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Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: The DEBBRAH trial

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Abstract

Background. Trastuzumab deruxtecan (T-DXd) has shown durable antitumor activity in pretreated patients with HER2-positive advanced breast cancer (ABC), but its efficacy has not yet been evaluated in patients with active brain metastases (BMs). DEBBRAH aims to assess T-DXd in patients with HER2-positive or HER2-low ABC and central nervous system involvement.

Methods. This ongoing, five-cohort, phase II study (NCT04420598) enrolled patients with pretreated HER2-positive or HER2-low ABC with stable, untreated, or progressing BMs, and/or leptomeningeal carcinomatosis. Here, we report findings from HER2-positive ABC patients with non-progressing BMs after local therapy (n = 8; cohort 1), asymptomatic untreated BMs (n = 4; cohort 2), or progressing BMs after local therapy (n = 9; cohort 3). Patients received 5.4 mg/kg T-DXd intravenously once every 21 days. The primary endpoint was 16-week progression-free survival (PFS) for cohort 1 and intracranial objective response rate (ORR-IC) for cohorts 2 and 3.

Results. As of October 20, 2021, 21 patients received T-DXd. In cohort 1, 16-week PFS rate was 87.5% (95%CI, 47.3-99.7; $P < .001$). ORR-IC was 50.0% (95%CI, 6.7-93.2) in cohort 2 and 44.4% (95%CI, 13.7-78.8; $P < .001$) in cohort 3. Overall, the ORR-IC in patients with active BMs was 46.2% (95%CI, 19.2-74.9). Among patients with measurable intracranial or extracranial lesions at baseline, the ORR was 66.7% (12 out of 18 patients; 95%CI, 41.0-86.7), 80.0% (95%CI, 28.4-99.5) in cohort 1, 50.0% (95%CI, 6.7-93.2) in cohort 2, and 66.7% (95%CI, 29.9-92.5) in cohort 3. All responders had partial responses. The most common adverse events included fatigue (52.4%; 4.8% grade ≥3), nausea (42.9%; 0% grade ≥3), neutropenia (28.6%; 19% grade ≥3), and constipation (28.6%; 0% grade ≥3). Two (9.5%) patients suffered grade 1 interstitial lung disease/pneumonitis.

Conclusions. T-DXd showed intracranial activity with manageable toxicity and maintained the quality of life in pretreated HER2-positive ABC patients with stable, untreated, or progressing BMs. Further studies are needed to validate these results in larger cohorts.

Key Points

- HER2+ ABC patients with stable BMs who received T-DXd had 16-week PFS rate of 87.5%.
- ORR-IC of HER2+ ABC patients with asymptomatic untreated and progressing BMs was 50.0% and 44.4%, respectively.

Importance of the Study

Treatment for patients with breast cancer brain metastases (BMs) includes a local approach with radiotherapy or surgery and systemic therapy. Although patients with stable BMs are often included in randomized trials, those with BMs untreated or progressing to prior local therapy are usually excluded from participation in most clinical trials. This manuscript describes primary results from three cohorts of the phase II DEBBRAH trial focusing on the efficacy and safety of trastuzumab deruxtecan (T-DXd) in HER2-positive advanced breast cancer (ABC) patients with stable or progressing BMs after local therapy and asymptomatic untreated BMs. T-DXd demonstrated encouraging intracranial and extracranial activity, along with generally manageable toxicity and preserved quality of life, for the treatment of pretreated patients with stable or active HER2-positive BMs. Longer follow-up, along with data from additional cohorts of this trial will further guide the use of T-DXd in HER2-positive or HER2-low ABC patients with BMs and/or leptomeningeal carcinomatosis.

Approximately 30%-50% of patients with HER2-positive advanced breast cancer (ABC) will develop brain metastases (BMs).[1] Although the outcome of HER2-positive patients with breast cancer BMs (BCBMs) has improved with the introduction of new HER2-targeted agents, their prognosis remains poor.[2,3] This might be explained by the challenging delivery of many therapies to the central nervous system (CNS) due to the blood-brain barrier (BBB), a highly selective diffusion barrier that limits the entry of toxins and drug substances into the brain.[2] Although BMs can increase permeability by impairing the BBB,[2] most drugs do not reach therapeutic levels in the CNS.[4]

Treatment for patients with BCBMs includes a local approach with radiotherapy (stereotactic radiosurgery [SRS], stereotactic radiotherapy [SRT], or whole-brain radiation therapy [WBRT]) or surgery, and systemic therapy.[4–6] Although patients with stable BCBMs (those who have received prior therapy and are radiographically stable) are often included in randomized trials, those with active BCBMs (defined as BMs untreated or progressing to prior local therapy) are usually excluded from participation in most clinical trials.[7–9] Moreover, a significant number of clinical trials also do not include BM-related outcomes in their primary or co-primary endpoints.[4] Until the HER2CLIMB trial, there was limited clinical evidence for systemic management of patients with active BCBMs.[10] HER2CLIMB was the first randomized study to demonstrate an improved antitumor activity in terms of progression-free survival (PFS) and overall survival (OS) of a tucatinib-based therapy in heavily pretreated patients with HER2-positive ABC, including those with active BMs.[10] Accordingly, tucatinib plus trastuzumab and capecitabine is currently the widely used treatment for HER2-positive ABC patients with active BCBMs.

The antibody-drug conjugate trastuzumab deruxtecan (T-DXd; formerly DS-8201a) initially showed an encouraging and durable antitumor activity in heavily pretreated HER2-positive ABC patients who had previously received trastuzumab emtansine (DESTINY-Breast01 trial).[11] The superiority of T-DXd over trastuzumab emtansine was also subsequently confirmed in HER2-positive ABC patients previously treated with a taxane and trastuzumab (DESTINY-Breast03 trial). T-DXd significantly reduced the risk of disease progression or death by 72.0% compared with trastuzumab emtansine with a manageable toxicity profile.[12] Based on these results, T-DXd has become the new standard of care in the second-line treatment of patients with HER2-positive ABC.[6,13]

DESTINY-Breast01 and DESTINY-Breast03 highlighted the intracranial response and long-lasting clinical activity of T-DXd in HER2-positive ABC patients; however, both studies excluded patients with active BCBMs.[11,12,14] The antitumor activity of T-DXd appears to be superior to that of tucatinib plus trastuzumab and capecitabine, although no head-to-head comparison studies have been conducted. Nevertheless, tucatinib-based therapy represents the preferred regimen for patients with active BCBMs because the intracranial activity of T-DXd in these patients has not yet been elucidated.[15]

To bridge this knowledge gap, we conducted the DEBBRAH study to evaluate the efficacy and safety of T-DXd in patients with HER2-positive and HER2-low ABC with a history of BMs and/or leptomeningeal carcinomatosis. Here, we exclusively present results from HER2-positive ABC patients with stable, untreated, or progressing BMs included in three cohorts of this study.

Patients and Methods

Study Design and Patients

This is an ongoing, single-arm, open-label, five-cohort, phase II study conducted across 18 sites in Spain and Portugal (ClinicalTrials.gov identifier: NCT04420598). Eligible patients were ≥18 years old, with histologically confirmed HER2-positive or HER2-low ABC with stable, untreated, or progressing BMs and/or leptomeningeal carcinomatosis with positive cerebrospinal fluid cytology. Additional requirements were: Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (0-2 in cohort 5), ≥1 measurable brain lesion (cohorts 2-4), life expectancy over 12 weeks, prior treatment with a taxane and a HER2-targeted therapy (if HER2-positive patients), with ≥1 chemotherapy regimen (if HER2-low and estrogen receptor-negative), or with ≥1 chemotherapy and 1 endocrine regimen (if HER2-low and estrogen receptor-positive) in the metastatic setting, and left ventricular ejection fraction ≥50% within 28 days before enrollment. Hormone receptor and HER2 status assessments were done locally. HER2-positive status was defined as immunohistochemistry (IHC) 3+, in situ hybridization (ISH) ratio ≥2.0, or average HER2 copy number ≥6.0 signals. HER2-low status was defined as IHC 2+/ISH-negative or IHC 1+. Corticosteroids were allowed as long as patients have been on a stable dose for ≥4 weeks (highest acceptable dose was 8 mg dexamethasone twice daily or equivalent). Full eligibility criteria are listed in the Data Supplement.

Patients were enrolled into one of the five cohorts based on HER2 status and CNS involvement: those with HER2-positive ABC and stable BMs after local treatment with radiotherapy and/or surgery are assigned to cohort 1; those with HER2-positive or HER2-low ABC and asymptomatic untreated BMs to cohort 2; those with HER2-positive ABC and progressing BMs after local treatment with radiotherapy and/or surgery to cohort 3; those with HER2-low ABC and progressing BMs after local treatment with radiotherapy and/or surgery to cohort 4; and those with HER2-positive or HER2-low ABC and untreated leptomeningeal carcinomatosis to cohort 5. Patients with stable BMs were defined as those asymptomatic for ≥4 weeks, with or without corticosteroids. Results from cohorts 4 and 5 and the HER2-low subgroup of patients from cohort 2 will be reported separately.

This study was conducted in compliance with the Declaration of Helsinki and in accordance with regulatory requirements and International Conference on Harmonization Good Clinical Practice guidelines. The study protocol was approved by institutional review boards and independent ethics committees at each site, and all patients provided written informed consent.

Treatment and Assessments

Patients received 5.4 mg/kg T-DXd as an intravenous infusion on day 1 of each 21-day cycle until progressive disease (PD), unacceptable toxicity, elective withdrawal from the study, or study completion. The first dose was infused for approximately 90 minutes, and if no infusion-related reactions were observed, subsequent doses were infused for approximately 30 minutes.

Dose interruptions and reductions were permitted for T-DXd as defined by prespecified guidelines in the protocol. Concomitant endocrine therapy was not allowed in patients with hormone receptor-positive status (estrogen receptor and/or progesterone receptor).

Computed tomography or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis and brain MRI were performed at baseline, every 6 weeks up to 24 weeks, and every 9 weeks after that. Bone scans were performed at baseline and repeated during the study only if bone involvement was found at baseline.

Safety was assessed in all patients who received ≥1 dose of study treatment using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

Outcomes

The primary endpoint for cohort 1 was 16-week PFS defined as the rate of patients without progression or death for any cause determined locally by the investigator, as per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria for intracranial lesions and Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 for extracranial and overall lesions. The primary endpoint for cohorts 2 and 3 was intracranial objective response rate (ORR-IC) determined locally by the investigator, using the RANO-BM criteria. Radiological confirmation of objective response was not required.

Secondary endpoints included investigator-assessed PFS, ORR, clinical benefit rate (CBR), disease control rate, time to response, duration of response (DoR), the best percentage of change from baseline in the size of tumor lesions as per RANO-BM for intracranial lesions and per RECIST v.1.1 for extracranial and overall measurable lesions; time to WBRT and/or SRS/SRT (only for cohort 2); OS; and safety as per NCI-CTCAE v.5.0.

The following endpoints were considered exploratory: overall change from baseline in patient-reported global health status/quality of life (GHS/QoL) through the use of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BR23 questionnaires; time to deterioration in global QoL; time to deterioration in pain; time to next systemic therapy; and the relationship between tissue- and/or blood- and/or cerebrospinal fluid-based biomarkers and patient clinical characteristics and outcome.

Some secondary endpoints (DoR, OS, and time to WBRT and/or SRS/SRT) and all exploratory endpoints apart from GHS/QoL are still being analyzed and are not included in this report. The definition of all endpoints is provided in the Data Supplement.

Statistical Analysis

The local, one-sided, type I error was 0.05 for each primary endpoint. The sample size was planned with the optimal Simon's two-stage design for cohort 1 and the one-stage A'Hern design for cohorts 2 and 3.[16] The one-sided uniformly minimum-variance unbiased estimator-based test for cohort 1 and exact binomial test for cohorts 2 and 3 were used. The primary analysis for cohort 1 was designed to test the null and alternative hypotheses that the true 16-week PFS rates were ≤5% and ≥40%, respectively. The same null and alternative hypotheses have been planned for the ORR-IC analyses for cohorts 2 and 3. We expected a lower ORR-IC than ORR achieved in the DESTINY-Breast01 trial (60.9%; 95% confidence intervals [95% CI], 53.4-68.0), in which 87% of patients did not have BCBMs.[11] Thus, we estimated that 8 patients in cohort 1, 10 (including HER2-low ABC patients) in cohort 2, and 7 in cohort 3 would be needed to attain 80% power in each cohort at the nominal level of one-sided α of 0.05. The *P*-value for cohort 2 was not provided because only data of HER2-positive patients were reported.

The Clopper-Pearson methodology was used to calculate the two-sided 95% CI for the 16-week PFS and response rate. We used the Kaplan-Meier method to estimate the distribution of time-to-event endpoints of time to response and PFS; corresponding two-sided 95% CI were calculated with the Brookmeyer and Crowley methods. Safety data were summarized with descriptive statistics. Changes from baseline in patient-reported outcomes were analyzed in patients who completed baseline and at least one follow-up questionnaire using *t*-test and Wilcoxon test. Time to deterioration of GHS/QoL (≥10-point decrease from baseline) was analyzed as a time-to-event endpoint. Statistical computation was performed with R v.4.0.2.

Results

Patient Disposition and Baseline Characteristics

Between June 29, 2020 and July 19, 2021, 59 patients were screened for eligibility, and 21 HER2-positive patients were enrolled in cohorts 1-3, as reported here. At the time of data cutoff (October 20, 2021), enrollment was ongoing for cohorts 4 and 5 (Figure 1). All enrolled patients were female, and the median age was 53 years (range, 36.0-77.0). The number of metastatic organ sites varied widely between cohorts, as did the number of previous lines of therapy for advanced disease. In cohort 1, four (50.0%) patients had CNS metastatic involvement at baseline, all of which were non-measurable lesions. All the patients in cohorts 2 and 3 had the measurable intracranial disease at baseline. Seven (87.5%), four (100%), and five (55.6%) patients also

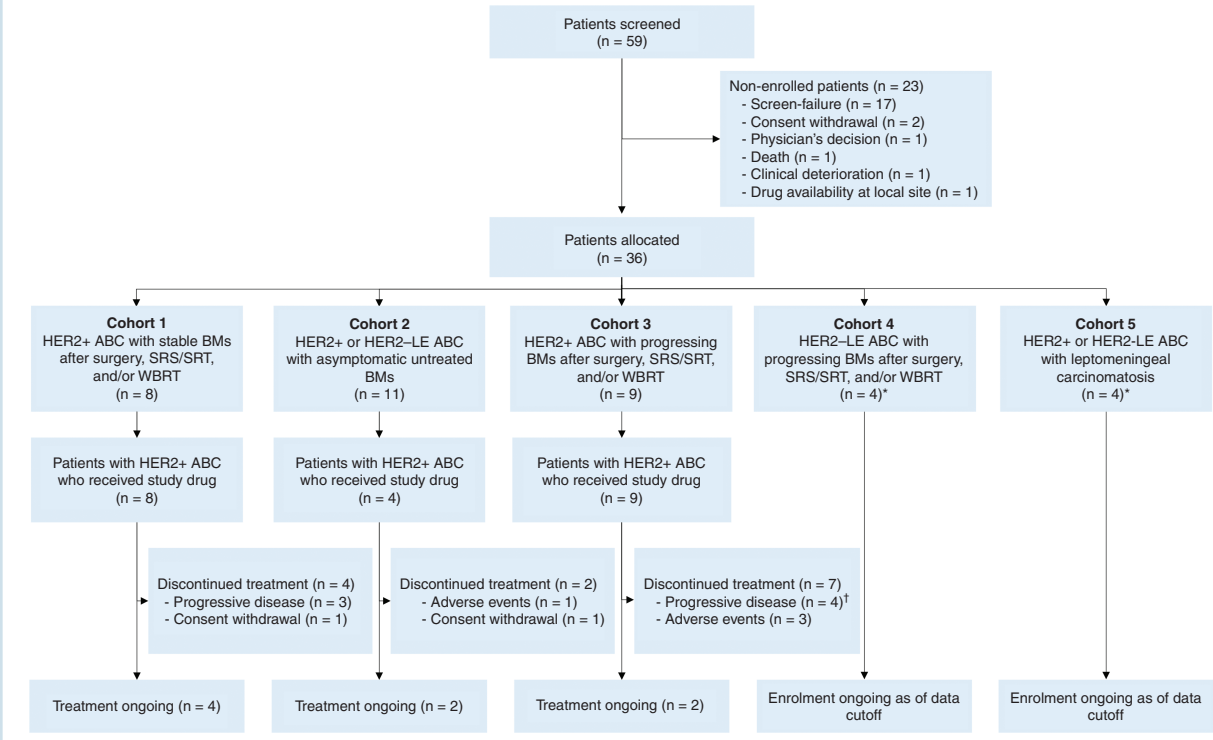

Fig. 1 Patient enrollment and disposition at data cutoff. *Not reported in this article. Patient recruitment in cohorts 4 and 5 was ongoing at the time of data cutoff. †One patient reported an intraventricular hemorrhage related to disease progression as serious adverse event. The reason of discontinuation reported for this patient is progressive disease. Abbreviations: ABC, advanced breast cancer; BMs, brain metastases; HER2-LE, HER2-low; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

Table 1 Patient Demographics and Baseline Characteristics

Characteristic	Cohort 1 (n = 8)	Cohort 2 (n = 4)	Cohort 3 (n = 9)	All Patients (n = 21)
Age, years				
Median	45.5	57.5	53.0	53.0
Range	36.0-65.0	37.0-77.0	37.0-61.0	36.0-77.0
Female sex	8 (100)	4 (100)	9 (100)	21 (100)
Caucasian race	8 (100)	4 (100)	9 (100)	21 (100)
ECOG performance status[a]				
0	5 (62.5)	4 (100)	6 (66.7)	15 (71.4)
1	3 (37.5)	0	3 (33.3)	6 (28.6)
HER2 status[b]				
IHC 3+	6 (75.0)	4 (100)	7 (77.8)	17 (81.0)
IHC 2+/ISH amplified	2 (25.0)	0	2 (22.2)	4 (19.0)
Hormone receptor status				
ER- and/or PgR-positive	7 (87.5)	2 (50.0)	7 (77.8)	16 (76.2)
ER- and PgR-negative	1 (12.5)	2 (50.0)	2 (22.2)	5 (23.8)
CNS metastatic disease[c]	4 (50.0)	4 (100)	9 (100)	17 (81.0)
Non-CNS metastatic disease	7 (87.5)	4 (100)	5 (55.6)	16 (76.2)
Measurable lesions[c]				
Intracranial	0	4 (100)	9 (100)	13 (61.9)
Extracranial	5 (62.5)	2 (50.0)	2 (22.2)	9 (42.9)
All	5 (62.5)	4 (100)	9 (100)	18 (85.7)
Metastatic organ sites				
1	4 (50.0)	0	2 (22.2)	6 (28.6)
2	1 (12.5)	1 (25.0)	5 (55.6)	7 (33.3)
≥3	3 (37.5)	3 (75.0)	2 (22.2)	8 (38.1)
Prior lines of therapy for ABC[d]				
1	2 (25.0)	0	1 (11.1)	3 (14.3)
2	2 (25.0)	0	3 (33.3)	5 (23.8)
3	1 (12.5)	0	0	1 (4.8)
4	1 (12.5)	1 (25.0)	0	2 (9.5)
≥5	2 (25.0)	3 (75.0)	5 (55.6)	10 (47.6)
Prior systemic therapy				
Trastuzumab	8 (100)	4 (100)	9 (100)	21 (100)
Pertuzumab	8 (100)	3 (75)	7 (77.8)	18 (85.7)
Trastuzumab emtansine	4 (50.0)	2 (50.0)	6 (66.7)	12 (57.1)
Other HER2-targeted therapy	3 (37.5)	1 (25.0)	7 (77.8)	11 (52.4)
Hormone therapy	5 (62.5)	2 (50.0)	6 (66.7)	13 (61.9)
Other systemic therapy	8 (100)	4 (100)	9 (100)	21 (100)
Best response to prior therapy				
CR or PR	2 (25.0)	1 (25.0)	5 (55.6)	8 (38.1)
SD ≥24 weeks	1 (12.5)	1 (25.0)	1 (11.1)	3 (14.3)
SD <24 weeks	1 (12.5)	1 (25.0)	1 (11.1)	3 (14.3)
PD	2 (25.0)	1 (25.0)	2 (22.2)	5 (23.8)
Not evaluable	2 (25.0)	0	0	2 (9.5)
Prior therapy for BMs				
WBRT	4 (50.0)	0	6 (66.7)	10 (47.6)
SRS/SRT	3 (37.5)	0	4 (44.4)	7 (33.3)
Surgery	3 (37.5)	0	3 (33.3)	6 (28.6)

Abbreviations: ABC, unresectable locally advanced or metastatic breast cancer; BMs, brain metastases; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PD, progressive disease; PgR, progesterone receptor; PR, partial response; SD, stable disease; SRS/SRT, stereotactic radiosurgery/stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

All values are No. (%) unless otherwise specified.

[a]ECOG performance status scores range from 0 to 5, with higher score indicating greater disability.

[b]HER2 status was evaluated locally. HER2-positive status was defined as IHC 3+, ISH ratio ≥2.0, or average HER2 copy number ≥6.0 signals.

[c]Four patients in cohort 1 had no BMs at baseline: of them, 3 patients underwent surgery (1 of them also received SRS/SRT), and 1 patient received WBRT and SRS/SRT. The remaining 4 patients had no measurable BMs at baseline: of them, 3 patients received WBRT, and 1 patient received SRS/SRT.

[d]Prior therapies for ABC do not include hormone therapy.

had non-CNS metastatic involvement in cohorts 1, 2, and 3, respectively (Table 1).

At data cutoff, eight (38.1%) of 21 patients continued treatment. The primary reasons for treatment discontinuation included PD (33.3%), adverse events (AEs; 19.0%), and consent withdrawal (9.5%) (Figure 1). The median duration of follow-up was 8.4 months (range, 1.4-12.6) for all patients, 8.5 months (range, 4.5-12.6) for cohort 1, 1.8 months (range, 1.4-7.2) for cohort 2, and 8.8 months (range, 2.1-10.8) for cohort 3.

Clinical Activity

Cohort 1 met the primary endpoint, with seven (87.5%) of eight patients alive without PD 16 weeks after initiating treatment (95% CI, 47.3-99.7; $P < .001$). At data cutoff, three (37.5%) patients experienced PD; of these patients, one (12.5%) had intracranial PD, and two (25%) had extracranial PD. In cohort 2, two of the four patients had partial intracranial responses (PRs; ORR-IC 50.0% [95% CI, 6.7-93.2]), and no patient experienced intracranial PD. In cohort 3, four of the nine patients experienced intracranial PRs, meeting the primary endpoint (ORR-IC 44.4% [95% CI, 13.7-78.8]; $P < .001$). Additionally, one (11.1%) patient had stable disease (SD) lasting ≥24 weeks, three (33.3%) patients had SD <24 weeks, and one (11.1%) patient had PD as the best response in cohort 3. At data cutoff, four (44.4%) patients experienced PD; all patients had intracranial PD, and one (11.1%) patient also had extracranial PD. Overall, the ORR-IC in patients with active BMs (cohorts 2 and 3) was 46.2% (95% CI, 19.2-74.9; Figure 2).

Among patients with measurable intracranial or extracranial lesions at baseline, the ORR was 66.7% (12 out of 18 patients; 95% CI, 41.0-86.7), 80.0% (95% CI, 28.4-99.5) in cohort 1, 50.0% (95% CI, 6.7-93.2) in cohort 2, and 66.7% (95% CI, 29.9-92.5) in cohort 3. All responders had PRs. Moreover, most of the patients had a reduction in tumor size of both intracranial and extracranial lesions (Figure 2). CBR was 72.2% (13 out of 18 patients; 95% CI, 46.5-90.3), 80.0% (95% CI, 28.4-99.5) in cohort 1, 50.0% (95% CI, 6.7-93.2) in cohort 2, and 77.8% (95% CI, 40.0-97.2) in cohort 3. Finally, the disease control rate was 88.9% (16 out of 18 patients; 95% CI, 65.3-98.6), 80.0% (95% CI, 28.4-99.5) in cohort 1, 100.0% (95% CI 39.8-100.0) in cohort 2, and 89.9% (95% CI, 51.8-99.7) in cohort 3 (Data Supplement).

The median time to response was 3.4 months (95% CI, 6.9-NA) for measurable intracranial lesions, 1.5 months (95% CI, 1.3-NA) for measurable extracranial lesions, and 2.7 months (95% CI, 1.4-5.5) for all measurable lesions.

At the time of this analysis, DoR and PFS were still immature, with an events rate of 38.1% and 8.4 months of median follow-up. The PFS rate at 6 months was 78.7% (95% CI, 52.7-91.5) and 61.4% at 9 months (95% CI, 31.0-81.6) for all included patients.

Safety

The median relative dose intensity of T-DXd was 99.2% (range, 81.0-101.0) in cohort 1, 98.9% (range, 91.5-101.0) in cohort 2, and 90.5% (range, 86.2-102.5) in cohort 3 (Data Supplement).

Nineteen of 21 (90.5%) patients experienced ≥1 AE, and grade 3-4 AEs occurred in 5 of the 21 (23.8%) patients (Data Supplement). The most common AEs were fatigue (52.4%), nausea (42.9%), neutropenia (28.6%), and constipation (28.6%). The reported grade 3-4 AEs were neutropenia (19.0%) and fatigue (4.8%) (Table 2). AEs led to a dose interruption in seven (33.3%) patients and a dose reduction in three (14.3%) patients. Four (19.0%) patients discontinued treatment because of an AE, including interstitial lung disease (ILD)/pneumonitis, fatigue, neutropenia, and SARS-CoV-2 infection with concomitant staphylococcal pneumonia (one patient each; Data Supplement).

Six (28.6%) patients experienced a serious AE. Among them, two patients (9.5%) had grade 1 ILD/pneumonitis. Both patients were treated with corticosteroids. One of them permanently discontinued the study treatment, whereas the other could resume treatment with T-DXd after the resolution of the event (Data Supplement).

Two (9.5%) deaths occurred during treatment because of either intraventricular hemorrhage related to PD and SARS-CoV-2 infection. No deaths were adjudicated as T-DXd induced by the investigators. A decrease in left ventricular ejection fraction or heart failure was not reported.

In all patients, the global QOL scale as assessed by the EORTC QLQ-C30 questionnaire was not significantly different at 24 weeks compared to baseline (mean score 58.3 ± 23.4 vs 60.7 ± 19.2, $P = .192$). No other significant improvement or deterioration was observed in the remaining QLQ-C30 and QLQ-BR23 scales throughout treatment among the three cohorts. The EORTC QLQ-C30 scale indicated that GHS/QoL did not decline at 24 weeks of treatment for 58.3% (95% CI, 30.7–78.2) of patients included in this analysis (Data Supplement).

Discussion

In this primary analysis of the DEBBRAH study, T-DXd demonstrated encouraging intracranial and extracranial activity, along with generally manageable toxicity and maintained QoL, for the treatment of pretreated patients with stable or active HER2-positive BCBMs.

To the best of our knowledge, this is the first published study to suggest the activity of T-DXd in patients with active BCBMs. Treatment with T-DXd led to 16-week PFS in 87.5% of patients in cohort 1 and ORR-IC of 50.0% in cohort 2 and 44.4% in cohort 3. Promising ORR, CBR, and disease control rates were also observed with T-DXd. Results from cohort 2 should be considered descriptive since formal testing has to be performed in the whole cohort of patients with HER2-positive or HER2-low ABC and asymptomatic untreated BMs.

Our ORR-IC (46.2%) does not significantly differ from the ORR (60.9%) reported in the DESTINY-Breast01 trial,[11] suggesting a comparable intracranial and extracranial efficacy of T-DXd. Previous studies also showed a similar effect in BCBMs patients who had received treatment with other HER2-targeted agents,[17–19] probably due to the higher loss of BBB integrity in this tumor subtype than in other breast cancer subtypes.[2] Consequently, anti-HER2 drugs have the potential to penetrate the brain more effectively.

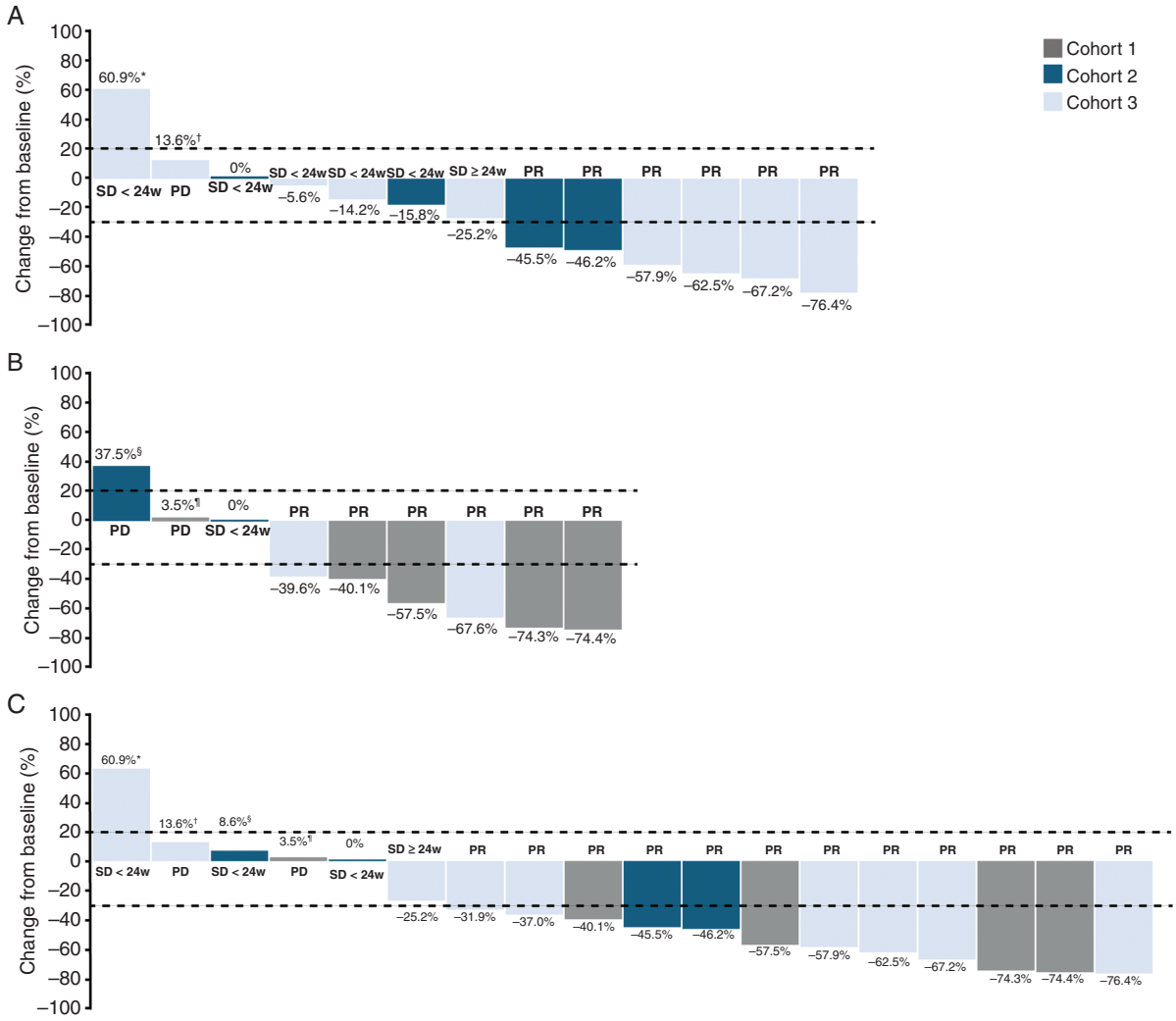

Fig. 2 Waterfall plots of best response in patients of cohorts 1-3 with measurable (A) intracranial lesions by RANO-BM, (B) extracranial lesions by RECIST v1.1, and (C) overall lesions by RECIST v1.1. Data cutoff for this analysis was October 20, 2021. Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for PR and PD, respectively. *Patient was evaluated as SD despite the 60.9% increase in tumor size. The investigator considered there was radiation necrosis instead of PD. †Patient had a new brain lesion and was evaluated as PD despite an increase in tumor size <20% (13.6%). §Patient showed a 37.5% increase in extracranial lesions (PD) and a 15.8% reduction in intracranial lesions. Overall increase of tumor lesions was 8.6%. The patient was considered as having PD for extracranial lesions and SD for intracranial and for all lesions. ¶Patient had a new lesion (liver) and was evaluated as PD despite an increase in tumor size <20% (3.5%). Abbreviations: 24w, 24 weeks; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

The toxicity profile of T-DXd was consistent with prior reports, with a similar incidence of grade ≥3 neutropenia and fatigue, and without an increase in the rates of overall and grade ≥3 nausea/vomiting, a typical T-DXd-related AE. This result is clinically very relevant in patients with CNS involvement, considering that it would be reasonable to anticipate higher gastrointestinal toxicity of T-DXd in this patient population. The incidence of ILD/pneumonitis was relatively low and in line with that reported in the DESTINY-Breast03 trial, with no grade 2-5 events.[12]

Patients with HER2-positive breast cancer and CNS metastatic involvement have historically been associated with poor prognosis and suffer from treatment-related AEs that further impact global QoL, encompassing physical, emotional, social, and cognitive functions.[20,21] Although efficacy outcomes are more easily measured, subjective symptoms and QoL of patients with BMs are increasingly recognized as a crucial endpoint of cancer care by patients as well as physicians and regulators. In this study, the overall GHS/QoL of most patients did not deteriorate from baseline at 6 months, suggesting that the T-DXd regimen may have served to preserve the QoL of pretreated patients with stable or active HER2-positive BCBMs.

Recent data from the DESTINY-Breast03 trial revealed consistent efficacy benefit of T-DXd over trastuzumab emtansine across all subgroups analyzed, including patients with stable BMs.[22,23] Among 82 patients with stable BMs at baseline, median PFS was 15.0 months (95% CI, 12.5-22.2) in T-DXd arm vs

Table 2 Adverse Events of Any Grade and Grade 3-4 Occurring in ≥10% of Patients by Cohort

Adverse Events	Cohort 1 (n = 8)		Cohort 2 (n = 4)		Cohort 3 (n = 9)		All Patients (n = 21)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any	8 (100)	2 (25.0)	3 (75.0)	0	8 (88.9)	3 (33.3)	19 (90.5)	5 (23.8)
Fatigue	5 (62.5)	1 (12.5)	2 (50.0)	0	4 (44.4)	0	11 (52.4)	1 (4.8)
Nausea	4 (50.0)	0	2 (50.0)	0	3 (33.3)	0	9 (42.9)	0
Constipation	4 (50.0)	0	1 (25.0)	0	1 (11.1)	0	6 (28.6)	0
Neutropenia	2 (25.0)	1 (12.5)	0	0	4 (44.4)	3 (33.3)	6 (28.6)	4 (19.0)
Diarrhea	1 (12.5)	0	1 (25.0)	0	3 (33.3)	0	5 (23.8)	0
Vomiting	2 (25.0)	0	1 (25.0)	0	2 (22.2)	0	5 (23.8)	0
Anemia	0	0	0	0	4 (44.4)	0	4 (19.0)	0
ALT increased	1 (12.5)	0	1 (25.0)	0	1 (11.1)	0	3 (14.3)	0
Alopecia	3 (37.5)	0	0	0	0	0	3 (14.3)	0
Bone pain	1 (12.5)	0	0	0	2 (22.2)	0	3 (14.3)	0
Dysarthria	0	0	0	0	3 (33.3)	0	3 (14.3)	0
Headache	1 (12.5)	0	0	0	2 (22.2)	0	3 (14.3)	0
Insomnia	1 (12.5)	0	0	0	2 (22.2)	0	3 (14.3)	0
Paresthesia	2 (25.0)	0	0	0	1 (11.1)	0	3 (14.3)	0
Thrombocytopenia	2 (25.0)	0	0	0	1 (11.1)	0	3 (14.3)	0
Urinary tract infection	1 (12.5)	0	0	0	2 (22.2)	0	3 (14.3)	0

Abbreviation: ALT, alanine aminotransferase.
All values are No. (%). Medical Dictionary for Regulatory Activities version 20.1 was used for coding of system organ class. Analysis was performed on the safety analysis population that included all patients who received ≥1 dose of T-DXd.

3.0 months (95% CI, 2.8-5.8) in trastuzumab emtansine arm (hazard ratio, 0.25; 95% CI, 0.13-0.45). However, the DESTINY-Breast03 trial precluded patients with clinically active BCBMs from being included. Other than DEBBRAH, three ongoing studies are evaluating T-DXd in HER2-positive active or stable BCBMs: DESTINY-Breast07, phase 1/2b[24]; DESTINY-Breast12, phase 3b/4[25]; and TUXEDO-1, phase 2.[26,27] Results from these trials will further help elucidate the efficacy of T-DXd in this patient population.

One of the strengths of DEBBRAH is that it follows the recommendation made by the U.S. Food and Drug Administration,[28] the American Society of Clinical Oncology and Friends of Cancer Research,[29] and the RANO-BM working group[30] to include patients with stable or active BMs in clinical trials, given the high unmet need these patients have for adequate treatment. The HER2CLIMB, DESTINY-Breast01, and DESTINY-Breast03 studies only evaluated response to HER2-targeted therapies with RECIST[10–12]; in contrast, we specifically assessed the intracranial response to T-DXd using RANO-BM and extracranial response using RECIST criteria. Our study is limited by having a non-randomized single-arm design; however, the use of three HER2-positive ABC cohorts enabled studying T-DXd in various settings. Other limitations of the current study comprise its heterogeneous patient population, including patients with a different number of prior lines of therapy and a high proportion of hormone receptor-positive disease in cohorts 1 and 3, its small sample size, and a short follow-up. Nevertheless, T-DXd activity is consistent regardless the hormone receptor status and number/type of prior therapies,[23] and based on the sample size estimation, the number of patients accrued for each cohort is sufficient to justify the use of the study drug in further clinical trials.

Conclusion

Our preliminary findings suggest that T-DXd could be a valuable treatment option for HER2-positive patients with stable or active BCBMs. Longer follow-up, along with data from cohorts 2, 4, and 5, will further guide the use of T-DXd in HER2-positive or HER2-low ABC patients with BMs and/or leptomeningeal carcinomatosis.

Keywords

advanced breast cancer | brain metastases | HER2-positive | T-DXd | trastuzumab deruxtecan

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