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Final results of the TUXEDO-3 phase II trial of patritumab deruxtecan (HER3-DXd) in active brain metastases (BMs) and leptomeningeal disease (LMD)

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Background

TUXEDO-3 (NCT05865990) is an international, multicenter, multicohort, single-arm, phase II trial evaluating the efficacy and safety of HER3-DXd, a HER3-directed antibody-drug conjugate (ADC) with a topoisomerase I-inhibitor payload, in newly diagnosed BMs or BMs progressing after prior local therapy (active BMs) from metastatic breast cancer (cohort 1) and advanced non-small cell lung cancer (cohort 2), and LMD from any solid malignancy (cohort 3). Primary endpoints (intracranial overall response rate [ORR] as per RANO-BM criteria in cohorts 1 and 2, and 3-month overall survival [OS] in cohort 3) were met. Here, we present the final OS results.

Methods

Primary endpoints and preliminary secondary endpoints have been previously published (cohort 1: Bartsch et al., Lancet Oncol, 2025; cohort 2: Fuereder et al., Lancet Oncol, 2025; and cohort 3: Preusser et al., Nat Med, 2025). Patients (pts) received intravenous HER3-DXd at a dose of 5.6 mg/kg Q3W until disease progression, unacceptable toxicity, death, or withdrawal for any reason. We now report the final OS analysis for all cohorts, and 12-month OS rate for cohort 3. OS was estimated using the Kaplan-Meier method, reporting the median OS and 12-month OS rate with 95% confidence intervals (CI) based on the log-log method.

Results

Between December 2023 and July 2024, 61 evaluable pts were enrolled from 8 Austrian and Spanish sites. At data cut-off, median follow-up (range) was 6.7 (1.4; 26.2), 5.7 (0.2; 27.2), and 5.4 (0.8; 23.1) months in cohorts 1, 2, and 3, respectively. Median OS was 7.9 months (95% CI, 5.7-12.8) in cohort 1, 6.7 months (95% CI, 3.3-15.3) in cohort 2, and 10.5 months (95% CI, 2.1-13.1) in cohort 3. 12-month OS rate in cohort 3 was 33.1% (95% CI, 12.8-55.2). Secondary endpoints including ORR, progression-free survival, clinical benefit rate, and disease control rate as per central review, safety, quality of life, and neurocognitive function analyses are ongoing and will be presented at the meeting.

Conclusions

The results confirm favorable OS and 12-month OS rate in pts with CNS involvement with HER3-DXd. The data support the therapeutic value of HER3-DXd and reinforce the role of ADCs as a promising treatment approach in secondary CNS disease.

Clinical trial identification

NCT05865990.

Legal entity responsible for the study

MEDSIR.

Funding

Daiichi Sankyo.

Disclosure

M. Preusser: Financial Interests, Personal, Advisory Board: Bayer, Bristol Myers Squibb, Novartis, Gerson Lehrman, CMC Contrast, GSK, Mundipharma, Roche, BMJ Journals, MedMedia, AstraZeneca, Abbvie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dohme, Tocagen, Adastra, Gan & Lee Pharmaceuticals, Servier, Milteny, Boehringer Ingelheim, Telix, Nerviano, ITM Oncologics; Financial Interests, Personal, Invited Speaker: Medscape; Financial Interests, Institutional, Research Grant, Clinical Trials and research: Boehringer-Ingelheim, Bristol Meyers Squibb, Roche, Daiichi Sankyo, Merck Sharp & Dohme, Novocure, GSK, Abbvie; Financial Interests, Institutional, Coordinating PI: PharmaMar; Financial Interests, , Coordinating PI: Novartis, Daiichii Sankyo; Non-Financial Interests, , Leadership Role, Brain Tumor Group Chair (current): EORTC; Non-Financial Interests, , Leadership Role, EANO Past-President (current): EANO; Non-Financial Interests, , Other, Member Multi-Site Guideline Advisory Group: ASCO; Non-Financial Interests, , Leadership Role: Nuclear Medicine and Neuro_Oncology (NMN). 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