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ORIGINAL ARTICLE

A pooled analysis of trastuzumab deruxtecan in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer with brain metastases

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Background: This exploratory pooled analysis investigated the efficacy and safety of trastuzumab deruxtecan (T-DXd) versus comparator treatment in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (mBC) with brain metastases (BMs) at baseline, categorized according to previous local treatment.

Patients and methods: T-DXd data were pooled from DESTINY-Breast01/-02/-03. Comparator data, from patients receiving physician's choice therapy and trastuzumab emtansine, were pooled from DESTINY-Breast02 and -03, respectively. Baseline BM status was assessed according to US Food and Drug Administration criteria. The endpoints included intracranial objective response rate (ORR; complete or partial response in the brain) per blinded independent central review (BICR) by RECIST version 1.1, time to intracranial response, intracranial duration of response (DoR), central nervous system progression-free survival (CNS-PFS) by BICR, overall survival (OS), and safety.

Results: A total of 148 patients who received T-DXd and 83 patients who received comparator treatment had BMs at baseline. In those treated with T-DXd, the intracranial ORR of patients with treated/stable and untreated/active BMs was 45.2% and 45.5%, respectively. The median (range) time to intracranial response was 2.8 months (1.1-13.9 months) and 1.5 months (1.2-13.7 months) in patients with treated/stable and untreated/active BMs, respectively. For those with treated/stable BMs, the median intracranial DoR was 12.3 [95% confidence interval (CI) 9.1-17.9] months, and for those with untreated/active BMs, it was 17.5 months (95% CI 13.6-31.6 months). The median CNS-PFS and OS were 12.3 months (95% CI 11.1-13.8 months) and not reached (95% CI 22.1 months-not estimable) in those with treated/stable BMs, and 18.5 months (95% CI 13.6-23.3 months) and 30.2 months (95% CI 21.3 months-not estimable) in those with untreated/active BMs, respectively. Drug-related treatment-emergent adverse events grade $\geq$3 were experienced by 43.2% of patients with BMs and 46.4% without BMs with T-DXd.

Conclusions: T-DXd demonstrated meaningful intracranial efficacy and clinical benefit in OS, with an acceptable and manageable safety profile in patients with HER2-positive mBC with treated/stable and untreated/active BMs.

Key words: metastatic breast cancer, HER2+, brain metastases, trastuzumab deruxtecan, pooled analysis, intracranial

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INTRODUCTION

Approximately 20% of patients with breast cancer (BC) have tumors that overexpress human epidermal growth factor receptor 2 (HER2).[1-5] Although HER2-targeted therapies have improved disease prognosis in patients with metastatic BC (mBC), most patients will experience disease progression.[6] Of the patients with advanced disease, up to 50% develop brain metastasis (BM) and these patients typically have a poor prognosis.[7,8] Although treatments for early BC are improving, they do not prevent the development of BM.[9] The incidence of BM in patients with HER2-positive mBC has increased due to increased life expectancy and novel treatments with adequate extracranial control; however, such treatments typically have limited activity in the central nervous system (CNS).[10] Furthermore, the manifestation of neurologic symptoms is a risk factor associated with worse overall survival (OS) outcomes in this patient population.[8]

Guidelines recommend that initial treatment of BMs should be dictated by the associated symptoms and typically involves locally directed therapies, including surgery, local radiotherapy, stereotactic radiosurgery, and/or whole-brain radiotherapy.[11,12] Nonetheless, there is still a need for more effective treatment options for patients with HER2-positive mBC with BMs, due to the high rate of intracranial progression within 6-12 months with current local therapies or systemic treatment options.[13-15] As the enrollment of patients with BMs is often limited in randomized clinical trials, the assessment of intracranial efficacy of investigational drugs in this subgroup of patients is difficult, particularly in patients with active BMs.[7,16,17] Per US Food and Drug Administration (FDA) criteria, patients with treated/stable BMs have received prior CNS-directed therapy for their BMs and their CNS disease is stable, whereas patients with active BMs have new (previously untreated) or progressive BMs that have not been subjected to CNS-directed therapy since documented progression.[16] Several studies investigating HER2-targeting agents have included patients with active BMs, including HER2CLIMB and HER2CLIMB-02.[18-24]

The antibody–drug conjugate trastuzumab deruxtecan (T-DXd) is approved by health authorities in several countries for the treatment of adults with unresectable or metastatic HER2-positive BC who have received at least one prior anti-HER2-based regimen, including patients with BMs, based on the results of the randomized phase III DESTINY-Breast03 trial.[25,26] Patients with BMs have also been enrolled in other clinical trials of T-DXd; however, to date, published results have only reported the systemic efficacy of T-DXd in patients with BM or the efficacy of T-DXd without regard to prior local BM treatments.[22,27] We report exploratory pooled intracranial efficacy and safety of T-DXd versus comparators in patients from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03 with BMs at baseline categorized according to previous local treatment status according to FDA criteria.[16]

METHODS

Individual trial study designs

DESTINY-Breast01 is a single-arm, phase II study of T-DXd in patients with unresectable and/or metastatic HER2-positive BC previously treated with trastuzumab emtansine (T-DM1).[28] DESTINY-Breast02 is a randomized, phase III study of T-DXd versus treatment of physician's choice chemotherapy in patients with unresectable or metastatic HER2-positive BC previously treated with T-DM1.[24] DESTINY-Breast03 is a randomized, phase III study of T-DXd versus T-DM1 in patients with unresectable or metastatic HER2-positive BC previously treated with trastuzumab and a taxane in a metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy.[25]

Ethics approval

The parent studies were approved by the institutional review board at each site and conducted in adherence with the International Conference on Harmonization Good Clinical Practice, the Declaration of Helsinki, and local regulations on the conduct of clinical research. All patients provided written informed consent before study participation. Individual trial designs and full eligibility criteria have been previously reported.[24,25,28]

Brain metastasis eligibility criteria in each trial

In DESTINY-Breast01, patients with asymptomatic and previously locally treated BMs were allowed, with prior radiotherapy for BMs within 60 days of registration/randomization prohibited.[28] In DESTINY-Breast02 and DESTINY-Breast03, only patients with asymptomatic BM at baseline were allowed throughout, with a required minimum of 2 weeks between the end of whole-brain radiotherapy and study enrollment.[24,25] Initially, patients with previously untreated and asymptomatic BM were eligible, but trial protocols were later amended to include only patients with previously treated and asymptomatic BMs.[24,25] Per FDA criteria, the population of patients from DESTINY-Breast02 and DESTINY-Breast03 consisted of a mix of treated/stable and untreated/active BMs.[16] In all three studies, continuous therapy with systemic corticosteroids and anticonvulsants was prohibited and the presence of BMs was not a stratification factor.[24,25,28,29]

Exploratory pooled study analysis plan

Ad hoc exploratory intracranial data were pooled retrospectively from patients randomly assigned to T-DXd 5.4 mg/kg intravenously every 3 weeks from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03. Comparator data were pooled from DESTINY-Breast02 and DESTINY-Breast03. In DESTINY-Breast02, comparator treatment was physician's choice therapy of trastuzumab 8 mg/kg intravenously on day 1 then 6 mg/kg one time daily + capecitabine 1250 mg/m^2 orally two times daily on days 1-

14 of a 21-day treatment cycle or lapatinib 1250 mg orally daily on days 1-21 + capecitabine 1000 mg/m^2 orally two times daily on days 1-14 of a 21-day treatment cycle.[24] In DESTINY-Breast03, the comparator treatment was T-DM1 3.6 mg/kg every 3 weeks.[25]

Assessment of brain metastases and intracranial response

All patients were required to have brain computed tomography (CT) or magnetic resonance imaging (MRI) scans at screening. In this exploratory pooled analysis, baseline BM status was identified for all patients by a blinded independent central review (BICR) irrespective of their BM status reported by investigators. BICR was blinded to the treatment assignment and to the prior local treatment status of BMs. BICR carried out measurement of target lesions and assessed the evolution of nontarget lesions at each time point, when possible. Measurement of target lesions and characterization of nontarget lesions were carried out in accordance with RECIST version 1.1 criteria.[30] Patients with baseline BMs per investigator assessment had continued regular brain imaging every 6 weeks (±7 days) from enrollment, independent of treatment cycle at the same frequency as extracranial tumor assessment, and scans were submitted to BICR for assessment of response in main studies. As required in the DESTINY-Breast02 and DESTINY-Breast03 protocols, investigators were recommended to provide post-end-of-treatment scans for continuous BICR assessment. For some patients, extracranial and brain images were submitted by investigators beyond progression. For patients without BM per investigator assessment, follow-up brain scans were only required if clinically indicated; therefore these patients were followed only for CNS progression-free survival (CNS-PFS) and not for response.

Exploratory efficacy endpoints

Exploratory intracranial endpoints were intracranial objective response rate (ORR), defined as complete response (CR) + partial response (PR) in the brain per BICR by RECIST, version 1.1, intracranial duration of response (DoR), CNS-PFS, defined as time from randomization until progression in brain or death, time to first and best intracranial response, and OS.

Safety

Safety data for patients with and without BM receiving T-DXd or comparators were pooled from all three trials. Medical Dictionary for Regulatory Activities versions were synchronized to version 25.0 across all studies for this analysis.

Statistical analysis

Formal statistical tests were not carried out, and intracranial assessments were not prespecified within the protocols.[24,25,28] Categoric outcomes were summarized with frequencies and percentages. Time-to-event estimates were calculated using the Kaplan—Meier method, and 95% confidence intervals (CIs) were calculated using the Brookmeyer—Crowley method. Hazard ratios were generated from a Cox model using the study as a random effect.

RESULTS

Patients

The retrospective exploratory pooled schema is shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.08.2347. A total of 148 and 703 patients assigned to T-DXd and 83 and 382 patients assigned to comparators made up the BM and non-BM pools, respectively. Data cut-offs for this pooled analysis: DESTINY-Breast01, 26 March 2021; DESTINY-Breast02, 30 June 2022; DESTINY-Breast03, 25 July 2022.

Baseline characteristics and prior therapies

Baseline characteristics by study drug for the BM and non-BM pools are shown in Table 1. The median age of patients with and without BMs assigned to T-DXd was 53.4 (range 22.4-81.6) years and 54.7 (range 27.9-96.0) years, and those assigned to comparators was 52.6 (range 26.0-78.2) years and 55.1 (range 20.2-86.5) years, respectively. The median time from the initial diagnosis of BC to randomization was longer in the BM pools compared with non-BM pools: 55.9 and 50.9 months with T-DXd and 53.0 and 47.3 months with comparators, respectively. There was a numerically higher proportion of patients with recurrent BC compared with *de novo* mBC in all treatment groups: 57.4% and 49.4% of patients in the T-DXd BM and non-BM pools and 61.4% and 68.1% of patients in the comparator BM and non-BM pools had recurrent BC, respectively. The median number of prior regimens in the metastatic setting was 3 for patients in the BM pools assigned to T-DXd (range 1.0-14.0) and comparators (range 1.0-15.0). Of the 148 patients with BMs at baseline who were assigned to T-DXd, 104 (70.3%) had received prior local treatment for their BM and were defined as having treated/stable BMs, and 44 (29.7%) had not received any prior treatment for their BM and were defined as having untreated/active BMs by FDA criteria.[16] Of the 83 patients with BMs at baseline who were assigned to comparators, 58 (69.9%) had treated/stable and 25 (30.1%) had untreated/active BMs. The median time since prior radiotherapy to the brain was 2.6 months (range 0.5-50.0 months) and 5.1 months (range 0.1-80.2 months) in patients with BMs treated with T-DXd and comparator, respectively. Of the 148 patients with BMs at baseline in the T-DXd arm, 42 (28.4%) had CT scans of the brain and 106 (71.6%) had MRI scans at baseline. Similarly, of the 83 patients with BMs at baseline in the pooled comparator arm, 25 (30.1%) had CT scans of the brain and 58 (69.9%) had MRI scans at baseline.

In patients assigned to T-DXd, 60.6% with treated/stable BMs and 79.5% with untreated/active BMs had only one or two brain lesions at baseline. By contrast, among patients

Table 1. Baseline characteristics and prior therapies

Baseline characteristics	T-DXd pool ($N = 851$)		Comparator pool ($N = 465$)	
	BM pool ($n = 148$)	Non-BM pool[a] ($n = 703$)	BM pool ($n = 83$)	Non-BM pool[a] ($n = 382$)
DESTINY-Breast clinical study, *n* (%)				
DESTINY-Breast01	19 (12.8)	165 (23.5)	0 (0)	0 (0)
DESTINY-Breast02	83 (56.1)	323 (45.9)	41 (49.4)	161 (42.1)
DESTINY-Breast03	46 (31.1)	215 (30.6)	42 (50.6)	221 (57.9)
Region, *n* (%)				
Europe	42 (28.4)	232 (33.0)	16 (19.3)	112 (29.3)
Asia	54 (36.5)	270 (38.4)	40 (48.2)	172 (45.0)
North America	19 (12.8)	92 (13.1)	6 (7.2)	34 (8.9)
Rest of world	33 (22.3)	109 (15.5)	21 (25.3)	64 (16.8)
Age (years), median (range)	53.4 (22.4-81.6)	54.7 (27.9-96.0)	52.6 (26.0-78.2)	55.1 (20.2-86.5)
Sex, *n* (%)				
Female	148 (100)	699 (99.4)	82 (98.8)	380 (99.5)
Male	0 (0)	4 (0.6)	1 (1.2)	2 (0.5)
Time from the initial diagnosis of BC to randomization (months), median (range)	55.9 (8.3-271.6)	50.9 (1.5-431.4)	53.0 (6.7-303.2)	47.3 (5.1-326.0)
Disease history, *n* (%)				
De novo mBC	44 (29.7)	188 (26.7)	32 (38.6)	121 (31.7)
Recurrent BC	85 (57.4)	347 (49.4)	51 (61.4)	260 (68.1)
Missing[b]	19 (12.8)	168 (23.9)	0 (0)	1 (0.3)
HER2 status (IHC), *n* (%)				
3+	131 (88.5)	583 (82.9)	73 (88.0)	318 (83.2)
2+	17 (11.5)	116 (16.5)	9 (10.8)	63 (16.5)
1+	0 (0)	3 (0.4)	0 (0)	1 (0.3)
Not evaluable	0 (0)	1 (0.1)	1 (1.2)	0 (0)
Hormone receptor, *n* (%)				
Positive	84 (56.8)	384 (54.6)	43 (51.8)	214 (56.0)
Negative	63 (42.6)	311 (44.2)	40 (48.2)	165 (43.2)
Indeterminate/Unknown/ Missing	1 (0.7)	8 (1.1)	0 (0)	3 (0.8)
Visceral disease, *n* (%)				
Yes	143 (96.6)	537 (76.4)	78 (94.0)	271 (70.9)
No	5 (3.4)	166 (23.6)	5 (6.0)	111 (29.1)
Prior regimens in the metastatic setting, *n* (%)				
Median (range)	3.0 (1.0-14.0)	3.0 (0-27.0)	3.0 (1.0-15.0)	2.0 (0-12.0)
0	0 (0)	2 (0.3)	0 (0)	1 (0.3)
1	16 (10.8)	108 (15.4)	14 (16.9)	99 (25.9)
2	41 (27.7)	192 (27.3)	27 (32.5)	110 (28.8)
3	35 (23.6)	156 (22.2)	22 (26.5)	89 (23.3)
4	18 (12.2)	71 (10.1)	9 (10.8)	39 (10.2)
≥5	38 (25.7)	174 (24.8)	11 (13.3)	44 (11.5)
Prior anti-HER2 therapy, *n* (%)				
Trastuzumab	148 (100)	700 (99.6)	83 (100)	381 (99.7)
Pertuzumab	104 (70.3)	497 (70.7)	59 (71.1)	255 (66.8)
T-DM1	102 (68.9)	487 (69.3)	41 (49.4)	161 (42.1)
HER2 TKI	17 (11.5)	51 (7.3)	14 (16.9)	39 (10.2)
Prior treatment for brain metastasis, *n* (%)				
None	44 (29.7)	642 (91.3)	25 (30.1)	359 (94.0)
Any prior treatment for BMs	104 (70.3)	61 (8.7)	58 (69.9)	23 (6.0)
RT alone	80 (54.1)	45 (6.4)	44 (53.0)	15 (3.9)
Surgery alone	5 (3.4)	6 (0.9)	5 (6.0)	5 (1.3)
RT and surgery	19 (12.8)	10 (1.4)	9 (10.8)	3 (0.8)
Time since prior RT to the brain (months), median (range)	2.6 (0.5-50.0)	7.5 (0.1-79.0)	5.1 (0.1-80.2)	14.6 (0.7-131.7)

RT includes whole-brain RT, brain-directed stereotactic RT, and brain-directed radiosurgery. Surgery includes any brain-directed surgery (craniotomy, metastasectomy in the brain, resection, or removal of brain lesion).

BC, breast cancer; BICR, blinded independent central review; BMs, brain metastases; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mBC, metastatic breast cancer; RT, radiation therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

[a]Patients with a reported history of BMs who did not have BMs at baseline by BICR were included in the non-BM pools.

[b]Missing data were from patients enrolled in the nonrandomized single-arm DESTINY-Breast01 trial.

assigned to comparators, fewer patients had only one or two brain lesions in the untreated/active BM subgroup (44.0%) compared with the treated/stable BMs subgroup (63.8%; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.08.2347).

Efficacy

Patients with treated/stable BMs experienced an intracranial ORR of 45.2% with T-DXd (47/104) and 27.6% (16/58) with comparators (Table 2). Of the patients assigned to T-DXd, 17 experienced a best overall intracranial response

Table 2. Exploratory intracranial efficacy summary per BICR

	T-DXd BM pool (n = 148)		Comparator BM pool (n = 83)	
	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall intracranial response, n (%)				
CR	17 (16.3)	7 (15.9)	2 (3.4)	0 (0)
PR	30 (28.8)	13 (29.5)	14 (24.1)	3 (12.0)
SD	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
PD	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
NE	4 (3.8)	5 (11.4)	1 (1.7)	2 (8.0)
Missing	2 (1.9)	3 (6.8)	6 (10.3)	0 (0)
Intracranial ORR[a] (CR + PR in the brain), n (%)	47 (45.2)	20 (45.5)	16 (27.6)	3 (12.0)
Intracranial DoR (months), median (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	NC[b]
CNS-PFS (months), median (95% CI)	12.3 (11.1-13.8)	18.5 (13.6-23.3)	8.7 (6.3-11.8)	4.0 (2.7-5.7)

This table considers both target and nontarget lesions at baseline. Lesions in previously irradiated areas were not considered measurable target lesions unless there was demonstrated progression in the lesion.

BICR, blinded independent central review; BMs, brain metastases; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; NC, not calculated; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

[a]Intracranial ORR was assessed per RECIST version 1.1.

[b]Intracranial DoR NC due to a small number of responders ($n < 10$).

of CR and 30 of PR. The median intracranial DoR was 12.3 months (95% CI 9.1-17.9 months) with T-DXd versus 11.0 months (95% CI 5.6-16.0 months) with comparators. Patients with treated/stable BMs assigned to T-DXd experienced a median time to intracranial response of 2.8 months (range 1.1-13.9 months), a median time to first intracranial response as PR of 1.8 months (range 1.1-7.1 months), and a median time to best intracranial response as CR of 5.6 months (range 1.2-13.9 months).

Patients with untreated/active BMs experienced an intracranial ORR of 45.5% (20/44) with T-DXd and 12.0% (3/25) with comparators. Of the patients treated with T-DXd, 7 experienced a best overall intracranial response of CR and 13 of PR. The median intracranial DoR was 17.5 months (95% CI 13.6-31.6 months) with T-DXd and was not calculated for the comparators due to the small number of responders ($n < 10$). Patients with untreated/active BMs assigned to T-DXd experienced a median time to intracranial response of 1.5 months (range 1.2-13.7 months), a median time to first intracranial response as PR of 1.4 months (range 1.2-5.6 months), and a median time to best intracranial response as CR of 4.1 months (range 2.6-13.7 months).

Most patients with measurable brain lesions at baseline and at least one postbaseline assessment assigned to T-DXd experienced a reduction in the size of their brain lesions (Figure 1). For patients with treated/stable BMs, the median CNS-PFS was 12.3 months (95% CI 11.1-13.8 months) with T-DXd and 8.7 months (95% CI 6.3-11.8 months) with comparators (Figure 2A), whereas for patients with untreated/active BMs, the median CNS-PFS was 18.5 months (95% CI 13.6-23.3 months) with T-DXd and 4.0 months (95% CI 2.7-5.7 months) with comparators (Figure 2B). For all patients with BMs, the median OS was not reached [NR; 95% CI 26.2 months-not estimable (NE)] with T-DXd and 18.8 months (95% CI 15.0-26.7 months) with comparators (Figure 3A). For patients assigned to T-DXd, the median OS in patients with treated/stable BMs was NR (95% CI 22.1 months-NE), and in patients with untreated/active BMs was 30.2 months (95% CI 21.3 months-NE; Figure 3B).

Any progressive disease (PD) was experienced by 88 patients (59.5%) with BMs assigned to T-DXd and 49 patients (59.0%) assigned to comparators (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.08.2347). Of the patients with BMs and PD, 43.2% assigned to T-DXd had intracranial progression as their first site of progression and 53.4% had extracranial only. Of those assigned to comparators, 26.5% experienced intracranial progression only as their first site of progression and 63.3% experienced extracranial progression only.

Safety

The median treatment duration with T-DXd was 12.7 months (range 0.7-45.1 months) and 5.6 months (range 0.1-43.0 months) with comparators. The overall drug-related safety summary is shown in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.08.2347. Most patients experienced one or more drug-related treatment-emergent adverse events (TEAEs): 94.5% (n = 138) and 98.9% (n = 691) of patients with and without BM assigned to T-DXd, respectively; and 94.0% (n = 78) and 88.5% (n = 330) assigned to comparators, respectively. Drug-related grade $\geq$3 TEAE rates were similar with T-DXd in the BM pool (n = 63, 43.2%) and the non-BM pool (n = 324, 46.4%). Among recipients of comparators, drug-related grade $\geq$3 TEAEs were similar in patients with (n = 30, 36.1%) and without BMs (n = 140, 37.5%). T-DXd-treated patients in the BM pool experienced similar rates of drug-related TEAEs associated with discontinuation and dose reduction to those in the non-BM pool; 14.4% (n = 21) compared with 17.3% (n = 121) and 21.2% (n = 31) compared with 24.6% (n = 172), respectively. For those receiving comparator drugs, 7.2% (n = 6) and 5.6% (n = 21) of patients with and without BMs experienced drug-related TEAEs associated with discontinuation, respectively, and 26.5% (n = 22) and 28.2% (n = 105)

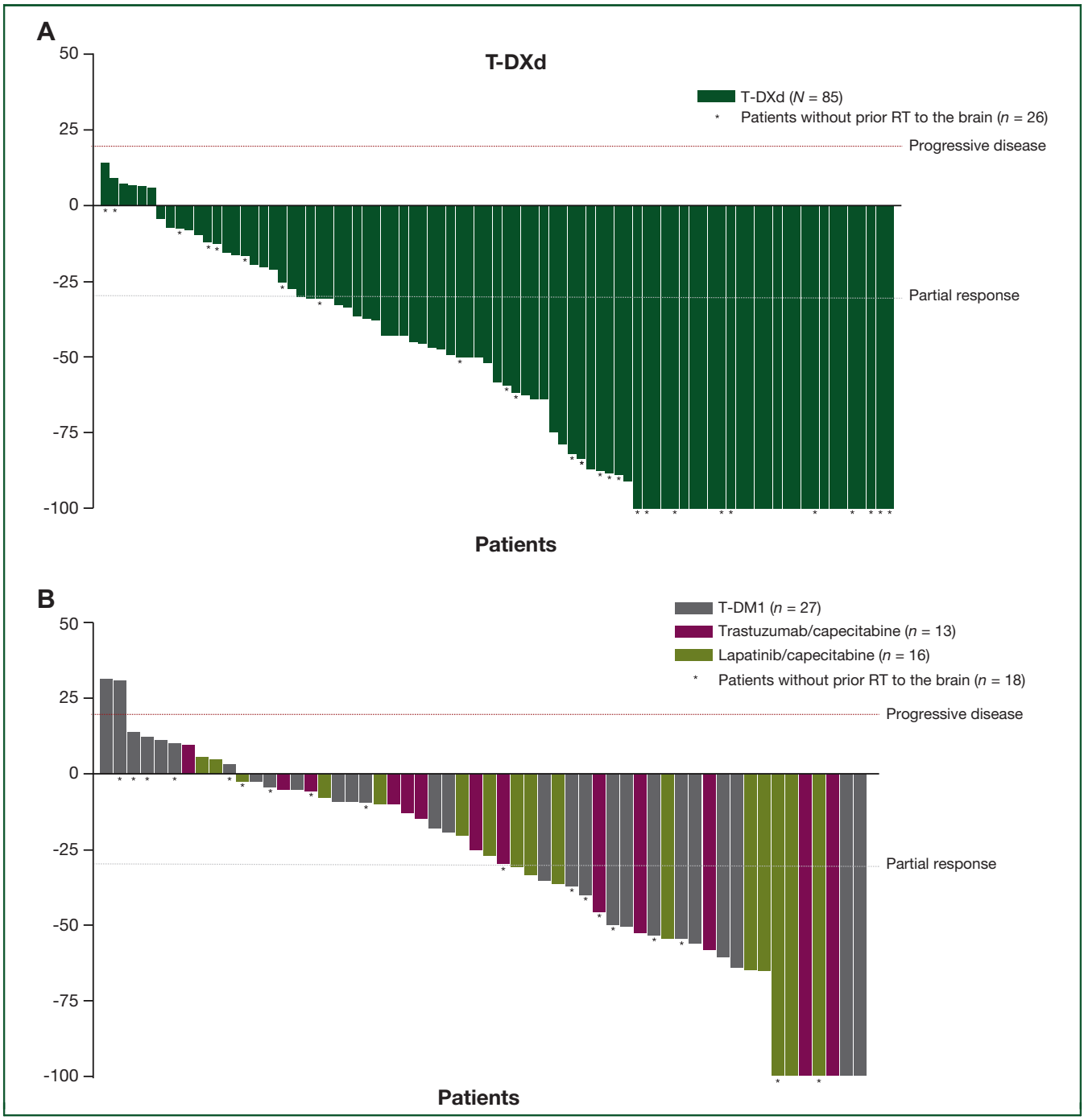

Figure 1. Best percentage change from baseline in sum of diameters of brain tumors. Best percentage change from baseline in sum of diameters of brain tumors in (A) patients randomly assigned to receive T-DXd or (B) patients randomly assigned to receive comparator.
RT, radiation therapy; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

of patients experienced drug-related TEAEs associated with dose reduction, respectively. There were no drug-related TEAEs associated with death in the T-DXd BM pool and seven (1.0%) in the non-BM pool; however, the population of patients with BMs was smaller. There were no drug-related TEAEs associated with death with comparators. Radiation necrosis was observed in six patients who received T-DXd (three grade 3, two grade 2, and one grade 1) and no patients treated with a comparator drug. The most common TEAEs leading to treatment discontinuation and dose reduction are shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.08.2347.

DISCUSSION

Previous analyses reported systemic efficacy of T-DXd in patients with HER2-positive mBC with BMs from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03.[22,24,25,28] The aim of this pooled analysis was to describe the population of patients with BM enrolled in

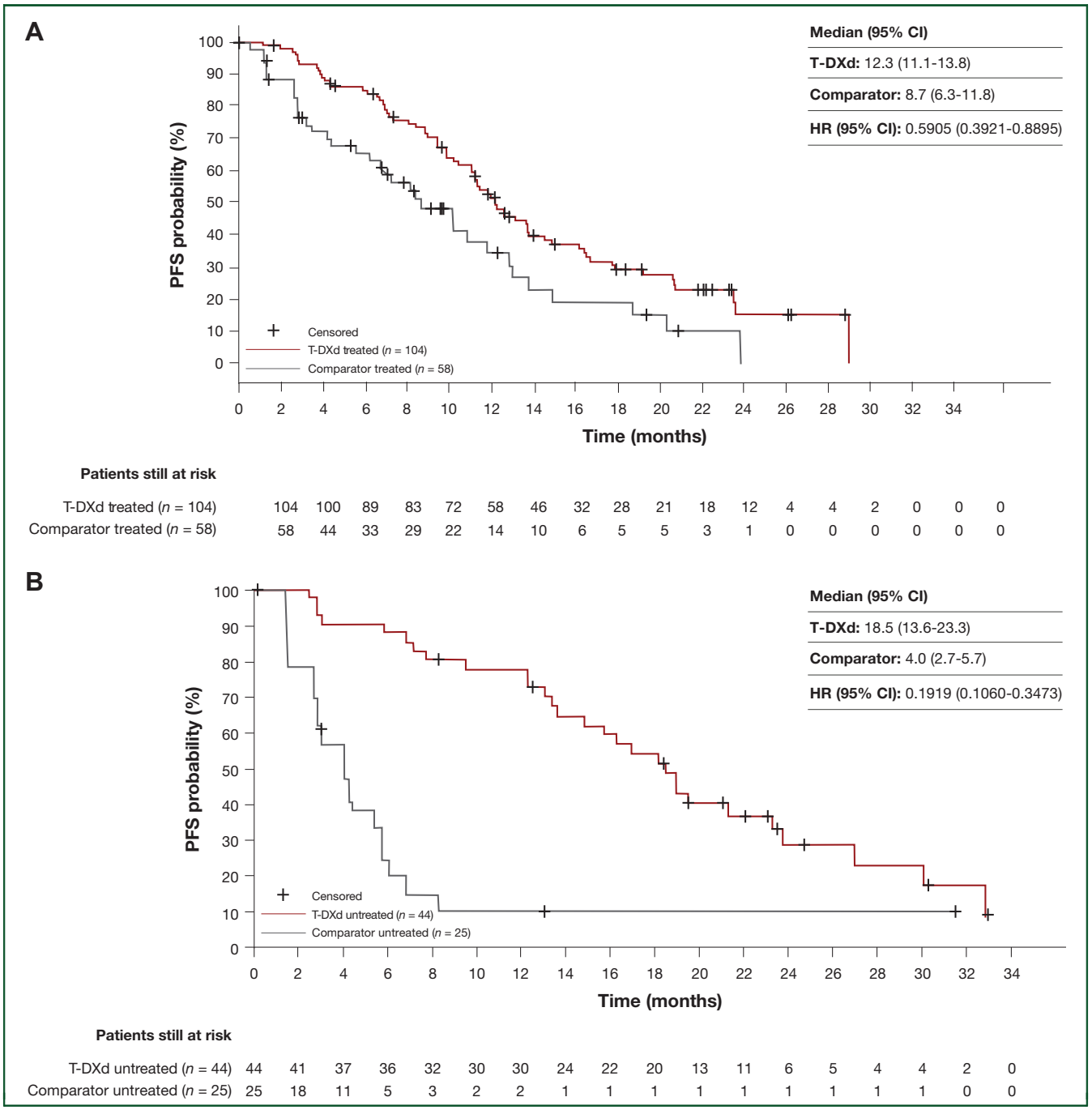

Figure 2. Kaplan–Meier curves of exploratory CNS-PFS per BICR. Kaplan-Meier curves of exploratory CNS-PFS per BICR in patients with (A) treated/stable brain metastasis at baseline and (B) untreated/active brain metastasis at baseline. Patients were censored according to the following: missed two or more consecutive tumor assessments, lacked postbaseline scan, ongoing without event, lost to follow-up, withdrew consent.
BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

the three pivotal T-DXd trials according to their prior local BM treatment status and to evaluate the intracranial efficacy of T-DXd and survival outcomes.

The population randomly assigned to T-DXd with baseline BMs in this pooled analysis consisted of 104 patients (70.0%) with previously locally treated/stable BMs and 44 patients (30.0%) with untreated/active BMs. Intracranial efficacy of T-DXd in patients with untreated/active BMs has not yet been reported in randomized trials. In this exploratory analysis, T-DXd demonstrated robust and consistent intracranial responses in patients with BMs, including those with previously untreated BMs. For patients with treated/stable BMs, intracranial ORR was 45.2% with T-DXd and 27.6% with comparators; and for patients with untreated/active BMs, it was 45.5% with T-DXd and 12.0% with comparators. Although patient numbers were small, numerically longer median intracranial DoR and CNS-PFS were observed in patients with untreated/active BMs

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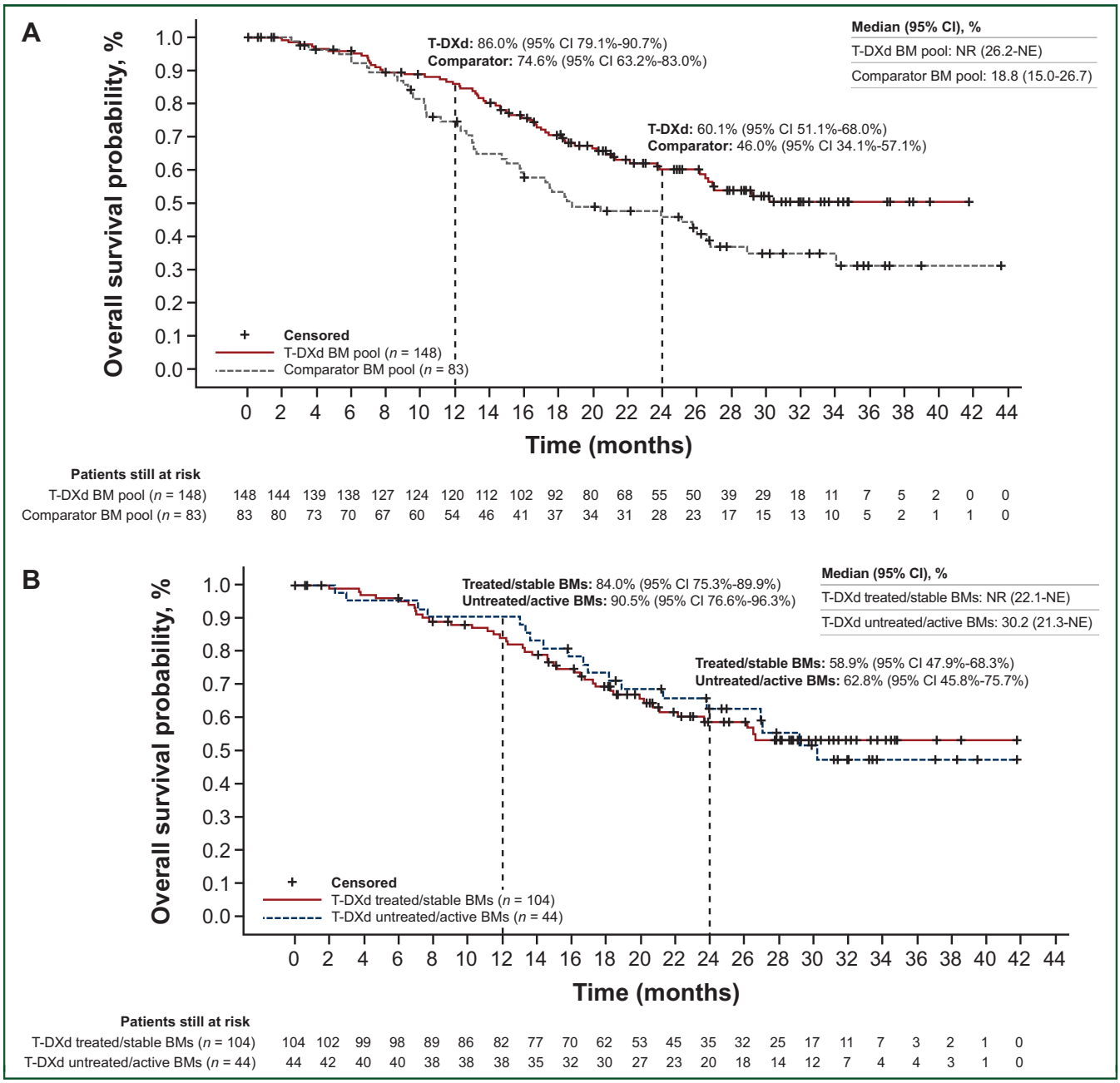

Figure 3. Kaplan–Meier curves of overall survival. Kaplan-Meier curves of overall survival in (A) patients randomized to receive T-DXd versus comparator and (B) patients randomized to T-DXd by prior local brain metastasis treatment status.
CI, confidence interval; NE, not estimable; NR, not reached; T-DXd, trastuzumab deruxtecan.

assigned to T-DXd versus comparator. In addition, substantial OS benefit was observed with T-DXd versus pooled comparators in all patients with BMs. The median OS was NR with T-DXd and 18.8 months with comparators. The median OS was NR for those with treated/stable BMs and 30.2 months for those with untreated/active BMs with T-DXd. The safety profile of T-DXd was acceptable and generally manageable for patients with and without BMs at baseline and was comparable to the safety profile observed in the overall patient population.[24,25,28]

Most patients in this analysis had recurrent BC, and while routine screening for BMs is not currently recommended, these patients have a high propensity to develop BMs.[12,31] Brain imaging typically occurs after symptoms of CNS involvement develop, and by this point, patients typically experience debilitating clinical symptoms and have limited treatment options.[12,32] Authors propose that early treatment of BMs may result in better outcomes for these patients. In the parent studies, brain MRI or CT scans were required for all patients at baseline, which identified a subgroup of patients with asymptomatic, previously locally untreated BMs, corresponding to 30% of all patients with BMs.[24,25,28] Efficacy outcomes demonstrated by T-DXd in the untreated/active BMs subgroup provide a rationale for the investigation of routine screening among all patients with HER2-positive mBC.[33] The current treatment landscape

for patients with HER2-positive mBC with BMs includes T-DM1, tucatinib, and T-DXd.[34,35]

The randomized, double-blind, phase II HER2CLIMB study evaluating trastuzumab and capecitabine in combination with either placebo or tucatinib in patients with previously treated HER2-positive mBC included patients with a history or presence of BMs at baseline, including treated stable and active (progressive and/or untreated) BMs.[18-20] With the tucatinib and placebo combinations, the median OS in the overall population was 24.7 and 19.2 months, respectively.[20] The intracranial ORR for those with active BMs was 47.3% (26/55) with the tucatinib combination compared with 20.0% (4/20) with the placebo combination, with a CNS-PFS of 9.9 months versus 4.2 months, respectively.[19] The randomized, phase III HER2CLIMB-02 study, evaluating T-DM1 in combination with either tucatinib or placebo in patients with unresectable locally advanced or metastatic HER2-positive BC, includes patients with active or treated/stable BMs. For patients with BMs, the median PFS was 7.8 months for those who received T-DM1 plus tucatinib and 5.7 months for those who received T-DM1 plus placebo.[21]

The single-arm, open-label, phase IIIb KAMILLA study evaluated T-DM1 in patients with previously treated HER2-positive advanced BC, including those with untreated, asymptomatic, or controlled BMs at baseline.[36] The median PFS and OS were 5.5 and 18.9 months for patients with BMs ($n = 398$), respectively. A $\geq$30% reduction in the sum of the largest diameters of target brain lesions was observed in 42.9% of patients.[36] The randomized, phase III EMILIA study evaluated T-DM1 versus lapatinib and capecitabine in previously treated patients with HER2-positive BC, including patients with asymptomatic CNS metastases previously treated with radiotherapy.[37,38] In a retrospective analysis of patients with CNS metastases, the median PFS was 5.9 months with T-DM1 ($n = 45$) versus 5.7 months with lapatinib plus capecitabine ($n = 50$), with a median OS of 26.8 versus 12.9 months, respectively.[38]

The intracranial efficacy of T-DXd observed in this study with a larger patient set expands upon preliminary evidence seen in the parent trials and in other smaller trials, including those with active BMs.

The single-arm, phase II DEBBRAH trial is evaluating T-DXd in patients with HER2-positive and HER2-low advanced BC with a history of BMs.[39] In patients with progressing BMs after local treatment, intracranial ORR was 44.4% (4/9 patients). In the prospective, single-arm phase II TUXEDO-1 study of T-DXd, intracranial ORR was 73.3% (11/15) at the primary data cut-off in patients with HER2-postive BC with active, newly diagnosed, or progressing BMs after previous local therapy.[40] As of the final outcome analysis, 60% of patients had progressive BMs, with a median PFS of 21.0 months (95% CI 13.3 months-NR) and median OS of NR (95% CI 22.2 months-NR).[41] The retrospective ROSET-BM study of T-DXd included patients with symptomatic, asymptomatic, active, and stable BM.[42,43] Intracranial ORR of all patients with BM at baseline ($n = 51$) at the primary analysis was 62.7%.[42] At the updated analysis, the median PFS for all patients was 14.6 months (95% CI 10.6-20.8 months); the median OS was 27.0 months (95% CI 16.4 months-NR) and NR (95% CI 10.8 months-NR) in patients with active and stable BMs, respectively.[43]

While cross-trial comparisons should be made with caution, the efficacy results observed here report numerically similar or greater intracranial ORRs, and longer median CNS-PFS and OS compared with other trials in this patient population with other anti-HER2-targeted therapies.[19-21,28,36-43] In addition, this pooled analysis assessed efficacy in a larger patient population and in patients with both active and stable BMs. It should be noted that eligibility criteria regarding BM vary across trials, and patients with active/progressing BMs could be enrolled in HER2CLIMB and HER2CLIMB-02.[18,21]

Of note, patients with active BMs that might require immediate local therapy, required corticosteroids, or were larger untreated lesions ($>$2.0 cm, unless approved by a medical monitor) were excluded from HER2CLIMB. However, if these patients were amenable to immediate local intervention, they were then eligible to be enrolled in HER2CLIMB. These patients were excluded from the DESTINY-Breast trials, and patients with active BMs represent a pool of patients naive to prior local therapy.[18,19,24,25,28]

The safety profile in patients with BMs was generally manageable with T-DXd and consistent with the safety profile in the overall patient populations in the parent studies.[24,25,28] At least one drug-related TEAE was experienced by most patients treated with T-DXd and with comparator drugs. Rates of drug-related grade $\geq$3 TEAEs were 43.2% and 46.4% in the BM and non-BM pools, respectively.

Limitations of this work are that intracranial endpoints were exploratory and not prespecified in the protocols, which could have introduced bias, and the patient numbers in each BM subgroup were small. Proper characterization of patients' baseline characteristics was difficult due to limitations of data capture for prior local treatments for BMs. Consequently, the authors were unable to distinguish treated/stable from treated/progressing BMs. Moreover, BICR was not able to identify brain lesions in accordance with prior local treatment status, and therefore assessment of intracranial response in patients with treated/stable BMs had certain limitations, whereas CNS-PFS was assessed appropriately. Furthermore, CNS-PFS was based on intracranial response, and there was no censoring rule for extracranial/systemic progression due to design limitations in the parent studies. Patients developing extracranial progression before intracranial progression were more likely to be censored for CNS-PFS assessments due to regular tumor assessments no longer being available. However, for some patients, post-end-of-treatment scans were submitted by investigators, which made continuous intracranial efficacy endpoints possible. Furthermore, brain scans were only mandated during study treatment for patients with BMs at baseline per investigator assessment or with

suspected progression in the brain. This limited the ability to report on rates of progression in the brain, including new asymptomatic brain lesions, for patients without baseline BMs, and limited the detection of new lesions in patients without baseline BMs to those who developed symptoms caused by BMs. Therefore it could not be ruled out that the intracranial response in some patients with treated/stable BM was due to the continuing effect of previous local therapy, including radiotherapy. In addition, although less than one-third of patients with BMs at baseline were evaluated by CT scans, it should be noted that CT scans are known to be less effective at detecting BMs than MRI scans, particularly for small lesions.[44] The number of BM lesions identified at baseline by BICR differed between the treated/stable and untreated/active BM subgroups, and therefore the patient populations were not completely balanced. Furthermore, because the study designs and patient populations were not identical across the parent studies, the results of this exploratory analysis may be subject to bias and confounding.[24,28,29]

This pooled analysis reports the intracranial efficacy of T-DXd and improved OS in patients with HER2-positive mBC and BMs versus comparators. For the first time, intracranial efficacy with T-DXd was reported in randomized studies in patients with untreated, active metastases. Results support T-DXd as an effective treatment option in patients with treated and untreated BMs, with an acceptable and manageable safety profile. Results also demonstrate further investigation is necessary for this patient population with poor prognosis and limited treatment options. Sequencing of therapies is an important ongoing question and given these data, the prospective evaluation of T-DXd in patients with BMs in the ongoing phase IIIb/IV DESTINY-Breast12 trial is warranted.[45] Furthermore, results support the investigation of the utility of active screening strategies for all patients with HER2-positive mBC to enable early detection of asymptomatic BMs, as well as the early introduction of effective systemic treatment options targeting intracranial and extracranial disease before the development of symptomatic BMs.

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