Abstract # 1507
Presentation ID: PS2-08-20

Translational analysis of cerebrospinal fluid (CSF) and plasma circulating tumor DNA (ctDNA) from breast cancer patients with leptomeningeal disease (LMD) treated with trastuzumab deruxtecan (T-DXd) in the DEBBRAH trial

SAN ANTONIO BREAST CANCER SYMPOSIUM®
Mays Cancer Center UT Health MD Anderson Cancer Center | AACR American Association for Cancer Research
December 9-12, 2025
San Antonio, Texas

Amanda Fitzpatrick [1,2], Thurkaa Shanmugalingam [1,2], Syed Haider [2], Marjan Iravani [2], Laia Garrigós[3,4], José Ángel García-Sáenz[5], Patricia Cortez[6], Fabricio Racca[7], Salvador Blanch[8], Manuel Ruiz-Borrego[9], Griselda Martrat[10], Mario Mancino[10], José Antonio Guerrero[10], José Manuel Pérez-García[3,10], Marta Vaz Batista[11], Sofia Braga[12], Antonio Llombart-Cussac[10,13,14], Javier Cortés[3,10,15-17].

[1]The Breast Cancer Now Research Unit, Innovation Hub, Guy's Cancer Centre, King's College London, UK, [2]The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, UK, [3]International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain, [4]Medical Oncology department, Hospital Universitari Dexeus, Barcelona, Spain, [5]Hospital Clínico San Carlos, Madrid, Spain, [6]IOB Madrid, Institute of Oncology, Hospital Beata María Ana, Madrid, Spain, [7]IOB Institute of Oncology, Quiron Group, Madrid, Barcelona, Spain, [8]Instituto Valenciano de Oncología, Valencia, Spain, Virgen del Rocío University Hospital, Sevilla, Spain, Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, US, [11]Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal; Medica Scientia Innovation Research (MEDSIR) - Oncoclinicas&Co, Jersey City, NJ, USA, [12]Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal, [13]Hospital Arnau de Vilanova, FISABIO, Valencia, Spain, [14]Translational Oncology Group, Department of Medicine, Facultad de Ciencias de la Salud, Universidad Cardenal Herrera-CEU, Alfara del Patriarca, Spain, [15]Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain, [16]IOB Madrid, Hospital Beata María Ana, Madrid, Spain, [17]Oncology Department, Hospital Universitario Torrejón, Ribera Group, Madrid, Spain

MEDSIR
MEDICA SCIENTIA INNOVATION RESEARCH

BACKGROUND

- Radiological response assessment in patients with LMD is challenging, particularly in clinical trials [1].
- **CSF ctDNA has emerged as a potential minimally invasive biomarker** for the diagnosis and disease monitoring of LMD [2,3].
- The **DEBBRAH trial** (NCT04420598) assessed **T-DXd** in HER2-positive and HER2-low **breast cancer patients** with brain metastases and/or **LMD**, with Cohort 5 dedicated to pathologically-confirmed LMD [4].
- This translational analysis aims to evaluate intra- and extracranial T-DXd activity through **serial ctDNA measurement in CSF and plasma** collected from patients in DEBBRAH Cohort 5, and to **determine molecular features associated with response and treatment resistance**.

METHODS & MATERIALS

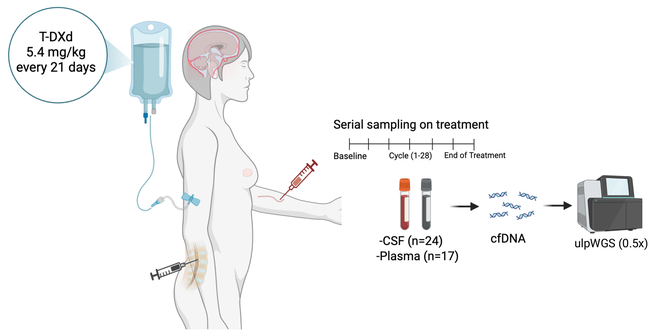
- Seven patients with cytology positive LMD were enrolled in DEBBRAH Cohort 5 and received **T-DXd 5.4 mg/kg intravenously every 21 days** (Figure 1).
- Radiological response was measured by **RECIST v.1.1** for extracranial disease and **RANO-BM** for intracranial lesions (Figure 2).
- CSF (non-mandatory) and plasma samples were collected and processed for circulating free DNA (cfDNA) isolation.
- Ultra-low pass whole genome sequencing (ulpWGS) was performed to measure ctDNA fraction using ichorCNA.

RESULTS

- **A swimmer plot** depicting the individual time on treatment and trial assessments is shown in Figure 2.
- **ctDNA was detected in all baseline CSF samples** (n= 6) (tumor fraction range 0.11 - 0.83), whereas ctDNA was only detected in three of seven baseline plasma samples (tumor fraction range 0.06 - 0.82).
- All four patients with serial CSF samples showed a **reduction or complete clearance** of ctDNA tumor fraction during T-DXd treatment (Figure 3A-E).
- An **increase in plasma ctDNA** was observed at end of treatment in three patients, suggesting a correlation with progression of extracranial disease (Figure 3B,C,F).

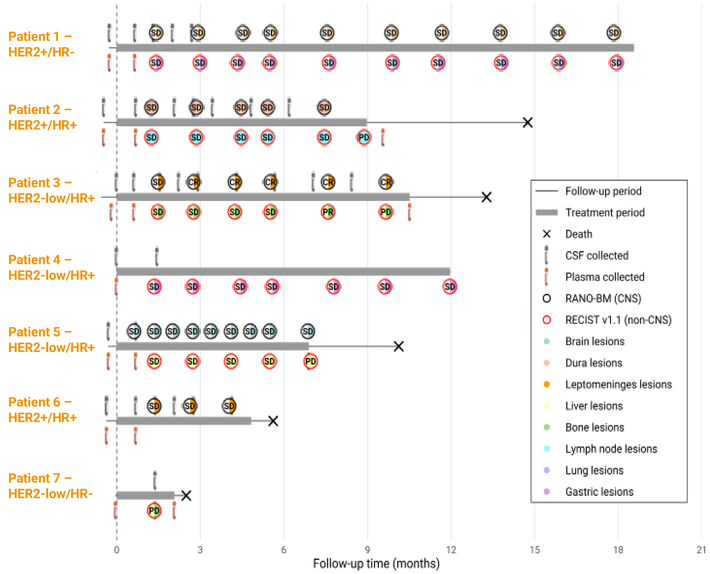
FIGURES and RESULTS

Figure 1. Methodology of CEBBRAH study



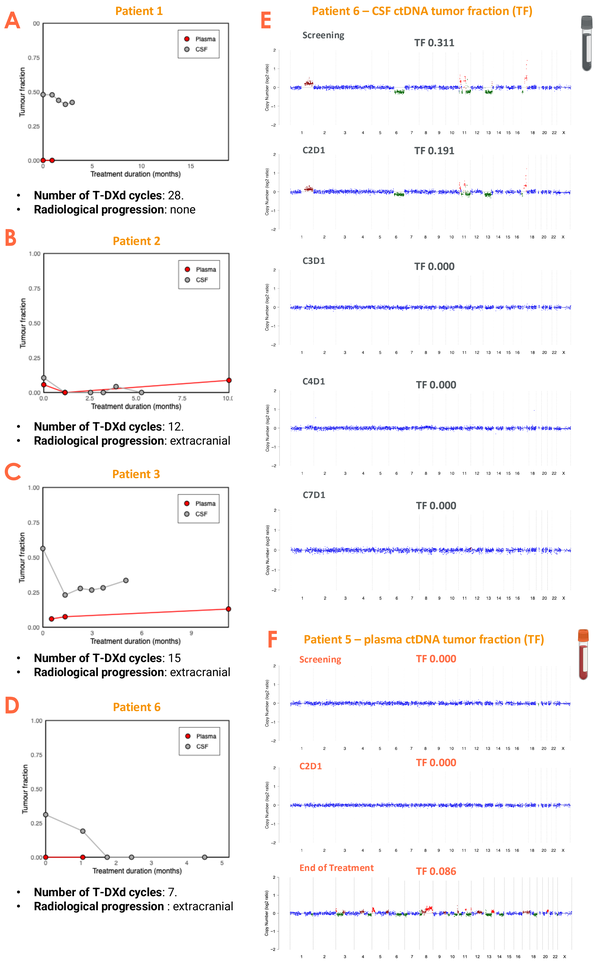
T-DXd: Trastuzumab deruxtecan; **CSF**: cerebrospinal fluid; **cfDNA**: cell-free DNA; **ulpWGS**: ultra-low pass whole genome sequencing.

Figure 2. Swimmer plot showing time on treatment and trial assessments



Response in each timepoint. SD: stable disease; **PD**: progressive disease; **PR**: partial response; **CR**: complete response.

Figure 3. CSF and plasma ctDNA dynamics during T-DXd therapy



Serial measurements of CSF and plasma tumor fraction (A , B, C, D) and representative **images** of **ulpWGS** of consecutive CSF samples in patient 6 (E) and of plasma in patient 5 (F). **TF**: tumor fraction. **ulpWGS**: ultra-low pass whole genome sequencing.

Scan here to view the lay language summary of this study

Scan here to view a PDF version of this poster. Copies obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from SABCS® and the authors of this poster.

CONCLUSIONS

- **CSF ctDNA,** rather than plasma ctDNA, shows potential as a disease biomarker in LMD.
- **Reduction and/or clearance** of CSF ctDNA appears to correlate with LMD control in a small cohort of patients who received intravenous T-DXd therapy.
- **CSF ctDNA analysis may assist in the diagnosis and monitoring of patients with suspected LMD** and negative cytology or uncertain LMD progression, respectively, although further validation is needed.

REFERENCES

1. Le Rhun E, et al. Neuro Oncol. 2019 21 (5):648-658
2. Fitzpatrick A, et al. Clin Cancer Res. 2022 28(6):1180-1191.
3. Fitzpatrick A, et al. Nat Commun. 2023 14(1):7408.
4. Vaz Batista M, et al. Med. 2025 6 (1):100502

PRESENTING AUTHOR

Amanda Fitzpatrick, MBChB PhD
amanda.fitzpatrick@kcl.ac.uk

ACKNOWLEDGEMENTS

The CEBBRAH team is grateful to all patients and their families, the trial teams of the participating sites, and Daiichi Sankyo for funding the CEBBRAH trial.