Presentation ID: P3-08-21
Abstract # SESS-545

SAN ANTONIO BREAST CANCER SYMPOSIUM®
Mays Cancer Center UT Health San Antonio MD Anderson Cancer Center
AACR American Association for Cancer Research

December 10-13, 2024
San Antonio, Texas

Trastuzumab-deruxtecan in HER2-low metastatic breast cancer patients with newly diagnosed or progressing brain metastases: The TUXEDO-4 phase II trial

Maximilian Marhold[1], Marta Vaz Batista[2,3], María Gión[4,5], Manuel Ruíz-Borrego[6], Isabel Blancas[7], Cristina Morales[8], Cristina Saavedra[5], Felipe Slebe[3], Marta Campolier[3], Juliana Carvalho Santos[3], José Antonio Guerrero-Martínez[3], Miguel Sampayo-Cordero[3], Rupert Bartsch[1], Matthias Preusser[1]

[1] Medical University of Vienna, Department of Medicine 1, Division of Oncology, Vienna, Austria. [2] Hospital Professor Doutor Fernando Fonseca EPE, Lisbon, Portugal. [3] Medica Scientia Innovation Research (MEDSIR) - Oncoclínicas&Co, Jersey City (New Jersey, USA), Sao Paulo (Brazil). [4] IOB Madrid, Institute of Oncology, Hospital Beata María Ana, Madrid, Spain. [5] Hospital Universitario Ramón y Cajal, Madrid, Spain. [6] Hospital Virgen del Rocío, Sevilla, Spain. [7] Hospital Universitario Clínico San Cecilio, Granada, Spain; Medicine Department, University of Granada, Granada, Spain; Instituto de Investigación Biosanitaria de Granada; Granada, Spain. [8] Hospital Universitario Reina Sofía, Córdoba, Spain.

BACKGROUND

- Metastatic breast cancer (mBC) is the second most common cause of brain metastases (BMs) and the leading cause of leptomeningeal disease (LMD) among all solid malignancies [1].
- Both BMs and LMD are associated with high morbidity and mortality, and treatment options are limited [2]. While BMs are commonly diagnosed late during the course of metastatic disease in patients with luminal BC, LMD is often diagnosed simultaneously [3].
- Trastuzumab-deruxtecan (T-DXd), an antibody-drug-conjugate (ADC) combining a HER2-directed antibody with a topoisomerase I inhibitor, has shown promising results in HER2-positive (IHC 3+ or IHC 2+/ISH-positive) mBC patients from the DESTINY-Breast01 and DESTINY-Breast03 trials [4,5], in HER2-positive mBC patients with active BMs or LMD from the TUXEDO-1 and DESTINY-Breast12 trials [6,7], and in HER2-low (IHC 1+ or IHC 2+/ISH-negative) mBC in the DESTINY-Breast04, and DESTINY-Breast06 trials [8,9].
- We therefore hypothesized that T-DXd could exhibit relevant clinical activity in HER2-low mBC patients with active (newly diagnosed or progressing after prior therapy) BMs with or without type II LMD.

STATISTICS

- The sample size was based on a Simon's two-stage design.
- Up to 27 patients will be enrolled (13 in stage I and 14 in stage II).
- Futility stop will occur if ≤ 2 intracranial (IC) responses in stage I. If ≥ 3 (23.1%) IC responses in stage I, additional patients will be recruited for stage II.
- Positivity of the trial defined if ≥ 8/27 (29.6%) patients exhibit IC response.
- Type I error is 5% and power 90%.

TRIAL ENROLLMENT

The TUXEDO-4 trial was opened for accrual on 5 June 2024 and is currently recruiting patients from 13 Austrian and Spanish sites. The number of patients enrolled until 4 November 2024 was 15.

TRIAL DESIGN

The TUXEDO-4 study is an international, multicenter, single-arm, two-stage optimal Simon's design, phase II trial (NCT06048718).

KEY INCLUSION CRITERIA

- Male or female patients ≥ 18 years.
- Radiologically documented metastatic disease.
- Locally documented HER2-low status: HER2 IHC score by local standard 1+ or 2+/ISH-negative.
- Asymptomatic untreated or progressing BMs after local treatment.
- Measurable disease by RANO-BM criteria.
- Presenting with ≥1 measurable brain lesion (≥10 mm per local radiological assessment).
- With or without untreated type II LMD per EANO-ESMO criteria.
- Able to provide a fresh tumor biopsy sample at baseline or an FFPE since last progression.
- ≥1 line of systemic treatment in the advanced setting.
- No prior treatment with T-DXd.
- Have not received any investigational agent within 28 days prior to initiation of treatment.
- ECOG PS ≤2, LVEF ≥50%.
- Life expectancy ≥ 12 weeks.

INTERIM ANALYSIS

If ≥ 3 responder patients in stage I, stage II will be carried out

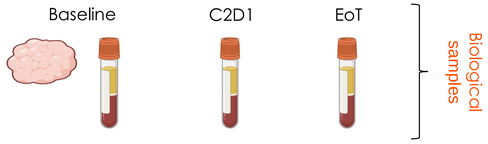
Stage I (N=13) | Stage II (N=14)

HER2-low advanced breast cancer with active BMs with or without type II LMD

T-DXd Q3W 5.4 mg/kg, IV

Until PD, death, or other discontinuation reason

- Tumor assessments by CT and MRI within 28 days prior to start of T-DXd.
- Treatment response every 6 weeks during the first 12 weeks.
- Further response assessments every 9 weeks, and at safety visit if T-DXd was stopped without radiological evidence of tumor progression.
- Reassessments in case of symptoms indicating PD.



PRIMARY ENDPOINT

- **ORR** as judged by best CNS response according to RANO-BM criteria.

SECONDARY ENDPOINTS

- **Bi-ORR** and **EC-ORR**
- **Bi-CBR** (defined by RECIST v1.1, CR+PR+SD ≥ 6 months).
- **Bi-DCR** (defined by RECIST v1.1, CR+PR+SD).
- **TTR**, **DoR**, and **best percentage of change in tumor burden.**
- **PFS**.
- **OS**.
- **Safety and tolerability** as per CTCAE v.5.0.
- **QoL** with EORTC QLQ-c30, the brain specific tool (BN20), and the breast specific tool BR45.
- **Neurocognitive function** as per EORTC QLQ-c30, the brain specific tool (BN20), and the breast specific tool BR45.

EXPLORATORY ENDPOINTS

- **Translational analyses** using tumor tissue samples, radiological images, and blood samples will be performed.

Abbreviations. **Bi-CBR:** Bicompartmental clinical benefit rate; **Bi-DCR:** Bicompartmental disease control rate; **Bi-ORR:** Bicompartmental objective response rate; **BMs:** Brain metastases; **C2D1:** Cycle 2, day 1; **CNS:** Central nervous system; **CR:** Complete response; **CT:** Computed tomography; **CTCAE:** Common terminology criteria for adverse events; **DoR:** Duration of response; **EC-ORR:** Extracranial objective response rate; **ECOG PS:** Eastern Cooperative Oncology Group Performance Status; **EORTC:** European Organization for Research and Treatment of Cancer; **EoT:** End of treatment; **EANO-ESMO:** European Association of Neuro-Oncology - European Society of Molecular Oncology; **FFPE:** formalin-fixed paraffin-embedded; **HER2:** Human epidermal growth factor receptor 2; **IHC:** Immunochemistry; **ISH:** *in situ* hybridization; **IV:** Intravenously; **KPS:** Karnofsky Performance Status; **LMD:** Leptomeningeal disease; **LVEF:** Left ventricular ejection fraction; **MRI:** Magnetic resonance imaging; **ORR:** Objective response rate; **OS:** Overall survival; **PD:** Progressive disease; **PFS:** Progression-free survival; **PR:** Partial response; **Q3W:** Once every three weeks; **QLQ:** Quality of life questionnaire; **QoL:** Quality of life; **RANO-BM:** Response assessment in neuro-oncology – brain metastasis criteria; **RECIST:** Response evaluation criteria in solid tumors; **T-DXd:** Trastuzumab deruxtecan; **TTR:** Time to response.

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ACKNOWLEDGEMENTS

The TUXEDO-4 team thanks all the patients and their families who will be involved in this study, as well as the trial teams of the participating sites. We also thank Daiichi-Sankyo for funding this trial.

CONTACT INFORMATION

Maximilian Marhold, MD, PhD
Email: maximilian.marhold@meduniwien.ac.at

Scan here to view the lay language summary of this study.