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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

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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

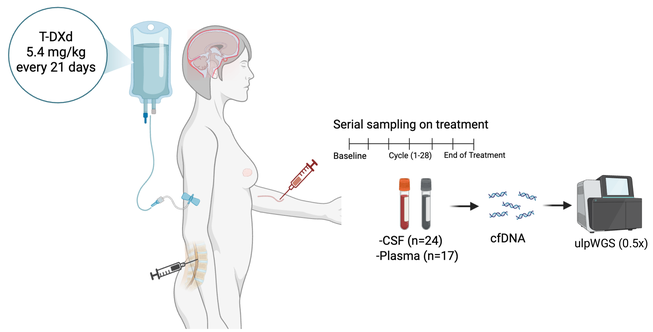
- Seven patients with cytology positive LMD were enrolled in DEBBRAH Cohort 5 and received **T-DXd 5.4 mg/kg intravenously every 21 days** (Figure 1).
- Radiological response was measured by **RECIST v.1.1** for extracranial disease and **RANO-BM** for intracranial lesions (Figure 2).
- CSF (non-mandatory) 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).

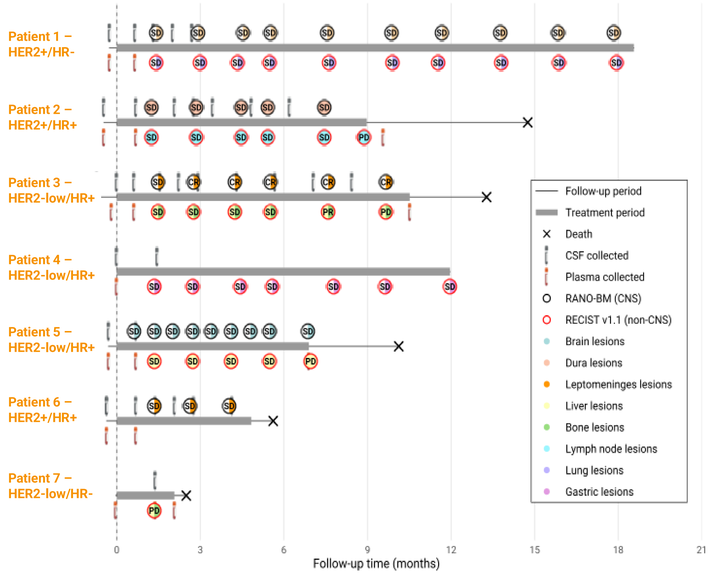
FIGURES and RESULTS

Figure 1. Methodology of CEBBRAH study



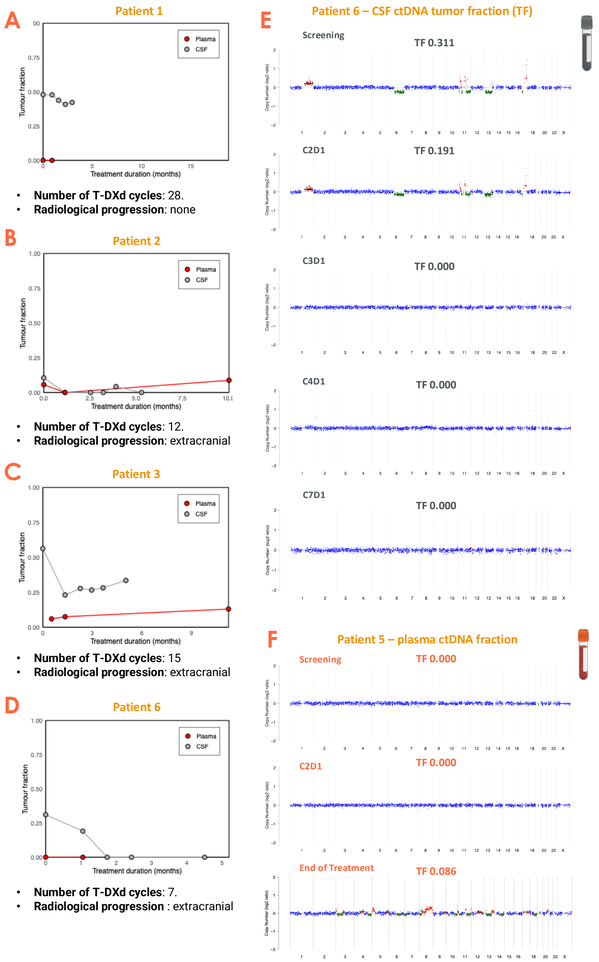
T-DXd: Trastuzumab deruxtecan; **CSF**: cerebrospinal fluid; **cfDNA**: cell-free DNA; **ulpWGS**: ultra-low pass whole genome sequencing.

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



- **Number of T-DXd cycles**: 28.
- **Radiological progression**: none

- **Number of T-DXd cycles**: 12.
- **Radiological progression**: extracranial

- **Number of T-DXd cycles**: 15
- **Radiological progression**: extracranial

- **Number of T-DXd cycles**: 7.
- **Radiological progression** : extracranial

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

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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.

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