

Intracranial activity of trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients with active brain metastases: results from the first stage of the phase II TUXEDO-1 trial

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Background

Brain metastases (BM) are frequently diagnosed in HER2-positive breast cancer (BC) and are associated with high morbidity and mortality. Trastuzumab deruxtecan (T-DXd) is a novel antibody-drug conjugate approved for the treatment of HER2-positive metastatic BC but has not been specifically investigated in the context of active BM¹. Here, we present preliminary results of the prospective, single-centre, single-arm, phase II TUXEDO-1 trial investigating T-DXd in HER2-positive BC patients with active BM.

Methods

TUXEDO-1 enrolls adult patients with HER2-positive BC and newly diagnosed BM or BM with radiological progression after prior local therapy, prior exposure to trastuzumab and pertuzumab, and no indication for immediate local therapy. The primary endpoint is intracranial response rate (RR) centrally assessed by Response Assessment in Neuro-Oncology (RANO)-BM criteria. Secondary endpoints consist of extracranial RR, progression-free survival, overall survival, safety, and quality-of-life. Based on a Simon's two-stage phase II design with a RR under alternative hypothesis of >60% and under null hypothesis of <26%, six evaluable patients with 3 responses are required for the first stage and additional 9 patients for the second stage. The null hypothesis will be rejected with a type I error rate of 5% and a power of 80% if at least 7 responses are observed in the overall sample.

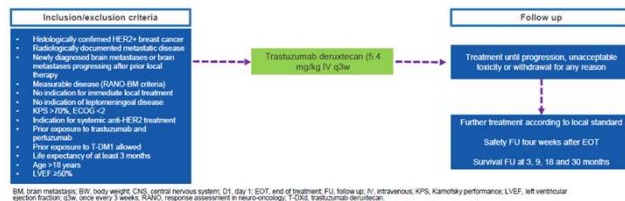


Figure 1 - Study design

Results

By the data cut-off 25th of August 2021, recruitment for the trial has been completed with a total of 15 patients having received a least one dose of T-DXd. The median age is 49 years, 60% of patients received prior radiotherapy for BM, and 60% of patients received prior T-DM1 therapy. At a median follow-up time of 6.5 months (range 1-12), 12 patients are still on treatment.

T-DXd yielded an intracranial response in 5/6 participants (83.3%) enrolled in the first stage (3/4 progressing after prior local therapy); thus, the trial progressed to the second stage. Main toxicities in the overall sample consisted of grade I/II nausea, neutropenia, and fatigue. One case of interstitial lung disease was detected (CTC grade II); one patient with pre-existing diabetes experienced a reversible symptomatic drop of left-ventricular ejection fraction.

Characteristics	N=15	100%
Sex		
female	14	93.3
male	1	6.7
Age at inclusion, years	median (range)	49 (30-76)
Subtype		
HR+/HER2+	12	80
HR-/HER2+	3	20
Status of extracranial disease at inclusion		
no evidence of extracranial disease	4	26.7
stable disease	4	26.7
progressive disease	7	46.7
ECOG at inclusion		
0	9	60
1	6	40
GPA index at inclusion		
2,5	3	20
3,0	11	73.3
Prior local therapy of BM		
yes	1	6.7
no	9	60
Prior T-DM1 therapy		
yes	9	60
no	6	40

Abbreviations: HR: hormone receptor, HER2: human epidermal growth factor receptor 2, ECOG: Eastern Cooperative Oncology Group, GPA: Graded Prognostic Assessment, BM: brain metastasis, T-DM1: Trastuzumab Emtansin

Table 1 - Patient characteristics

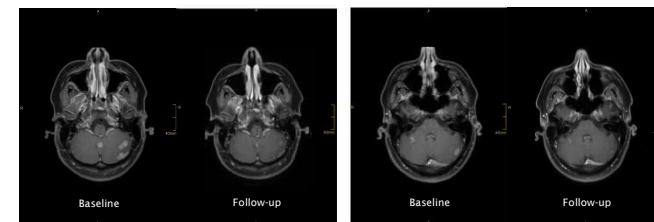


Figure 2 - Intracerebral response on cerebral MRI
A 37-year-old woman with bilateral cerebellar breast cancer brain metastases. T1-weighted contrast enhanced cerebral magnetic resonance images (MRI) at baseline (left) and follow-up (right) after 10 applications of therapy with T-DXd showing an ongoing partial response according to RANO criteria.

Conclusion

Based on clinically relevant preliminary activity in HER2-positive BC patients with active BM, TUXEDO-1 met the criteria to move to the second stage. TUXEDO-1 has meanwhile finished patient recruitment. The final response analysis is pending.

References, Disclosure Statement & Contact

1. S M, C S, T Y, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med 2020; 382: 610-21.

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