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Abstract # SESS-671 / Presentation ID: P5-03-11

# DEMETHER: A single-arm phase II trial to evaluate the efficacy and safety of subcutaneous pertuzumab and trastuzumab maintenance after induction treatment with trastuzumab deruxtecan for previously untreated HER2[+] advanced breast cancer

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## BACKGROUND

- HER2 (human epidermal growth factor receptor 2) is overexpressed in 15-20% of all breast cancers. [1]
- Pertuzumab combined with trastuzumab and taxanes is the standard first-line therapy for HER2[+] advanced breast cancer (ABC) based on the results from CLEOPATRA trial.[2]
- Trastuzumab deruxtecan (T-DXd) has demonstrated unprecedented antitumor activity in patients (pts) with previously treated HER2[+] ABC [3] and has the potential to move into the first-line treatment of this patient population (DESTINY-Breast09).[4]
- Despite a manageable toxicity profile, prior studies have raised safety concerns about potential serious adverse events associated with its use and a potential negative impact on quality of life (QoL). [3] Moreover, T-DXd discontinuation rates due to adverse events were 18.0% and 23.7% in the DESTINY-Breast02 and DESTINY-Breast03, respectively.[5,6]
- The rationale of the DEMETHER study is to find the right balance between T-DXd shorter treatment duration, given the time to response of 1.64 months observed in the DESTINY-Breast03,[3] and subcutaneous fixed-dose combination of pertuzumab and trastuzumab maintenance therapy to ensure efficacy and tolerance in previously untreated HER2[+] ABC pts.

## STATISTICS

- The primary analyses will be performed using the maximum likelihood method for exponential distributions, with a one-sided significance level of 2.5% for both endpoints.
- Primary analysis estimated the 1-year PFS rate and the 3-year OS rate.
- Applying sequentially rejective test, the type I error will be controlled at 5% level.
- A sample size of 165 pts will allow to achieve 80% power.

## TRIAL ENROLLMENT

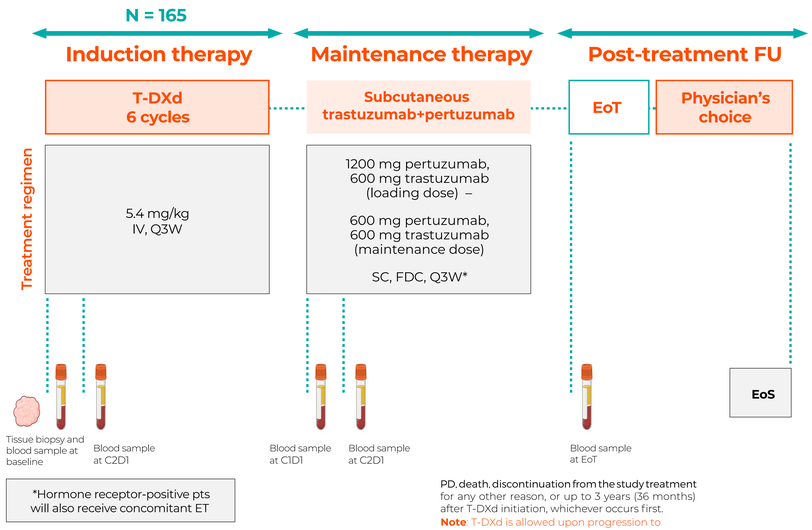
The DEMETHER trial initiated recruitment in June 2024. The number of potentially recruiting sites is expected to be 47, with 13 pts recruited as of 21st October 2024.

## TRIAL DESIGN

The DEMETHER study is an international, multicenter, open-label, single-arm phase II trial (NCT06172127).

### KEY INCLUSION CRITERIA

- ≥18 years of age.
- Centrally-confirmed HER2[+] (IHC 3+, IHC 2+ & ISH+) ABC.
- Stable brain metastasis allowed.
- No prior systemic treatment for advanced disease (one prior line of ET is allowed for ABC).
- Participants may have received CT or HER2-targeted therapy in the (neo)adjuvant setting with a disease-free interval from completion of the systemic treatment (excluding ET) to metastatic diagnosis ≥ 12 months.
- No prior treatment with T-DXd in the (neo)adjuvant setting.
- Evaluable disease according to RECIST v.1.1.
- ECOG PS 0-1.
- LVEF ≥ 55% (ECHO or MUGA scan)
- Adequate hematologic and organ function




*An **interim analysis** will be performed on the first 62 pts with measurable lesions; if at least 44 pts show objective response, the trial will continue.

PD, death, discontinuation from the study treatment for any other reason, or up to 3 years (36 months) after T-DXd initiation, whichever occurs first.
**Note**: T-DXd is allowed upon progression to subcutaneous trastuzumab+pertuzumab.

### PRIMARY OBJECTIVES

- 1-year PFS rate according to RECIST v.1.1
- 3-year OS rate

### SECONDARY OBJECTIVES

- PFS
- OS
- ORR, CBR, TTR, DoR, Best percentage of change in tumor burden as per RECIST v.1.1
- QoL (EORTC, QLQ-C30, QLQ-BR45, EQ-5D-5L)
- Safety and toxicity according to the NCI-CTCAE v.5.0

### EXPLORATORY OBJECTIVES

- Biomarkers of sensitivity/resistance
- ctDNA monitoring

**Abbreviations:** **ABC:** advanced breast cancer; **pts:** patients; **CBR:** clinical benefit rate; **CT:** chemotherapy; **ctDNA:** circulating tumor DNA; **DoR:** duration of response; **ECHO:** echocardiography; **ECOG PS:** Eastern Cooperative Oncology Group Performance Status; **EoS:** end of study; **EoT:** end of treatment; **ET:** endocrine therapy; **FDC:** fixed-dose combination; **FU:** follow up; **IHC:** immunohistochemistry; **ISH:** *in situ* hybridization; **IV:** intravenously; **LVEF:** left ventricular ejection fraction; **MUGA:** multigated acquisition; **ORR:** objective response rate; **OS:** overall survival; **PD:** progressive disease; **PFS:** progression-free survival; **Q3W:** every 3 weeks; **QoL:** quality of life; **SC:** subcutaneously; **T-DXd:** trastuzumab deruxtecan; **TTR:** time to response.

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