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Outcome of patritumab deruxtecan (HER3-DXd) in patients with HER2-positive metastatic breast cancer and CNS involvement previously treated with trastuzumab deruxtecan: A subanalysis of TUXEDO-3

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BACKGROUND

- TUXEDO-3 (NCT05865990) is an international, multicenter, multicohort, single-arm, phase II trial that enrolled patients with metastatic breast cancer (mBC) and newly diagnosed brain metastases (BMs) or BMs progressing after local therapy (active BMs) (cohort 1), advanced non-small cell lung cancer and active BMs (cohort 2), and leptomeningeal disease (LMD) from any solid tumors (cohort 3) to evaluate the efficacy and safety of the antibody-drug conjugate (ADC) patritumab deruxtecan (HER3-DXd).
- HER3-DXd showed central nervous system (CNS) activity in all heavily pretreated cohorts [1-3]. As in the U31402-A-J101 trial [4], HER3-DXd activity was observed irrespective of the BC subtype in cohort 1 of TUXEDO-3, showing that HER3-DXd may be a promising novel therapeutic option for patients with BC and CNS involvement [3].
- The number of available ADCs across stages and lines of therapy in BC is growing, but evidence on their optimal sequencing remains limited [5]. This highlights an important unmet need, especially in the context of CNS involvement.
- The DESTINY-Breast12 trial demonstrated clinically meaningful activity of trastuzumab deruxtecan (T-DXd) in patients with HER2-positive BC BMs previously treated with trastuzumab emtansine (T-DM1) [6]. However, evidence remain scarce regarding optimal treatment strategies for patients progressing on T-DXd.
- HER3, highly expressed in BMs of HER2-positive BC, contributes to resistance to HER2-directed therapies (e.g., trastuzumab or lapatinib) by forming heterodimers with HER2, which promote cancer cell survival and proliferation via Phosphoinositide 3-kinase/Protein kinase B (PI3K/AKT) and src-family kinase (SRC) signaling pathways [7].
- We performed an unplanned *post-hoc*, descriptive, pooled efficacy analysis of TUXEDO-3 patients with HER2-positive mBC and CNS involvement who had received prior T-DXd.

STUDY DESIGN

- The study design of the TUXEDO-3 subanalysis is shown in Figure 1.
- This is a *post-hoc*, descriptive, pooled efficacy analysis of the TUXEDO-3 study that specifically included patients with HER2-positive mBC and CNS involvement (either active BMs or LMD) who received T-DXd prior to the start of the TUXEDO-3 trial.

Figure 1. Study design of the TUXEDO-3 pooled efficacy analysis.

aNSCLC: Advanced non-small cell lung cancer; **BMs**: Brain metastases; **CNS**: Central nervous system; **HER2**: Human epidermal growth factor receptor 2; **HER3-DXd**: Patritumab deruxtecan; **LMD**: Leptomeningeal disease; **mBC**: Metastatic breast cancer; **T-DXd**: Trastuzumab deruxtecan.

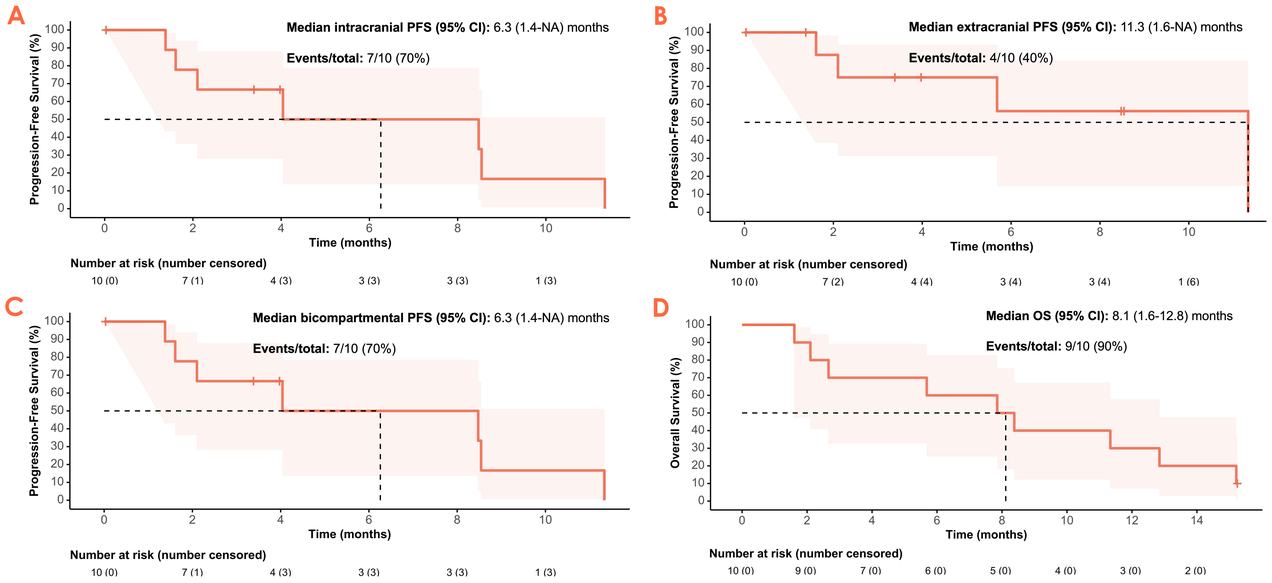
METHODS

- Patients with HER2-positive mBC with active BMs (cohort 1) or LMD (cohort 3) who had received T-DXd prior to start the TUXEDO-3 trial were eligible for this analysis.
- HER3-DXd (5.6 mg/kg) was intravenously administered in 21-day cycles until progression of disease, unacceptable toxicity, death or withdrawal for any other reason.
- This analysis evaluated progression-free survival (PFS) for bicompartmental, intracranial and extracranial lesions, and overall survival (OS).
- Survival estimates were analyzed using the Kaplan-Meier method and 95% confidence intervals (CIs).

RESULTS

- From 12 December 2023 to 2 July 2024, a total of 35 patients with mBC and CNS involvement (active BMs [N=21] and LMD [N=14]) were enrolled. Ten (28.6%) patients had HER2-positive mBC (9 with active BMs and 1 with LMD, who also had parenchymal BMs).
- Out of the 10 patients, 1 (10%) showed a 2+ HER2 expression with positive in situ hibridization, and 9 (90%) had a 3+ HER2 expression by immunohistochemistry.
- All 10 patients had received prior T-DXd, 3 (30.0%) had additional T-DM1, and 6 (60%) received tucatinib. Three (30%) received T-DXd as last treatment line prior to enrollment.
- In the HER2-positive mBC population, median age was 54.5 (range: 35.0-75.0) years, and the number of previous lines for advanced disease was 4.0 (range: 2.0-7.0). Median time from last prior T-DXd was 12.4 (range: 0.5-26.7) months.
- At data cutoff (6 September 2025), no patients remained on treatment and one continued in follow-up. Median follow-up was 8.1 (range: 2.0-15.2) months, and median treatment duration was 3.2 (range: 0.0-10.3) months.
- Median PFS was 6.3 months for intracranial lesions as per RANO-BM criteria (Figure 2A), and 11.3 months for extracranial lesions (Figure 2B) and 6.3 months for bicompartmental lesions (Figure 2C) as per RECIST v.1.1. Median OS was 8.1 months (Figure 2D).

Figure 2. Kaplan-Meier estimates of progression-free survival for intracranial (A), extracranial (B) and bicompartmental lesions (C), and overall survival (D).



CI: Confidence interval; **NA**: Not achieved; **OS:** Overall survival; **PFS:** Progression-free survival.

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CONCLUSIONS

- HER3-DXd showed promising PFS and OS in patients with HER2-positive mBC and active BMs/LMD who had been previously treated with T-DXd.
- Despite the small sample size, these findings suggest a potential strategy for sequential ADC treatment in a patient population with no established standard of care.
- With a median PFS exceeding 6 months, further investigation of HER3-DXd in patients with CNS involvement progressing on T-DXd is warranted.

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