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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

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Background

- Leptomeningeal carcinomatosis (LMC) occurs in approximately 10% of patients (pts) with advanced breast cancer (ABC) and represents a devastating complication that is associated with a poor prognosis due to limited available therapeutic options [1]. Historically, data have shown that without treatment, the median overall survival (OS) of these pts is around 4–6 weeks and, if treated, the median OS can increase to approximately 2-4 months[2].
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate containing a humanized monoclonal anti-HER2 antibody linked to a potent topoisomerase I inhibitor as the cytotoxic drug [3]. Unlike other antibody-drug conjugates, T-DXd has a released payload that easily crosses the cell membrane and possesses a short half-life, leading to a potent cytotoxic effect on neighboring tumor cells (called "bystander effect") with a reduced systemic exposure [4,5].
- Limited data from retrospective studies also suggest a significant antitumor activity of T-DXd in HER2[+] ABC pts with LMC [1,6], but the efficacy of T-DXd in pts with HER2-low ABC and LMC has not been specifically assessed. Moreover, these pts are rare and usually excluded from participation in most clinical trials and, therefore, there is a lack of prospective data.

Objective

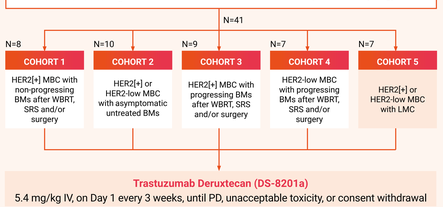
- To assess the efficacy and safety of T-DXd in HER2[+] and HER2-low ABC pts with brain metastases and/or LMC. Here, we report primary results from **cohort 5,** which included **pts with pathologically confirmed LMC.**

Study design

Figure 1. Study Design of DEBBRAH (NCT04420598)

Key Eligibility Criteria

- Female or male pts aged ≥18 years.
- HER2[+] or HER2-low ABC pts with stable, progressing, or untreated BMs and/or LMC.
- ECOG PS 0 or 1 (0–2 for **cohort 5**).
- Pts with HER2[+] ABC: prior taxane-based regimen and ≥1 prior line of HER2-targeted therapy in the metastatic setting.
- Pts with HER2-low ABC and:
  - HR[-]: ≥1 prior regimen of CT in the metastatic setting.
  - HR[+]: 1 prior line of ET and ≥1 prior regimen of CT in the metastatic setting.
- **Cohorts 2, 3, 4:** Measurable brain disease on T1-weighted, gadolinium-enhanced MRI.
- **Cohort 5:** LMC with positive CSF cytology results.



Abbreviations: ABC, advanced breast cancer; **BMs,** brain metastases; **CSF**, Cerebrospinal fluid; **CT**, chemotherapy; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ET**, endocrine therapy; **HR**, hormone receptor; **IV**, intravenously; **LMC**, leptomeningeal carcinomatosis; **MBC**: metastatic breast cancer; **MRI**, magnetic resonance imaging; **SRS**, stereotactic radiosurgery; **WBRT**, whole-brain radiation therapy.

Methods

- This is an international, investigator-initiated, open-label, multicenter, single-arm, five-cohort, phase 2 trial (NCT04420598) **(Figure 1)**.
- Pts received T-DXd until progressive disease (PD), unacceptable toxicity, consent withdrawal, or death.

Primary Endpoint

Cohort 5

- To assess the median OS.

Secondary Endpoints

Cohort 5

- To assess the median progression-free survival (PFS), overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), duration of response (DoR), and best percentage of change in tumor burden 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 lesions and overall lesions; and safety per NCI-CTCAE v.5.0.

Exploratory Endpoints

Cohort 5

- To assess patient reported outcomes using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-30) and QLQ-BR23.
- To evaluate predictive and/or prognostic factors on plasma and/or tissue biopsies and/or cerebrospinal fluid (CSF) samples.

Study Assessments

- Tumor imaging of thorax and abdomen by computerized tomography scan or MRI performed at baseline, every 6 weeks for the first 6 months and, thereafter, every 9 weeks until the end of the study visit.
- Brain MRI performed at baseline, every 6 weeks for the first 6 months, and every 9 weeks thereafter, unless clinically suspected brain progression.
- Axis assessment by MRI together with spinal tap for CSF collection every 3 weeks for the first 12 weeks, every 6 weeks thereafter, and at the time of treatment progression or study termination.

Statistics

- Sample size was planned to attain an 80% power at nominal level of one-sided α of 0.05 in each cohort (described below for cohort 5).

Cohort 5

- Analysis based on the one-sided maximum likelihood exponential test.
- H0: median OS≤2 months; Ha: median OS≥6 months.

Results

1. Recruitment and Patient Disposition

- From April 14, 2021, through April 5, 2022, 7 pts were enrolled into cohort 5, across 6 hospitals in Spain **(Table 1)**.
- Data cutoff date: April 4, 2023
- The median follow-up was 12 months (range, 2.5-18.6 months)

Table 1. Patient Demographic Characteristics at Baseline

Baseline characteristics, n (%)	Cohort 5 (N = 7)
Age, median (range), years	57 (42-69)
ECOG PS, %	
0	3 (42.9%)
1	2 (28.6%)
2	2 (28.6%)
Measurable systemic disease at baseline (N=4)	
Intracranial	1 (14.3%)
Extracranial	3 (42.9%)
Number of metastatic organ sites *	
< 3	6 (85.7%)
≥ 3	1 (14.3%)
HER2 status, %	
Positive	3 (42.9%)
Low	4 (57.1%)
HR status, %	
ER+ and/or PgR+	5 (71.4%)
ER- and PgR-	2 (28.6%)
Any prior local therapy for CNS disease, %	
WBRT	0 (0%)
SRS/SRT	0 (0%)
Surgery	0 (0%)
Number of previous lines in advance disease	
Median (Min; Max)	4 (1; 8)
Duration in months of last prior therapy	1.9
Median (Min; Max)	(0.7; 15)
Previous systemic cancer therapy, %	
Anti-HER2	3 (42.9%)
Chemotherapy	7 (100%)
Endocrine therapy	3 (42.9%)

- Abbreviations: CNS: central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HR: hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PgR, progesterone receptor; SRS/SRT, stereotactic radiosurgery/stereotactic radiotherapy; WBRT, whole-brain radiation therapy.
- n (%), number of patients (percentage based on N); N, Number of patients in the FAS population
- * Excluding the leptomeningeal carcinomatosis

2. Efficacy in Patients with LMC

- **Median OS** was **13.3 months** (95% CI, 2.5-NR, p<0.001) meeting the primary endpoint **(Figure 2)**.
- **Median PFS** was **8.9 months** (95% CI, 2.1-NR) **(Figure 3)**.
- Five of the 7 pts (71.4%, 95% CI: 29.0-96.3) had a prolonged stabilization (≥24 weeks) by RECIST v.1.1. One of them had a complete intracranial response by RANO-BM. **(Table 2 and Table 3)**.
- Of the 5 pts who have progressed, **none had intracranial progression** or clinical worsening of leptomeningeal symptoms at the time of treatment failure.
- At data cutoff, 2 (28.6%) pts remained on therapy **(Table 3)**.

Figure 2. OS

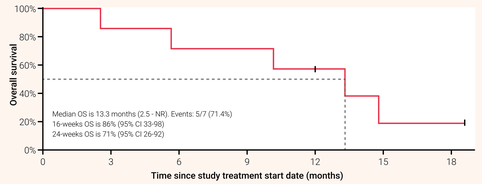


Figure 3. PFS according to RANO-BM and RECIST v1.1

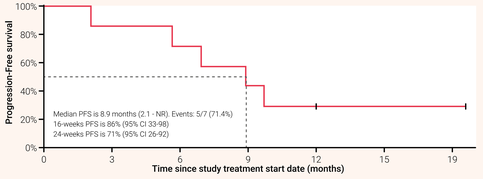


Table 2. Best Response based on Intracranial, Extracranial, and Overall Lesions

	Intracranial	Extracranial	All lesions
Best Overall Response	n = 7	n = 7	n = 7
CR	1 (14.3%)*	0 (0%)	0 (0%)
SD ≥ 24w	1 (14.3%)	2 (28.6%)	2 (28.6%)
SD < 24w	0 (0%)	0 (0%)	0 (0%)
Non-CR/Non-PD ≥ 24w	2 (28.6%)	3 (42.9%)	3 (42.9%)
Non-CR/Non-PD < 24w	1 (14.3%)	0 (0%)	1 (14.3%)
PD	0 (0%)	1 (14.3%)	1 (14.3%)
NE	2 (28.6%)	1 (14.3%)	0 (0%)
Objective Response Rate (ORR)	n = 5	n = 6	n = 7
Yes	1 (20%)	0 (0%)	0 (0%)
No	4 (80%)	6 (100%)	7 (100%)
Clinical Benefit Rate (CBR)	n = 5	n = 6	n = 7
Yes	4 (80%)	5 (83.3%)	5 (71.4%)
No	1 (20%)	1 (16.7%)	2 (28.6%)

*Patient 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 BOR was defined as Non-CR/Non-PD.

Table 3. 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 ≥ 24w	SD ≥ 24w	SD ≥ 24w
HER2+/ HR+	5.6	Yes	5.6	PD	Non-CR/Non-PD < 24w	NE	Non-CR/Non-PD < 24w
HER2+/ HR-	18.6	No	18.6	No	Non-CR/Non-PD ≥ 24w	Non-CR/Non-PD ≥ 24w	Non-CR/Non-PD ≥ 24w
HER2-low/ HR+	10.1	Yes	6.9	PD	Non-CR/Non-PD ≥ 24w	SD ≥ 24w	SD ≥ 24w
HER2-low/ HR+	13.3	Yes	9.7	PD	CR	Non-CR/Non-PD ≥ 24w	Non-CR/Non-PD ≥ 24w
HER2-low/ HR+	11.9	No	11.9	No	NE	Non-CR/Non-PD ≥ 24w	Non-CR/Non-PD ≥ 24w
HER2-low/ HR-	2.5	Yes	2.0	PD	NE	PD	PD

3. Safety in Patients with LMC

- Median duration of treatment was 9.0 months (range, 2.1-18.6).
- The most common treatment emergent adverse events (TEAEs) of any grade (G) were nausea (57.1%; 14.3% G3), fatigue (42.9%; 0% G3), vomiting (42.9%; 0% G3), headache (42.9%; 0% G3), urinary tract infection (42.9%; 0% G3), and anemia (42.9%; 0% G3). No cases of interstitial lung disease/pneumonitis were reported **(Table 4)**.
- Serious unrelated TEAEs occurred in 4 (57.1%) of 7 pts, and 1 pt experienced a related serious TEAE (nausea G3).
- No treatment-related deaths were reported.

Table 4. Related TEAEs Occurring in ≥15% of Patients with LMC

System Organ Class Preferred term, n (%)	Overall (n=7)	
	Any grade	Grade 3
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	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, 7 patients who were enrolled in the cohort 5, received at least one dose of study drug and were included in the safety set.

Conclusions

Despite the limited sample size, T-DXd showed promising activity with no new safety concerns in HER2[+] and HER2-low pts with previously untreated, pathologically confirmed LMC.

Further investigation is needed in larger cohorts to validate the substantial response of LMC to T-DXd in this population.

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