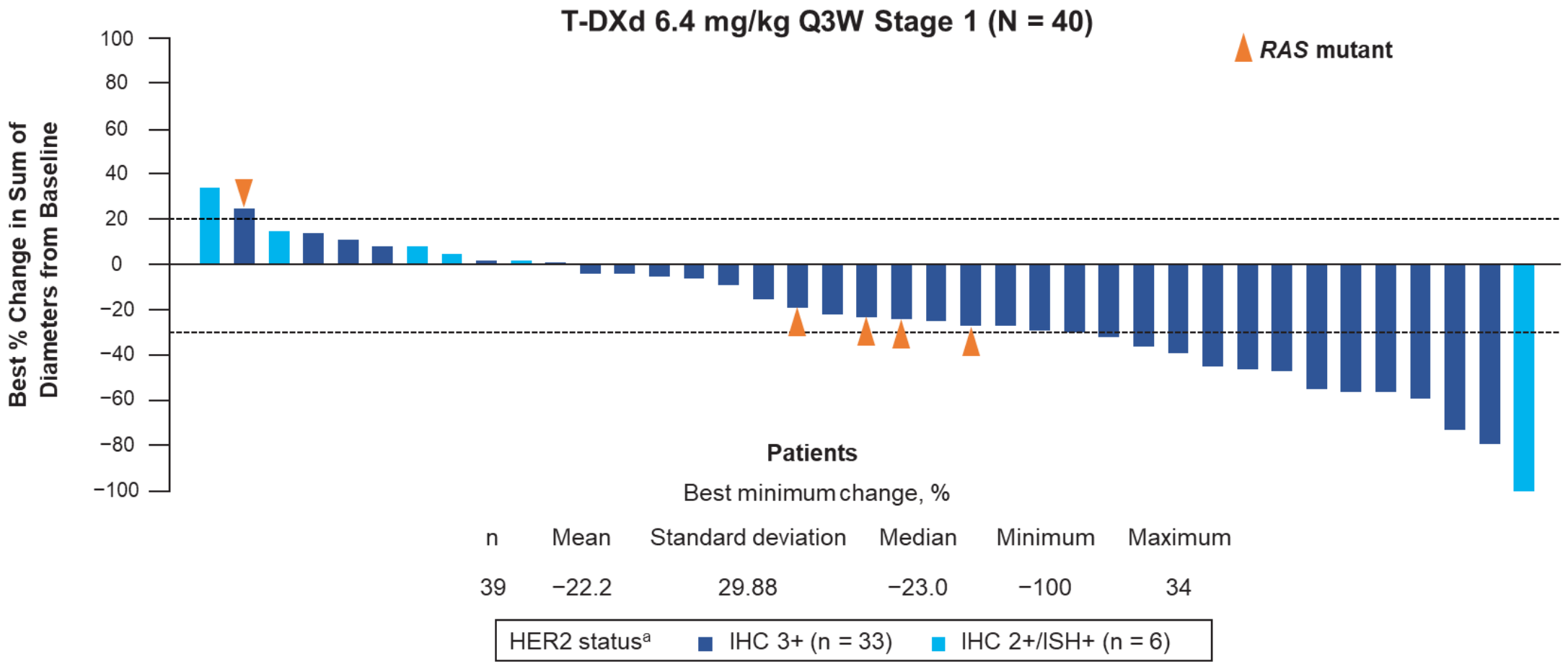
ASCO 2023 #3501 Oral

Best Percentage Change in Sum of Diameters by BICR for T-DXd 5.4 mg/kg



BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

Best Percentage Change in Sum of Diameters by BICR for T-DXd 6.4 mg/kg

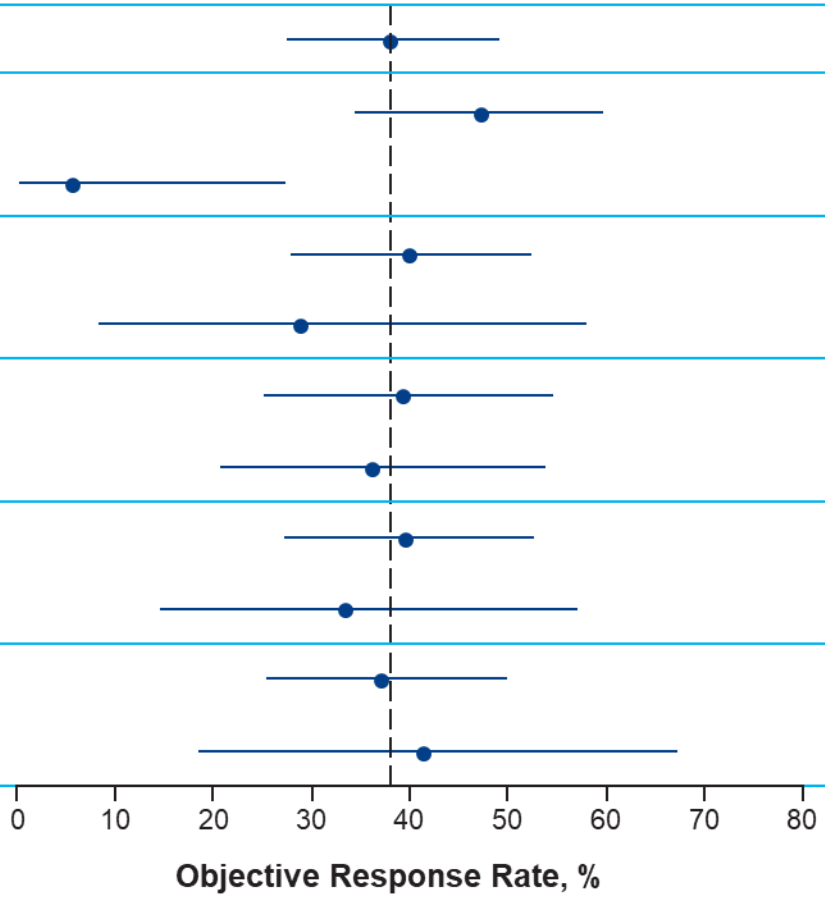


BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

ASCO 2023 #3501 Oral

Best Overall Response by BICR by Subgroup With T-DXd 5.4 mg/kg

		ORR, % (n/N)	95% CI[a]
All patients (5.4 mg/kg)	**N = 82**	**37.8 (31/82)**	27.3-49.2
HER2 status	IHC 3+	**46.9 (30/64)**	34.3-59.8
	IHC 2+/ISH+	**5.6 (1/18)**	0.1-27.3
***RAS* status**	Wild-type	**39.7 (27/68)**	28.0-52.3
	Mutant[b]	**28.6 (4/14)**	8.4-58.1
ECOG PS	0	**39.1 (18/46)**	25.1-54.6
	1	**36.1 (13/36)**	20.8-53.8
Primary tumor site	Left colon[c]	**39.3 (24/61)**	27.1-52.7
	Right colon[d]	**33.3 (7/21)**	14.6-57.0
Prior anti-HER2 treatment	No	**36.9 (24/65)**	25.3-49.8
	Yes	**41.2 (7/17)**	18.4-67.1



BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All *RAS*m responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.

Overall Safety Summary

n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
TEAEs	**40 (97.6)**	**42 (100)**	**82 (98.8)**	**39 (100)**
Drug-related	38 (92.7)	38 (90.5)	76 (91.6)	37 (94.9)
TEAEs grade ≥3	**20 (48.8)**	**21 (50.0)**	**41 (49.4)**	**23 (59.0)**
Drug-related	16 (39.0)	18 (42.9)	34 (41.0)	19 (48.7)
Serious TEAEs	**8 (19.5)**	**12 (28.6)**	**20 (24.1)**	**12 (30.8)**
Drug-related	4 (9.8)	7 (16.7)	11 (13.3)	6 (15.4)
TEAEs associated with drug discontinuation	**3 (7.3)**	**5 (11.9)**	**8 (9.6)**	**3 (7.7)**
Drug-related	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
TEAEs associated with dose reduction	**9 (22.0)**	**6 (14.3)**	**15 (18.1)**	**10 (25.6)**
Drug-related	9 (22.0)	6 (14.3)	15 (18.1)	9 (23.1)
TEAEs associated with drug interruption	**19 (46.3)**	**20 (47.6)**	**39 (47.0)**	**19 (48.7)**
Drug-related	13 (31.7)	9 (21.4)	22 (26.5)	10 (25.6)
TEAEs associated with death	**1 (2.4)**	**3 (7.1)**	**4 (4.8)**	**3 (7.7)**
Drug-related	1 (2.4)[b]	0	1 (1.2)[b]	0[c]

Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]Patient experienced grade 5 hepatic failure. [c]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

TEAEs in ≥20% of Patients[a]

n (%)	T-DXd 5.4 mg/kg Q3W Total N = 83[b]		T-DXd 6.4 mg/kg Q3W Stage 1 N = 39	
	Any-grade	Grade ≥3	Any-grade	Grade ≥3
Any TEAEs	82 (98.8)	41 (49.4)	39 (100)	23 (59.0)
Nausea	48 (57.8)	7 (8.4)	22 (56.4)	0
Fatigue[c]	38 (45.8)	8 (9.6)	18 (46.2)	2 (5.1)
Neutropenia[d]	25 (30.1)	14 (16.9)	18 (46.2)	11 (28.2)
Decreased appetite	25 (30.1)	2 (2.4)	6 (15.4)	0
Anemia[e]	22 (26.5)	8 (9.6)	16 (41.0)	9 (23.1)
Thrombocytopenia[f]	21 (25.3)	5 (6.0)	14 (35.9)	5 (12.8)
Alopecia	20 (24.1)	0	11 (28.2)	0
Constipation	20 (24.1)	0	5 (12.8)	0
Diarrhea	19 (22.9)	2 (2.4)	11 (28.2)	0
Vomiting	17 (20.5)	4 (4.8)	3 (7.7)	0

Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.
Febrile neutropenia occurred in 1 patient in both Stage 1 (grade 3) and Stage 2 (grade 1) treated with T-DXd 5.4 mg/kg and 1 patient treated with T-DXd 6.4 mg/kg (grade 4)
[a]Based on the total population treated with T-DXd 5.4 mg/kg. [b]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [c]Fatigue includes the preferred terms asthenia, fatigue, malaise and lethargy. [d]Neutropenia includes the preferred terms neutrophil count decreased and neutropenia. [e]Anemia includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [f]Thrombocytopenia includes the preferred terms platelet count decreased and thrombocytopenia.

Adjudicated Drug-Related ILD/Pneumonitis by Independent Adjudication Committee

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)	0	1 (1.2)	2 (5.1)
Grade 2	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	1 (2.6)[b]

ILD, interstitial lung disease; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

Conclusions

- Promising antitumor activity was observed in patients with HER2+ mCRC at both the T-DXd 5.4 mg/kg and 6.4 mg/kg doses
  - Numerically higher cORR in patients who received T-DXd at 5.4 mg/kg than 6.4 mg/kg (37.8% and 27.5%, respectively)
  - Greater antitumor activity (ORR) was observed in patients with IHC 3+ HER2 status (n/N = 30/64; 46.9%) than those with IHC 2+/ISH+ HER2 status (n/N = 1/18; 5.6%) at the 5.4 mg/kg dose
  - Antitumor activity (ORR) was observed in patients with (28.6%) and without (39.7%) *RAS* mutations, and in patients who received prior anti-HER2 therapy (41.2%) at the 5.4 mg/kg dose
- Overall safety was acceptable, generally manageable, and consistent with the known safety profile of T-DXd, favoring the 5.4 mg/kg dose
  - All-grade adjudicated as drug-related ILD/pneumonitis rates were lower with T-DXd 5.4 mg/kg (8.4%) compared with T-DXd 6.4 mg/kg (12.8%)
  - There was no grade ≥3 ILD/pneumonitis cases in the 5.4 mg/kg arm, and there was 1 grade 5 drug-related ILD/pneumonitis case in the 6.4 mg/kg arm

These promising results support T-DXd 5.4 mg/kg as the optimal dose (as a single agent) in this patient population due to its positive benefit-risk profile

cORR, confirmed objective response rate; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; ORR, objective response rate; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.