

Impact of Baseline Brain Metastases on Outcomes to Trastuzumab Deruxtecan in *HER2*-Mutant NSCLC

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Background

Real-world data describing the impact of baseline central nervous system (CNS) disease on outcomes in patients with *HER2*-mutant non-small cell lung cancer (NSCLC) treated with trastuzumab deruxtecan (T-DXd) remain limited. This study evaluated clinical characteristics, CNS outcomes, and progression patterns among patients with *HER2*-mutant NSCLC treated with T-DXd in routine practice.

Methods

We conducted a retrospective single-center study of patients with advanced *HER2*-mutant NSCLC treated with T-DXd; patients treated with T-DXd as part of a clinical trial were excluded. Endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and cumulative incidence of CNS metastases.

Results

Fifty-eight patients were included. Median age at T-DXd start was 67 years (IQR 59–73); 66% were female and 67% were never-smokers. Most tumors harbored *HER2* exon 20 insertions (83%). Prior to T-DXd, 81% received platinum-based chemotherapy and 64% immune checkpoint inhibitors; 9% had received a *HER2* TKI and 10% T-DM1. T-DXd was most often administered as second-line therapy (71%). CNS disease involvement, defined as any history of brain metastases (treated or untreated), was present in nineteen patients (33%) at T-DXd initiation. Compared to patients who never had CNS involvement, patients with CNS involvement were younger (61 vs 69 years, $p = 0.03$), more likely to have bone

metastases (84% vs 56%, $p = 0.04$), and more likely to have tumors with concurrent *TP53* mutations (84% vs 54%, $p = 0.024$) and *HER2* amplification (21% vs 2.6%, $p = 0.019$). The ORR to T-DXd among patients with CNS disease at baseline was 58% (11/19) compared with 54% (21/39) in patients without CNS involvement ($p = 0.77$). The median PFS was 8.2 months (95% CI 5.8–13.0) for the whole cohort; 8.5 months (95% CI 5.7–23.0) without CNS disease at T-DXd initiation and 6.8 months (95% CI 4.2–11.0) with CNS disease (HR 2.0; 95% CI 1.1–3.8; $p = 0.027$). Median OS was 19 months (95% CI 11.0–43.0) in the overall cohort; the median OS was 26 months (95% CI 9.3–NR) without CNS involvement at T-DXd initiation and 19 months (95% CI 10.0–NR) with CNS disease (HR 1.3; 95% CI 0.60–2.6; $p = 0.50$). The most common sites of first progression on T-DXd were CNS (44%), lung (41%), and bone (25%). CNS progression as the first site occurred more frequently in patients with baseline CNS disease (61% vs 30%, $p = 0.068$). The cumulative incidence of CNS metastases from T-DXd start was 33% at baseline, 50% at 12 months, 52% at 24 months, and 63% at 36 months.

Conclusions

In this real-world cohort, T-DXd demonstrated outcomes consistent with clinical trial findings. One-third of patients had CNS metastases at treatment start, which was associated with shorter PFS but similar OS compared with those without CNS involvement. The progressive rise in CNS metastases during T-DXd therapy and shorter PFS among patients with baseline brain metastases highlight the need for a better understanding of sequencing strategies with emerging CNS-active HER2 inhibitors.