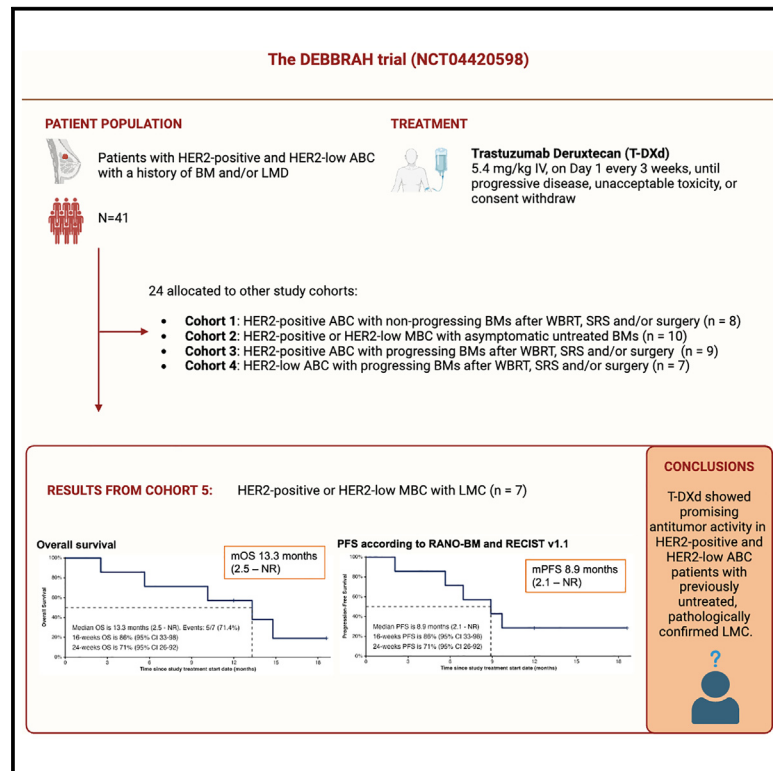


The DEBBRAH trial: Trastuzumab deruxtecan in HER2-positive and HER2-low breast cancer patients with leptomeningeal carcinomatosis

Graphical abstract



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In brief

Leptomeningeal disease is associated with poor survival. Vaz Batista et al. evaluated the efficacy and safety of trastuzumab deruxtecan in a cohort of patients with HER2-positive/-low breast cancer with previously untreated, pathologically confirmed leptomeningeal disease. The results demonstrate promising antitumor activity with a manageable safety profile. Further prospective studies are needed to confirm these findings.

Highlights

- T-DXd revealed a significant median OS of 13.3 months and a median PFS of 8.9 months
- T-DXd showed remarkable intracranial and extracranial activity with a CBR of 71.4%
- The safety profile was consistent with that observed in previous studies with T-DXd

Translation to Patients

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Article

The DEBBRAH trial: Trastuzumab deruxtecan in HER2-positive and HER2-low breast cancer patients with leptomeningeal carcinomatosis

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CONTEXT AND SIGNIFICANCE Leptomeningeal disease leads to poor outcomes due to limited treatment options. With no specific approved drugs for patients with advanced breast cancer with brain metastases and/or leptomeningeal disease, the DEBBRAH trial is investigating the efficacy and safety of trastuzumab deruxtecan in this specific patient population. Here, Vaz Batista et al. report the results of cohort 5, which specifically included patients with human epidermal growth factor receptor 2 (HER2)-positive and HER2-low breast cancer with pathologically confirmed leptomeningeal disease. The authors demonstrated promising anti-tumor activity of trastuzumab deruxtecan with no new safety concerns. These findings highlight the need for further investigation into the management of patients with breast cancer with leptomeningeal involvement and suggest the possibility of making this challenging condition more treatable with the introduction of new therapies.

SUMMARY

Background: Leptomeningeal disease (LMD) is associated with poor survival and diminished quality of life. Trastuzumab deruxtecan (T-DXd) has shown remarkable intracranial and extracranial activity in human epidermal growth factor receptor 2 (HER2)-positive and HER2-low advanced breast cancer (ABC). The DEBBRAH trial was designed to evaluate its efficacy and safety in patients with HER2-positive and HER2-low ABC with a history of brain metastases (BMs) and/or LMD. Here, we report results from cohort 5, which specifically included patients with pathologically confirmed LMD.

Methods: This single-arm, open-label, five-cohort, phase 2 trial enrolled seven patients in cohort 5 who received 5.4 mg/kg T-DXd intravenously every 21 days until disease progression or unacceptable toxicity.



The primary endpoint was overall survival (OS). Key secondary endpoints included progression-free survival (PFS) and safety profile.

Findings: At data cutoff (April 4, 2023), the median duration of follow-up was 12.0 months (range, 2.5–18.6). The median OS was 13.3 months (95% confidence interval [CI], 5.7–NA, $p < 0.001$), meeting the primary endpoint. The median PFS was 8.9 months (95% CI, 2.1–NA). Two (28.6%) of seven patients remained on treatment after 18.6 and 11.9 months, respectively. Of the five patients who progressed and died, none had intracranial progression or clinical worsening of leptomeningeal symptoms. Notably, 71.4% (95% CI, 29.0–96.3) achieved prolonged stabilization (≥ 24 weeks) by response evaluation criteria in solid tumors (RECIST) v.1.1. No unexpected safety signals and no treatment-related deaths were observed.

Conclusions: T-DXd showed promising antitumor activity in patients with HER2-positive and HER2-low ABC with previously untreated, pathologically confirmed LMD. These encouraging data warrant further investigation to address the unmet need in this difficult-to-treat condition.

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INTRODUCTION

Leptomeningeal disease (LMD) occurs in approximately 10% of patients with advanced breast cancer (ABC) and represents a devastating clinical entity that is associated with a poor prognosis with limited available therapeutic options.¹ In consequence, LMD represents a major challenge in patients with ABC.

The demonstration of malignant cells in cerebrospinal fluid (CSF) is the current gold standard for the diagnosis of LMD. However, conventional CSF cytology has low sensitivity, and therefore, frequently, several CSF samples are required to confirm the diagnosis of LMD. Accordingly, many patients do not have an unequivocal pathological confirmation of LMD.

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate consisting of a humanized anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody linked to a topoisomerase I inhibitor payload through a tetrapeptide-based cleavable linker that has demonstrated remarkable intracranial and extracranial efficacy in patients with HER2-positive and HER2-low ABC in different studies.^{2–7}

Limited data from retrospective studies also suggest significant antitumor activity of T-DXd in patients with HER2-positive breast cancer with LMD,^{1,8} but the efficacy of T-DXd in patients with HER2-low breast cancer and LMD has not been specifically assessed. Moreover, these patients are systematically excluded from participation in most clinical trials, and therefore, there is a lack of prospective data.

The DEBBRAH study was designed to evaluate the efficacy and safety of T-DXd in patients with HER2-positive and HER2-low breast cancer with a history of brain metastases and/or LMD. Here, we present the final results from patients with HER2-positive and HER2-low breast cancer with previously untreated, pathologically confirmed LMD who were included in cohort 5.

RESULTS

Patient disposition and baseline characteristics

Between April 2021 and April 2022, a total of seven patients with LMD were enrolled in cohort 5 (Figure 1). Radiographic findings of LMD and a positive baseline CSF were confirmed in all pa-

tients. The median age was 55 years (range, 40–67). Of the seven patients, three (42.9%) were HER2-positive, and four (57.1%) were HER2-low. Synchronous extracranial metastases were found in six patients (85.7%), two of whom (28.6%) also presented brain metastases. At baseline, three patients (42.9%) had measurable disease. Of these, two had measurable lesions in the liver, and one had measurable lesions in the brain. The median number of previous lines of therapy for advanced disease was 4 (range, 1–8), with no patient having undergone prior local treatment and/or intrathecal therapy for central nervous system involvement (Table 1).

Clinical activity

At data cutoff (April 4, 2023), the median duration of follow-up was 12.0 months (range, 2.5–18.6). A total of two (28.6%) of the seven patients were alive and remained on treatment after 18.6 (HER2-positive patient) and 11.9 (HER2-low patient) months. The other five patients (71.4%) discontinued treatment due to progressive disease and died. Of these patients who progressed, none had radiological intracranial progression or clinical worsening of leptomeningeal symptoms at the time of treatment failure, four (57.1%) presented extracranial progression, and one (14.3%) had a clinical progression (Figure 2).

The median overall survival (OS) was 13.3 months (95% confidence interval [CI], 5.7–not achieved [NA] $p < 0.001$), meeting the primary endpoint (Figure 3). The 1-year OS rate was 57.1% (95% CI, 30.1–100.0) for all included patients. The patient with the shortest survival time (2.5 months) was later identified by central assessment as HER2-negative.

The median progression-free survival (PFS) was 8.9 months (95% CI, 4.9–NA) according to response evaluation criteria in solid tumors (RECIST) v.1.1 criteria (Figure 4). The 1-year PFS was 28.6% (95% CI, 8.9–92.2) for all included patients.

No objective responses were observed extracranially, but five of the seven patients (71.4%) had a prolonged stabilization (≥ 24 weeks) by RECIST v.1.1 for an overall clinical benefit rate (CBR) of 71.4% (95% CI, 29.0–96.3). One patient (14.3%), initially presenting with non-measurable disease, achieved a complete response of the intracranial lesion by response assessment in neuro-oncology brain metastases (RANO-BM) criteria. Individual data for HER2/hormone

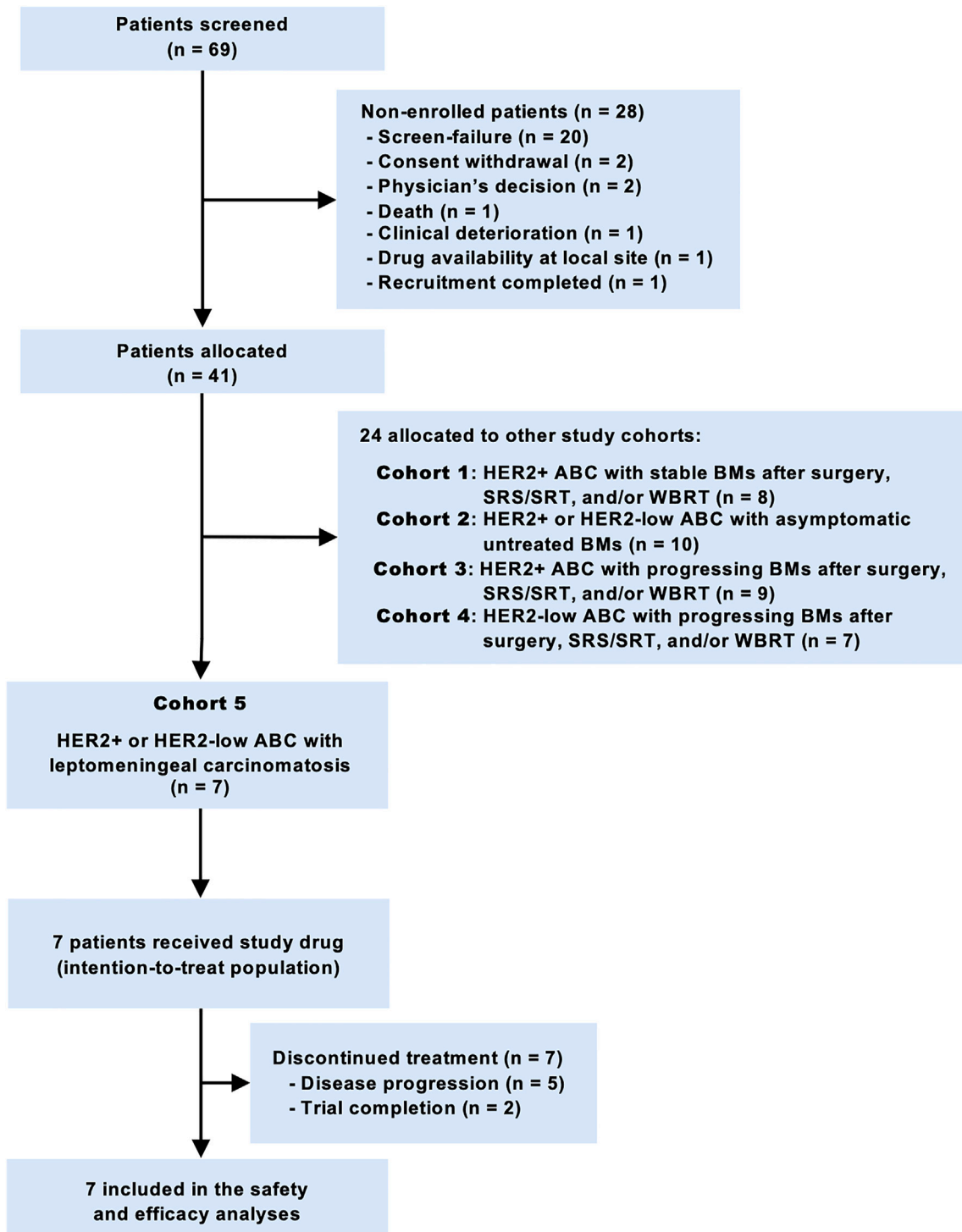


Figure 1. Patient enrollment and disposition

ABC, advanced breast cancer; BMs, brain metastases; HER2, human epidermal growth factor receptor 2; HER2-positive: HER2+; SRS, stereotactic radio-surgery; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

Table 1. Baseline characteristics of patients with leptomeningeal disease

Baseline characteristics	Cohort 5, N = 7
Age, median (min; max), years	55.0 (40.0; 67.0)
Female sex, n (%)	7 (100)
ECOG performance status, ^a n (%)	
0	3 (42.8)
1	2 (28.6)
2	2 (28.6)
HER2 status, ^b n (%)	
Positive	3 (42.9)
Low	4 (57.1)
Hormone receptor status, n (%)	
ER+ and/or PgR+	5 (71.4)
ER– and PgR–	2 (28.6)
Measurable disease at baseline, n (%), N = 3	
Intracranial	1 (14.3)
Extracranial	3 (42.9)
No. of metastatic sites, ^c n (%)	
<3	6 (85.7)
≥3	1 (14.3)
Metastatic organ sites, n (%)	
Bone	3 (42.9)
Liver	3 (42.9)
Brain ^c	2 (28.6)
Lung	2 (28.6)
Lymph nodes	1 (14.3)
Other ^d	2 (28.6)
No. of previous lines of therapy for advanced disease, median (min; max)	
Duration of last prior therapy, median (min; max), months	1.9 (0.7; 15)
Prior systemic therapy, n (%)	
Anti-HER2	3 (42.9)
Trastuzumab	3 (42.9)
Pertuzumab	3 (42.9)
Trastuzumab emtansine	3 (42.9)
Lapatinib	1 (14.3)
Chemotherapy	7 (100)
Endocrine therapy	3 (42.9)
Prior local therapy for brain metastases, n (%)	
WBRT	0 (0)
SRS/SRT	0 (0)
Surgery	0 (0)

All values are n (%) unless otherwise specified (percentage based on N). ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor 2; PgR, progesterone receptor; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.

^aECOG performance status scores range from 0 to 5, with a higher score indicating greater disability.

^bHER2 low was defined as immunohistochemistry 1+ or 2+ and ISH negative. One HER2-low patient was later identified as HER2 negative by central assessment.

^cExcluding leptomeningeal carcinomatosis.

^dOne patient had a non-target lesion in the eye, and another had non-target lesions in the stomach and intestines.

receptor status, OS, PFS, and best overall response are detailed in [Table 2](#) and [Figure S1](#).

Safety analysis

The median relative dose intensity of T-DXd was 99.0% (interquartile range, 93.1–100.6) in all patients, and the median duration of the treatment was 9.0 months (range, 2.1–18.6).

All patients experienced at least one treatment-emergent adverse event (TEAE), and there were no grade (G) 4 or 5 TEAEs registered. The most common non-hematological TEAEs of any grade were nausea (57.1%; 14.3% G3), fatigue (42.9%; 0% G3), vomiting (42.9%; 0.0% G3), headache (42.9%; 0.0% G3), and urinary tract infection (42.9%; 0.0% G3). Anemia (42.9%; 0.0% G3) and thrombocytopenia (28.6%; 14.3% G3) were the most frequent hematological TEAEs. No cases of interstitial lung disease/pneumonitis were reported. Serious unrelated TEAEs occurred in four (57.1%) patients, and one patient experienced a serious related TEAE (G3 nausea). No treatment-related deaths were reported ([Table 3](#)).

None of the seven patients experienced a TEAE leading to a dose reduction or discontinuation of T-DXd. Two (28.6%) patients had their study treatment temporarily withheld due to serious TEAEs unrelated to the study treatment. These serious TEAEs included G3 pneumonia lasting 9 days and G3 pneumothorax lasting 5 days.

Patient-reported outcomes

There was no significant decrease in global health status at 24 weeks using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (mean score, 41.7 ± 25.3 vs. 56.7 ± 10.9; *p* = 0.197). Similarly, no other parameters within the QLQ-C30 and QLQ-BR23 scales were significantly affected at 24 weeks ([Table S3](#)).

DISCUSSION

In the DEBBRAH study, T-DXd suggested promising antitumor activity for the treatment of patients with HER2-positive and HER2-low breast cancer with previously untreated, pathologically confirmed LMD.

To the best of our knowledge, this is the only prospective study that has evaluated the efficacy of T-DXd in this patient population and the unique clinical data reported in patients with HER2-low ABC.

Treatment with T-DXd led to a remarkable median OS of 13.3 months. These results are encouraging considering that LMD is a condition with a dismal prognosis. Without treatment, the median OS of these patients is around 4–6 weeks, and if they are treated, the median OS can increase to approximately 2–4 months.⁹ Additionally, the CBR (71.4%) and median PFS (8.9 months) were also encouraging.

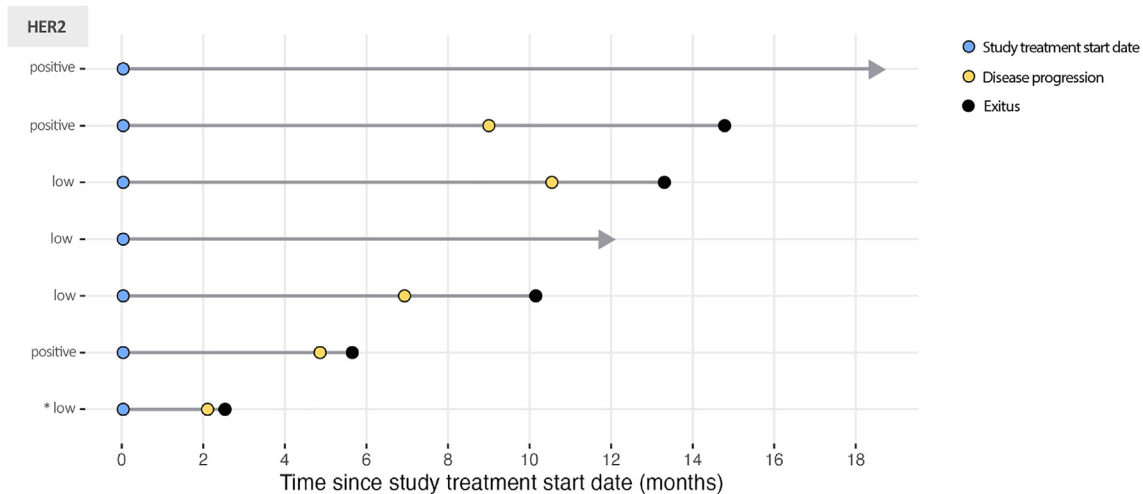


Figure 2. Swimmer plot of patient status

*This patient was initially classified as HER2 low and later centrally assessed as HER2 negative.

The retrospective chart review study ROSET-BM evaluated the efficacy and safety of T-DXd in a standard-of-care setting in 104 heavily pretreated patients with HER2-positive breast cancer with brain metastases and/or LMD.⁸ A total of 17 (16.3%) patients had active brain metastases and LMD, and only two (1.9%) patients had exclusively LMD. A pathological confirmation of LMD was not mandatory in this study. Among 19 patients with LMD, the 1-year PFS and OS rates were 60.7% (95% CI, 34.5–79.1) and 87.1% (95% CI, 57.3–96.6), respectively.

Recently, Alder and colleagues reported the activity of T-DXd in another retrospective study that included eight heavily pretreated patients with HER2-positive breast cancer and LMD.¹ Only three patients had a positive baseline CSF cytology, whereas three had negative CSF cytology, and two patients were not tested. In contrast to the DEBBRAH trial, patients could have received treatment for LMD. Accordingly, seven patients had been treated with prior whole-brain radiation therapy, and two patients had also received intrathecal therapy with trastuzu-

mab. The median OS was 10.4 months (range, 158–514 days), with six patients still alive at the data cutoff.

Consequently, the results from both retrospective studies are in line with the median OS achieved in the DEBBRAH trial, confirming that LMD could be a more treatable condition with the introduction of new HER2-targeted agents. The combination of capecitabine, trastuzumab, and tucatinib has also demonstrated a similar median OS in 17 patients with HER2-positive breast cancer with LMD defined as positive CSF cytology and/or radiographic findings in a single-arm, phase 2 study.¹⁰ A total of five patients (29.0%) had a pathological confirmation of LMD, and eight patients (47.0%) had negative CSF cytology. The median OS was 11.9 months (95% CI, 4.1–NA), with seven patients (41.0%) alive after a median follow-up of 17 months.

We have previously reported the main strengths of the DEBBRAH trial.⁷ For this cohort, main strengths include the mandatory pathological confirmation of LMD through a positive baseline CSF cytology and the quality of the results, considering

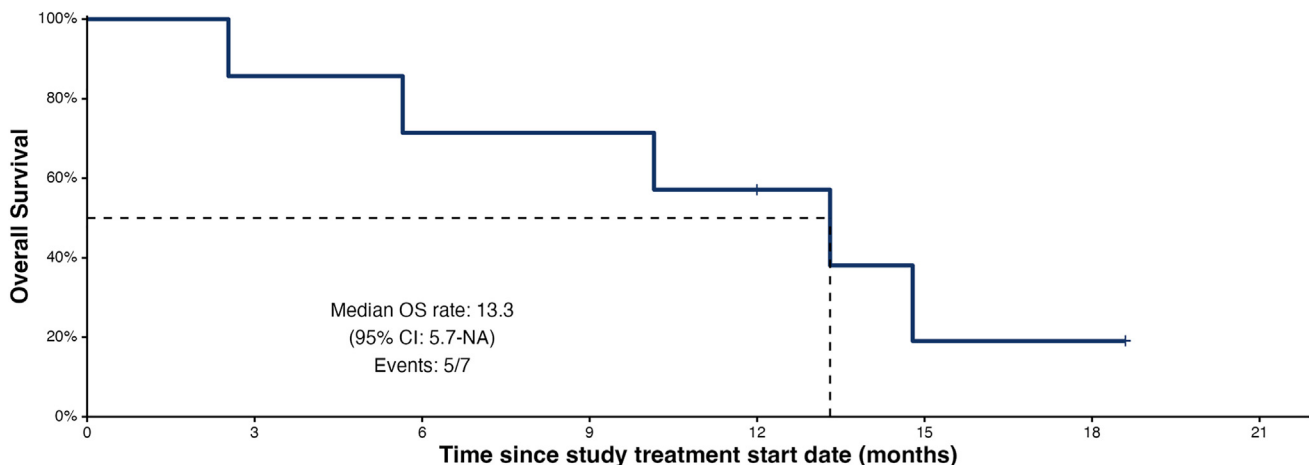


Figure 3. Overall survival in patients with leptomeningeal disease

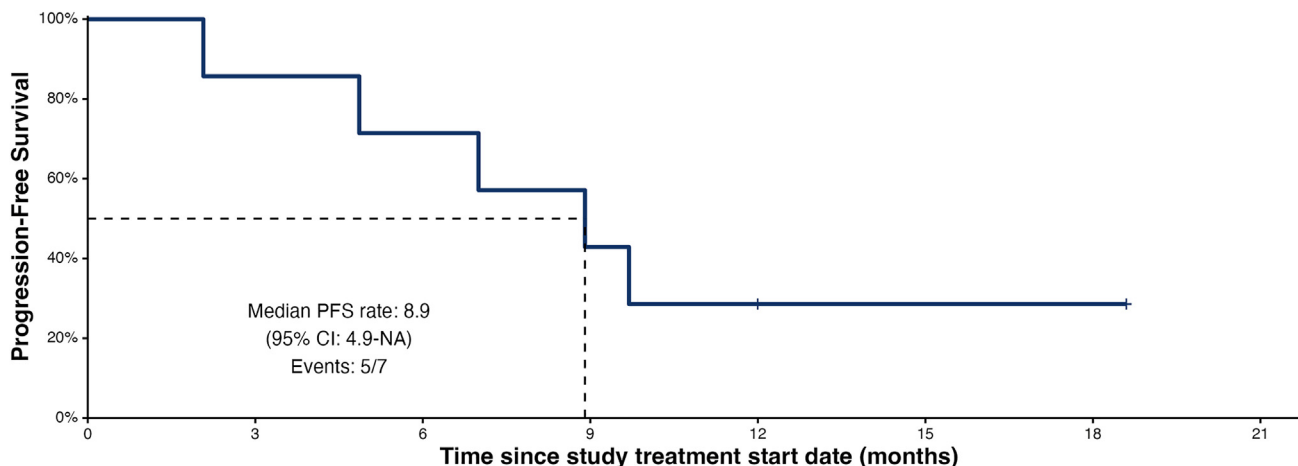


Figure 4. Progression-free survival in patients with leptomeningeal disease according to RECIST v.1.1

that they have been prospectively collected and obtained with well-established analyses and procedures.

A translational substudy is planned using CSF samples from these patients. However, the collection of these samples was not without risks for some patients, and unfortunately, only five patients agreed to provide post-baseline CSF samples. Circulating tumor DNA in the CSF, which is more abundant than in plasma, could help to facilitate and confirm the diagnosis of LMD and also monitor the treatment response.^{11–14}

In conclusion, T-DXd showed promising activity with no new safety concerns in patients with HER2-positive and HER2-low breast cancer with previously untreated, pathologically confirmed LMD. These preliminary data warrant further investigation to address the unmet need in this difficult-to-treat condition and represent a potential shift toward a more treatable disease.

Limitations of the study

The main limitations include the small sample size and lack of a neurocognitive scale in the study assessments despite the overall change from baseline in patient-reported global health status/

quality of life using the EORTC QLQ-C30 and QLQ-BR23 questionnaires being an exploratory endpoint. Therefore, while we have quality-of-life data, we do not have results from a specific neurocognitive scale to assess changes in the clinical neurological condition of these patients.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Dr. Javier Cortés (javier.cortes@maj3.health).

Materials availability

This study did not generate new reagents.

Data and code availability

Data collected within this study will be made available to researchers after contacting the [lead contact](#) and upon revision and approval based on scientific merit by the DEBBRAH trial management group (which includes a qualified statistician) of a detailed proposal for their use. The data required for the approved, specified purposes, the trial protocol, and the statistical analysis plan will be provided after the completion of a data sharing agreement that

Table 2. Summary of responses

HER2/HR status	OS		PFS		Best response		
	Months	Death	Months	Events	RANO-BM	RECIST extracranial	RECIST all lesions
HER2+/HR+	14.8	yes	8.9	PD	SD ≥ 24 w	SD ≥ 24 w	SD ≥ 24 w
HER2+/HR+	5.6	yes	5.6	PD	non-CR/non-PD <24 w	NE	non-CR/non-PD <24 w
HER2+/HR–	18.6	no	18.6	no	Non-CR/non-PD ≥24 w	non-CR/non-PD ≥24 w	non-CR/non-PD ≥24 w
HER2-low/HR+	10.1	yes	6.9	PD	non-CR/non-PD ≥24 w	SD ≥ 24 w	SD ≥ 24 w
HER2-low/HR+	13.3	yes	9.7	PD	CR ^a	non-CR/non-PD ≥24 w	non-CR/non-PD ≥24 w
HER2-low/HR+	11.9	no	11.9	no	NE	non-CR/non-PD ≥24 w	non-CR/non-PD ≥24 w
HER2-low/HR– ^b	2.5	yes	2.0	PD	NE	PD	PD

CR, complete response; HER2, human epidermal growth factor receptor 2; HR: hormone receptor; NE, non-evaluable; OS, overall survival; PFS, progression-free survival; PD, progression disease; RANO-BM, response assessment in neuro-oncology brain metastases; RECIST, response evaluation criteria in solid tumors; SD, stable disease; w, weeks.

^aPatient with non-measurable disease only at baseline had a complete disappearance of the intracranial lesion and negative CSF. Extracranial lesions persisted. Intracranial BOR was defined as CR, and extracranial and overall BORs were defined as non-CR/non-PD.

^bThis patient was later identified as HER2 negative by central assessment.

Table 3. Treatment-emergent adverse events occurring in $\geq 15\%$ of patients with leptomenigeal disease

System organ class preferred term	Overall (N = 7)	
	Any grade, n (%)	Grade 3, n (%)
Any	7 (100)	3 (42.9)
Hematological	4 (57.1)	1 (14.3)
Anemia	3 (42.9)	0 (0)
Thrombocytopenia	2 (28.6)	1 (14.3)
Non-hematological	7 (100)	3 (42.9)
Nausea	4 (57.1)	1 (14.3)
Headache	3 (42.9)	0 (0)
Fatigue	3 (42.9)	0 (0)
Urinary tract infection	3 (42.9)	0 (0)
Vomiting	3 (42.9)	0 (0)
Gamma-glutamyltransferase increased	2 (28.6)	1 (14.3)
Constipation	2 (28.6)	0 (0)
Diplopia	2 (28.6)	0 (0)
Dizziness	2 (28.6)	0 (0)

At data cutoff, the 7 patients who were enrolled in cohort 5 received at least one dose of study drug and were included in the safety set.

will be set up by the study sponsor, beginning 1 month and ending 5 years after article publication. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. Estimate time frame for response will be within 30 days. Please, address requests for data to the [lead contact](#).

The code for the calculation of sample size and the analysis of the primary endpoint of this manuscript is reported in supplementary methods ([Method S1](#). R code for sample size and primary analysis calculation. Related to [STAR Methods](#)).

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AUTHOR CONTRIBUTIONS

Conception and design, S.B., J.C., M.V.B., J.M.P.-G., and A.L.-C.; data analysis, M.S.-C. and D.A.-L.; data interpretation, all authors; manuscript writing and review, all authors; final approval of manuscript, all authors; accountable for all aspects of the work, all authors.

DECLARATION OF INTERESTS

M.V.B. reports participating in a consulting/advisory board for AstraZeneca; participating as an invited speaker for Daiichi Sankyo and Nutricia; and receiving travel fees from AstraZeneca, Daiichi Sankyo, Pfizer, and GSK. J.M.P.-G. reports having a consulting or advisory role for Lilly, Roche, Eisai, Daiichi Sankyo, AstraZeneca, and Seattle Genetics; receiving travel compensation from Roche; and employment at MEDSIR. J.A.G.-S. declares consultative and advisory services for Seagen, AstraZeneca, Daiichi Sankyo, Novartis, Gilead, and Menarini; consultancy/speaker fees from Celgene, Eli Lilly, Eisai, MSD, Exact Sciences, Tecnofarma, Nolver (Adium), Asofarma, and Roche; institution and research funding from AstraZeneca; and travel support from Gilead, AstraZeneca, and Daiichi Sankyo. M.R.-B. reports serving as a consultant to Roche and Puma and receiving honoraria from Roche/Genentech, Pfizer, and Novartis. M.F.-A. reports participating in an advisory board for Seagen and Daiichi Sankyo-AstraZeneca and speakers' bureau from Novartis and Lilly. M.G. reports

receiving honoraria from Roche, Novartis, Gilead, and Daiichi Sankyo and travel compensation from Roche, Pfizer, and Daiichi Sankyo. G.M. is a full-time employee at MEDSIR. D.A.-L. is a full-time employee at MEDSIR. J.P.-E. is a full-time employee at MEDSIR. M.S.-C. reports participating in an advisory board for Optimapharm, Ability Pharma, and MD Anderson and is a full-time employee at MEDSIR. A.L.-C. reports receiving research support from Roche, Agendia, Lilly, Pfizer, Novartis, Merck Sharp & Dohme, Gilead, and Daiichi Sankyo; consulting or advisory roles for Lilly, Roche, Pfizer, and Novartis; speakers' bureaus from Lilly, AstraZeneca, and Merck Sharp & Dohme; travel support from Roche, Pfizer, and AstraZeneca; and stock or other ownership of MEDSIR and Initia-Research. S.B. reports participating in a consulting/advisory board for Daiichi Sankyo, AstraZeneca, Novartis, and Roche; participating as an invited speaker for Daiichi Sankyo, AstraZeneca, Novartis, and Roche. J.C. reports serving as a consultant/advisor to Roche, Celgene, Cellestia, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex, Polyphor, Lilly, Merck Sharp & Dohme, GSK, Leuko, Bioasis, Clovis Oncology, Boehringer Ingelheim, Ellipses, HiberCell, Biolnvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, and Expres2ion Biotechnologies; receiving honoraria from Roche, Novartis, Celgene, Eisai, Pfizer, Samsung Bioepis, Lilly, Merck Sharp & Dohme, and Daiichi Sankyo; research funding to the Institution from Roche, Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Eisai, F. Hoffman-La Roche, Guardant Health, Merck Sharp & Dohme, Pfizer, Piquar Therapeutics, Puma C, and Queen Mary University of London; stock of MEDSIR, Nektar Pharmaceuticals, and Leuko (relative); travel, accommodations, and expenses from Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, and Gilead; and the following patents: (1) "Pharmaceutical Combinations of A PI3k Inhibitor And A Microtubule Destabilizing Agent," Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde, WO 2014/199294 A, ISSUED; and (2) "Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy," Aleix Prat, Antonio Llombart, Javier Cortés, US 2019/0338368 A1, LICENSED.

STAR METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- [EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS](#)
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 - Study design and participants

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 - Statistical analysis
- **ADDITIONAL RESOURCES**

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.medj.2024.08.001>.

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REFERENCES

1. Alder, L., Trapani, D., Bradbury, C., Van Swearingen, A.E.D., Tolaney, S.M., Khasraw, M., Anders, C.K., Lascola, C.D., Hsu, L., Lin, N.U., and Sammons, S. (2023). Durable responses in patients with HER2+ breast cancer and leptomeningeal metastases treated with trastuzumab deruxtecan. *NPJ Breast Cancer* 9, 19. <https://doi.org/10.1038/s41523-023-00519-0>.
2. (2022). (2022). ENHERTU® (Fam-trastuzumab Deruxtecan-Nxki) [package insert] (Daiichi Sankyo Inc.). Basking Ridge.
3. Hurvitz, S.A., Hegg, R., Chung, W.-P., Im, S.-A., Jacot, W., Ganju, V., Chi, J.W.Y., Xu, B., Hamilton, E., Madhusudan, S., et al. (2023). Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet* 401, 105–117. [https://doi.org/10.1016/S0140-6736\(22\)02420-5](https://doi.org/10.1016/S0140-6736(22)02420-5).
4. André, F., Park, Y.H., Kim, S.-B., Takano, T., Im, S.-A., Borges, G., Lima, J.P., Aksoy, S., Gregori, J.G., Laurentiis, M.D., et al. (2023). Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 401, 1773–1785. [https://doi.org/10.1016/S0140-6736\(23\)00725-0](https://doi.org/10.1016/S0140-6736(23)00725-0).
5. Modi, S., Saura, C., Yamashita, T., Park, Y.H., Kim, S.-B., Tamura, K., Andre, F., Iwata, H., Ito, Y., Tsurutani, J., et al. (2020). Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N. Engl. J. Med.* 382, 610–621. <https://doi.org/10.1056/NEJMoa1914510>.
6. Modi, S., Jacot, W., Yamashita, T., Sohn, J., Vidal, M., Tokunaga, E., Tsurutani, J., Ueno, N.T., Prat, A., Chae, Y.S., et al. (2022). Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N. Engl. J. Med.* 387, 9–20. <https://doi.org/10.1056/NEJMoa2203690>.
7. Pérez-García, J.M., Vaz Batista, M., Cortez, P., Ruiz-Borrego, M., Cejalvo, J.M., de la Haba-Rodríguez, J., Garrigós, L., Racca, F., Servitja, S., Blanch, S., et al. (2023). Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: The DEBBRAH trial. *Neuro Oncol.* 25, 157–166. <https://doi.org/10.1093/neuonc/noac144>.
8. Niikura, N., Yamanaka, T., Nomura, H., Shiraishi, K., Kusama, H., Yamamoto, M., Matsuura, K., Inoue, K., Takahara, S., Kita, S., et al. (2023). Treatment with trastuzumab deruxtecan in patients with HER2-positive breast cancer and brain metastases and/or leptomeningeal disease (ROSET-BM). *NPJ Breast Cancer* 9, 82–88. <https://doi.org/10.1038/s41523-023-00584-5>.
9. Nayar, G., Ejikeme, T., Chongsathidkiet, P., Elsamacidy, A.A., Blackwell, K.L., Clarke, J.M., Lad, S.P., and Fecci, P.E. (2017). Leptomeningeal disease: current diagnostic and therapeutic strategies. *Oncotarget* 8, 73312–73328. <https://doi.org/10.18632/oncotarget.20272>.
10. Stringer-Reasor, E.M., O'Brien, B.J., Topletz-Erickson, A., White, J.B., Lobbous, M., Riley, K., Childress, J., LaMaster, K., Melisko, M.E., Morikawa, A., et al. (2021). Pharmacokinetic (PK) analyses in CSF and plasma from TBCRC049, an ongoing trial to assess the safety and efficacy of the combination of tucatinib, trastuzumab and capecitabine for the treatment of leptomeningeal metastasis (LM) in HER2 positive breast cancer. *J. Clin. Oncol.* 39, 1044. https://doi.org/10.1200/JCO.2021.39.15_suppl.1044.
11. Mouliere, F., Mair, R., Chandrananda, D., Marass, F., Smith, C.G., Su, J., Morris, J., Watts, C., Brindle, K.M., and Rosenfeld, N. (2018). Detection of cell-free DNA fragmentation and copy number alterations in cerebrospinal fluid from glioma patients. *EMBO Mol. Med.* 10, e9323. <https://doi.org/10.15252/emmm.201809323>.
12. White, M.D., Klein, R.H., Shaw, B., Kim, A., Subramanian, M., Mora, J.L., Giobbie-Hurder, A., Nagabhushan, D., Jain, A., Singh, M., et al. (2021). Detection of Leptomeningeal Disease Using Cell-Free DNA From Cerebrospinal Fluid. *JAMA Netw. Open* 4, e2120040. <https://doi.org/10.1001/jamanetworkopen.2021.20040>.
13. Pentsova, E.I., Shah, R.H., Tang, J., Boire, A., You, D., Briggs, S., Omuro, A., Lin, X., Fleisher, M., Grommes, C., et al. (2016). Evaluating Cancer of the Central Nervous System Through Next-Generation Sequencing of Cerebrospinal Fluid. *J. Clin. Orthod.* 34, 2404–2415. <https://doi.org/10.1200/JCO.2016.66.6487>.
14. De Mattos-Arruda, L., Mayor, R., Ng, C.K.Y., Weigelt, B., Martínez-Ricarte, F., Torrejon, D., Oliveira, M., Arias, A., Raventos, C., Tang, J., et al. (2015). Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. *Nat. Commun.* 6, 8839. <https://doi.org/10.1038/ncomms9839>.
15. M. Vaz Batista, J.M. Pérez-García, A. Llombart Cussac, P. Cortez, M. Ruiz Borrego, J. De La Haba, J.M. Cejalvo, F. Racca, S. Servitja, S. Blanch, et al. 330TiP - Trastuzumab deruxtecan (T-DXd; DS-8201) in HER2-positive (HER2+) and HER2-low expressing (HER-LE) metastatic breast cancer (MBC) with brain metastases (BM) and/or leptomeningeal carcinomatosis (LMC): DEBBRAH. In (Ann. Oncol., pp. S457–S515. 10.1016/annonc/annonc689..
16. Vaz Batista, M., Pérez-García, J.M., Garrigós, L., García-Sáenz, J.A., Cortez, P., Racca, F., Blanch, S., Ruiz Borrego, M., Fernández, A., Fernández-Abad, M., et al. (2023). PS11-05- Trastuzumab Deruxtecan in Patients with HER2[+] or HER2-Low Advanced Breast Cancer and Pathologically Confirmed Leptomeningeal Carcinomatosis: Results from Cohort 5 of the DEBBRAH Study. *SABCS 2023*.
17. Wolff, A.C., Hammond, M.E.H., Allison, K.H., Harvey, B.E., Mangu, P.B., Bartlett, J.M.S., Bilous, M., Ellis, I.O., Fitzgibbons, P., Hanna, W., et al. (2018). Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch. Pathol. Lab Med.* 142, 1364–1382. <https://doi.org/10.5858/arpa.2018-0902-SA>.
18. Sampayo-Cordero, M., Miguel-Huguet, B., Malfettone, A., López-Miranda, E., Gion, M., Abad, E., Alcalá-López, D., Pérez-Escuredo, J., Pérez-García, J.M., Llombart-Cussac, A., and Cortés, J. (2023). A single-arm study design with non-inferiority and superiority time-to-event endpoints: a tool for proof-of-concept and de-intensification strategies in breast cancer. *Front. Oncol.* 13, 1048242. <https://doi.org/10.3389/fonc.2023.1048242>.
19. Hitchins, R.N., Bell, D.R., Woods, R.L., and Levi, J.A. (1987). A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. *J. Clin. Oncol.* 5, 1655–1662. <https://doi.org/10.1200/JCO.1987.5.10.1655>.
20. Grossman, S.A., Finkelstein, D.M., Ruckdeschel, J.C., Trump, D.L., Moy-nihan, T., and Ettinger, D.S. (1993). Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 11, 561–569. <https://doi.org/10.1200/JCO.1993.11.3.561>.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
SAS software	SAS Institute Inc	Version 9.4 https://www.sas.com/ ; RRID:SCR_009567
R	The R Foundation for Statistical Computing	Version 4.3.2 https://www.R-project.org/ ; RRID: SCR_001905
Other		
Trastuzumab Deruxtecan	Daiichi Sankyo and Astra Zeneca	DS-8201

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Ethical considerations

This study was conducted in compliance with the Declaration of Helsinki. It was approved by the competent regulatory authorities of Spain (AEMPS) and Portugal (INFARMED), the Ethics Committee of Fundación Instituto Valenciano de Oncología (Valencia, Spain), as well as the institutional review boards at each site. During participants recruitment, the potential participants received all relevant information (both orally and written) about the potential risks and benefits of the trial. All doubts were clarified before enrollment. The decision to participate in the study was voluntary and not remunerated. All patients provided written informed consent.

The characteristics of the participants in this trial are summarized in [Table 1](#). Information on socioeconomic status was not collected.

Study design and participants

DEBBRAH is a single-arm, open-label, five-cohort, phase 2 study conducted across 21 sites in Spain and Portugal. This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), NCT04420598. The study design has been already described.^{7,15,16}

Patients were enrolled into one of five cohorts based on HER2 expression (HER2-positive or HER2-low) and type of central nervous system involvement (stable brain metastases, active brain metastases, or LMD). HER2 status was assessed locally according to the American Society of Clinical Oncology/College of American Pathologists 2018 HER2 testing guidelines.¹⁷ HER2-low breast cancer was defined as HER2 immunohistochemistry (IHC) score 1+ or IHC score 2+ and *in situ* hybridization (ISH)-negative, whereas HER2-positive was defined as HER2 IHC 2+ and ISH-positive or IHC score 3+.¹⁷

Cohort 5 specifically included patients with either HER2-positive or HER2-low breast cancer with previously untreated, pathologically confirmed LMD defined as a positive baseline CSF cytology. Prior treatment with a taxane and a HER2-targeted therapy (if HER2-positive patients), excluding T-DXd, with at least one line of chemotherapy (if HER2-low and hormone receptor-negative), or with at least one line of chemotherapy and one line of endocrine therapy (if HER2-low and hormone receptor-positive) for advanced disease was mandatory. Additional requirements include an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, a life expectancy over 12 weeks, an adequate bone marrow function, and a left ventricular ejection fraction $\geq 50\%$ within 28 days before enrollment. No prior local and/or systemic treatment for LMD was permitted. Full eligibility criteria are listed in [Tables S1](#) and [S2](#).

METHODS DETAILS

Procedures

Study procedures have been previously reported.^{7,15,16} In brief, patients received 5.4 mg/kg of T-DXd as an intravenous infusion on day 1 of each 21-day cycle until progressive disease, unacceptable toxicity, death, withdrawal from study, or study completion. Prophylactic anti-emetic agents prior to infusion of T-DXd were recommended in accordance with the prescribing information or institutional guidelines.

A brain magnetic resonance imaging (MRI) and a whole-body computed tomography or MRI were conducted at baseline, every 6 weeks up to week 24, and every 9 weeks thereafter. Bone scans were carried out at baseline and repeated during study only if bone involvement was found at baseline, unless clinically or biochemically suspected bone progression.⁷

Patients had to agree to undergo spinal taps or had to be willing to have an Ommaya reservoir placed for CSF assessment, at baseline, every 3 weeks for 12 weeks, and every 6 weeks thereafter.¹⁶

Patient-reported outcomes were evaluated using the EORTC QLQ-C30 and the QLQ-BR23 breast cancer module questionnaires at baseline, on day 1 of cycles 2–4, followed by day 1 of every alternate cycle starting with cycle 6. Additionally, assessments were conducted at the end-of-treatment visit and every three months thereafter until the initiation of alternative anti-cancer therapy.

Outcomes

The primary endpoint for cohort 5 was OS, defined as the time from treatment initiation to death from any cause. Patients without documented death at the time of the final analysis were censored at the date of the last follow-up. Secondary endpoints were PFS, overall response rate, CBR, time to response, duration of response, and the best percentage of change from baseline in the size of tumor lesions using RANO-BM criteria for intracranial lesions and RECIST v.1.1 criteria for extracranial and overall lesions; and safety, following Common Terminology Criteria for Adverse Events version 5.0. Exploratory endpoints were patient-reported global health status/quality of life through the use of the EORTC QLQ-C30 and QLQ-BR23 questionnaires and the relationship between tissue -and/or blood- and/or CSF-based biomarkers, patient clinical characteristics and outcomes.^{7,16} Some secondary endpoints and all exploratory endpoints are currently under study and not reported here.

Statistical analysis

All treated patients that met the selection criteria were included in the efficacy and safety analysis. This study followed a one-stage time-to-event design for cohort 5. The primary analysis for cohort 5 was designed to test the null and alternative hypotheses that the true median OS were ≤ 2 months and ≥ 6 months, respectively. OS was tested with the maximum likelihood method for exponential distribution¹⁸ based on previous studies.^{19,20} We estimated that seven patients with five OS events are needed to attain an 80% power at the nominal level of one-sided α of 0.05. We assumed 18 months of accrual and a 6 months of follow-up period. A positive finding in cohort 5 was defined with a median OS ≥ 4.2 months.

OS and PFS were estimated using the Kaplan-Meier method, reporting the median with two-sided 95% CI from the Brookmeyer and Crowley method with log-log transformation. Clopper-Pearson methodology was used to calculate the 95% CI for clinical benefit. The R code for the calculation of sample size and the analysis of primary endpoint is reported in [Methods S1](#).

ADDITIONAL RESOURCES

The data were presented in part as poster spotlight presentation at the following meeting: 2023 San Antonio Breast Cancer Symposium in San Antonio, Texas, USA (December 5-9, 2023). "Trastuzumab Deruxtecan in patients with HER2[+] or HER2-Low Advanced Breast Cancer and Pathologically Confirmed Leptomeningeal Carcinomatosis: Results from Cohort 5 of the DEBBRAH Study". Presentation ID: PS11-05 (<https://doi.org/10.1158/1538-7445.SABCS23-PS11-05>).