OCTS-03

2024 SNO/ASCO CNS Metastases Conference

LEVERAGING MULTI-SECTOR COLLABORATION TO DISRUPT CNS METASTASES

A multicenter, open-label, single-arm, multicohort phase II clinical trial of trastuzumab deruxtecan in human epidermal growth factor receptor 2 (HER2)-positive and HER2-low advanced breast cancer with brain metastases and/or leptomeningeal carcinomatosis – The DEBBRAH study

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BACKGROUND

- Breast cancer is the second-leading cause of central nervous system (CNS) metastases among solid malignancies[1].
- HER2-targeted therapies has improved the outcomes for patients with HER2-positive breast cancer with brain metastases (BM), however prognosis remains poor, and these patients are often excluded from pivot clinical trials [2,3].
- Trastuzumab Deruxtecan (T-DXd) is an antibody-drug conjugate containing a humanized monoclonal anti-HER2 antibody linked to a potent topoisomerase I inhibitor [3].
- T-DXd is the second-line standard of care for patients with HER2-positive advanced breast cancer (ABC)[4,5] and is approved for previously treated HER2-low ABC [6].
- Encouraging antitumoral activity of T-DXd has been observed in HER2-positive ABC patients with CNS involvement [4, 7-11], however there is limited data for T-DXd for HER2-low tumors and CNS involvement.
- DEBBRAH evaluated the efficacy and safety of T-DXd in patients with HER2-positive and HER2-low ABC with BM and/or leptomeningeal carcinomatosis (LMC).

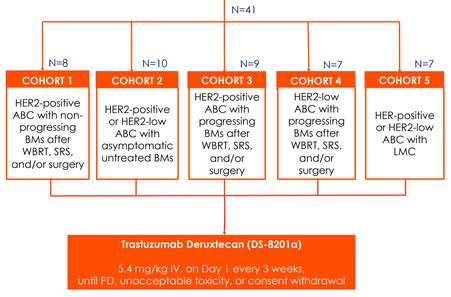
STUDY DESIGN

Figure 1: DEBBRAH (NCT04420598) Clinical Trial Design

International, investigator-initiated, open-label, multicenter, single-arm, five-cohort, phase 2 trial

KEY ELIGIBILITY CRITERIA

- Patients ≥18 years
- ECOG PS 0 or 1 (0–2 for **cohort 5**)
- Pts with HER2-positive 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; MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

OBJECTIVES

PRIMARY OBJECTIVES

Cohort 1: Assess the efficacy – in terms of 16-week progression-free survival (PFS) – of T-DXd after whole brain radiation therapy (WBRT), and/or stereotactic radiosurgery (SRS), and/or surgery

Cohorts 2, 3, and 4: Assess the efficacy – in terms of intracranial overall response rate (ORR-IC) – of T-DXd in each cohort

Cohort 5: Assess the efficacy – in terms of overall survival (OS) – of T-DXd

SECONDARY OBJECTIVES

Cohort 1: Assess PFS, ORR, clinical benefit rate (CBR), time to response (TTR), duration of response (DoR), and best percentage change in tumor burden per RANO-BM and RECIST v.1.1, OS, and safety and tolerability of T-DXd

Cohorts 2, 3, and 4: Assess PFS, CBR, TTR, DoR, best percentage change in tumor burden per RANO-BM and RECIST v.1.1, and ORR per RECIST v.1.1, OS, time to WBRT and/or SRS (only cohort 2), and safety and tolerability of T-DXd

Cohort 5: Assess PFS, ORR, CBR, TTR, DoR, best percentage change in tumor burden per RANO-BM and RECIST v.1.1, and safety and tolerability of T-DXd

STATISTICS

- Sample size was planned to attain an 80% power at nominal level of one-sided α of 0,05 in each cohort
- **Cohort 1**: Null hypothesis (H0): 16-week CNS-PFS ≤5%; Alternative hypothesis (Ha): 16-week CNS-PFS ≥40%
- **Cohorts 2, 3, and 4**: H0: ORR-IC ≤5%; Ha: ORR-IC ≥40%.
- **Cohort 5**: H0: median OS≤2 months; Ha: median OS≥6 months

RESULTS

- From July 22, 2020, through April 4, 2022, 41 patients from sites in Spain and Portugal were allocated to one of the five cohorts.
- One patient (1.4%) from cohort 4 was excluded due to protocol deviation and was excluded from efficacy analysis.
- At final analysis cut-off (April 4, 2023), with a median follow-up of 15.2 months (range: 2.1-30.1), 3 patients remained on treatment (cohort 4: 2 pts; cohort 4: 1 pt)
- A summary of patient baseline characteristics is included in **Table 1**.

Table 1: Patient baseline characteristics

Baseline characteristics, *n* (%)	Cohort 1 (*n* = 8)	Cohort 2 (*n* = 10)	Cohort 3 (n=9)	Cohort 4 (*n* = 6)	Cohort 5 (*n* = 7)
Age, median (range), years	46 (36-65)	54 (37-77)	53 (37-62)	62 (48-73)	55 (40-67)
ECOG PS, n(%)					
0	5 (62.5%)	9 (90.0%)	6 (66.7%)	1 (16.7%)	3 (42.9%)
1	3 (37.5%)	1 (10.0%)	3 (33.3%)	5 (83.3%)	2 (28.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)
Measurable disease at screening n(%)					
No	3 (37.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (57.1%)
Yes	5 (62.5%)	10 (100%)	9 (100%)	6 (100%)	3 (42.9%)
HER2 status (IHC, n(%))					
1+	0 (0.0%)	5 (50.0%)	0 (0.0%)	5 (83.3%)	4 (57.1%)
2+	2 (25.0%)	2 (20.0%)	2 (22.2%)	1 (16.7%)	0 (0.0%)
3+	6 (75.0%)	3 (30.0%)	7 (77.8%)	0 (0.0%)	3 (42.9%)
Hormone receptor status, n(%)					
ER- and PgR-	1 (12.5%)	3 (30.0%)	2 (22.2%)	3 (50.0%)	2 (28.6%)
ER+ and/or PgR+	7 (87.5%)	7 (70.0%)	7 (77.8%)	3 (50.0%)	5 (71.4%)
Number of previous lines for advance disease Median (Min; Max)	2.5 (1; 8)	6.5 (2; 8)	5 (1;13)	3 (2; 4)	4 (1; 8)
Previous systemic cancer therapy, n(%)					
Anti-HER2 therapy	8 (100%)	3 (30.0%)	9 (100.0%)	1 (16.7%)	3 (42.9%)
Chemotherapy	8 (100%)	10 (100%)	9 (100.0%)	6 (100%)	7 (100.0%)
Endocrine therapy	3 (37.5%	7 (70.0%)	4 (44.4%)	4 (66.7%)	3 (42.9%)
Prior therapy for CNS lesions n(%)					
WBRT	4 (50.0%)	0 (0.0%)	7 (77.8%)	5 (83.3%)	0 (0.0%)
SRS/SRT	3 (37.5%)	0 (0.0%)	5 (55.6%)	3 (50.0%)	0 (0.0%)
Surgery	4 (50.0%)	0 (0.0%)	3 (33.3%)	1 (16.7%)	0 (0.0%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; n(%), number of patients (percentage of patients); PgR, progesterone receptor; SRS/SRT, stereotactic radiosurgery/stereotactic radiotherapy; WBRT, whole-brain radiation therapy.

RESULTS

- Cohort 1 met its primary endpoint, with a 16-week PFS rate of 87.5% (95% CI, 47.3% - 99.7%; p<0.001) (**Figure 2**).
- Cohorts 2, 3, and 4 met their primary endpoints. The ORR-IC in Cohort 2 was 70.0% (95% CI 34.8% - 93.3%; p<0.001) (**Figure 3**), Cohort 3 was 55.6% (95% CI 21.2% - 86.3%; p<0.001) (**Figure 4**), and cohort 4 was 50.0% (95% CI 11.8% - 88.2%; p<0.001) (**Figure 5**).
- The median OS rate in cohort 5 was 13.3 months (95% CI, 2.5-NA; p<0.001) (**Figure 6**), achieving the primary endpoint.
- Forty patients (97.6%) experienced at least one treatment emergent adverse event (TEAEs). The most common TEAEs of any grade (G) were fatigue (60.9%; 4.9% G≥3), nausea (52.2%; 2.4% G≥3), anemia (31.7%; 0% G≥3), and vomiting (31.7%; 0% G≥3) (**Table 2**).
- No G4 TEAEs were reported but there were five deaths, one of which was a G5 drug-related pneumonitis.
- Two patients (4.9%) experienced interstitial lung disease (ILD) (G1: 1; G3: 1).
- Thirteen patients (31.7%) experienced serious TEAEs, with five considered related to the study treatment(adjudicated drug-related pneumonitis/ILD: 4 patients; nausea: 1 patient).

Figure 2: 16-week PFS in Cohort 1

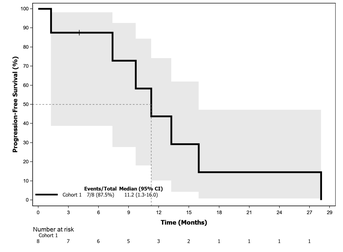


Figure 3: Waterfall plot of best change in Cohort 2 of CNS lesions

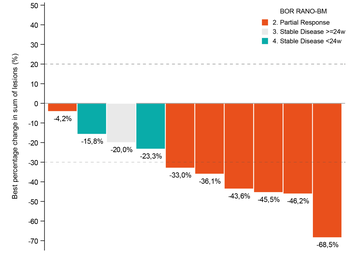
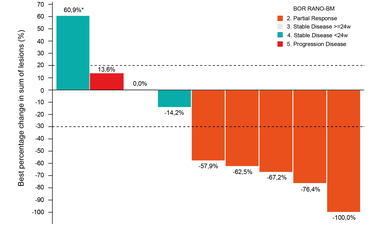


Figure 4: Waterfall plot of best change in Cohort 3 of CNS lesions



*Patient was evaluated as SD despite the 60.9% increase in tumor size. The investigator considered there was radiation necrosis instead of PD.

Figure 5: Waterfall plot of best change in Cohort 4 of CNS lesions

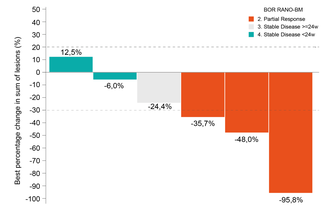


Figure 6: Overall survival in Cohort 5

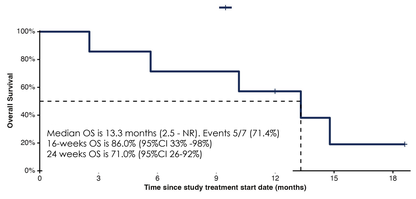


Table 2: TEAEs occurring in ≥ 20.0% of patients in cohorts 1-5

Overall (*N* = 41)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
TEAEs n(%)	12 (29.3)	25 (60.9)	8 (19.5)	0 (0.0)	5 (12.2)	40 (97.6)
Hematologic	12 (29.3)	4 (9.8)	6 (14.6)	0 (0.0)	0 (0.0)	22 (53.7)
Anemia	10 (24.4)	3 (7.3)	0 (0)	0 (0.0)	0 (0.0)	13 (31.7)
Neutropenia	3 (7.3)	3 (7.3)	4 (9.8)	0 (0.0)	0 (0.0)	10 (24.4)
Non-hematologic	15 (36.6)	25 (60.9)	5 (12.2)	0 (0.0)	5 (12.2)	40 (97.6)
Fatigue	15 (36.6)	8 (19.5)	2 (4.9)	0 (0.0)	0 (0.0)	25 (60.9)
Nausea	14 (34.2)	6 (12.2)	1 (2.4)	0 (0.0)	0 (0.0)	21 (51.2)
Vomiting	9 (21.9)	4 (9.8)	0 (0.0)	0 (0.0)	0 (0.0)	13 (31.7)
Constipation	12 (29.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (29.3)
Diarrhea	11 (26.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (26.8)
Urinary tract infection	4 (9.8)	5 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)	9 (21.9)
Headache	8(19.5)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	9 (21.9)

CONCLUSIONS

- T-DXd showed promising activity for patients with HER2-positive and HER2-low breast cancer with a history of BMs and/or leptomeningeal carcinomatosis.
- The safety profile was consistent with previous T-DXd trials, with a well tolerated and manageable safety profile.
- These encouraging data reinforce the need to include this patient population in clinical trials evaluating HER2-targeting therapies.

BIBLIOGRAPHY

1. Witzel et. al. Breast Cancer Res; 2016:18(8)
2. Nakada T, et al. Chem Pharm Bull (Tokyo) 2019;67(3):173-185.
3. Watase et. al. Cancers; 2021;13(5):1078
4. Bailleux et. al. Br J Cancer; 2021; 124(1):142-155.
5. Cortés et. al. N Engl J Med. 2022; 386(12): 1143-1154.
6. Hurvitz et. al. The Lancet. 2022; 401(10371):105-117.
7. Modi et. al. N Engl J Med. 2022 Jul 7;387(1):9-20.
8. Jerusalem GHM, et al. J Clin Oncol 2021;39:526.
9. Pérez-García JM, et al. Neuro Oncol. 2023; 25(1):157-166
10. Bartsch et. al. Nature Medicine. 2022; 28, 1840-1847
11. Hurvitz et. al. Annual of Oncology, 2023; 34(Suppl 2):S335-S336

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