Real-World Time to Next Treatment in HER2+ Breast Cancer Patients With Brain Metastases: Trastuzumab Deruxtecan vs. Tucatinib-Based Therapy as Second-Line Treatment

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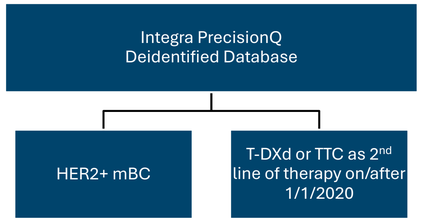
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Introduction

- Brain metastases (BrM) are a frequent and clinically challenging manifestation of HER2-positive (HER2+) metastatic breast cancer (mBC), affecting up to 50% of patients (pts) during the course of their disease.
- Current guidelines recommend trastuzumab deruxtecan (T-DXd) as the preferred second-line therapy for HER2+ mBC overall, while the combination of tucatinib, trastuzumab, and capecitabine (TTC) remains an important option for pts with brain metastases due to its proven intracranial activity and demonstrated efficacy in both active and stable BrM in the HER2CLIMB trial.
- However, there is a lack of real-world data directly comparing treatment outcomes with these regimens specifically among pts with BrM involvement.
- This study evaluates real-world time to next treatment (TTNT) among pts with prior HER2+ therapy and documented BrM treated with second-line T-DXd vs TTC.

Methods and Materials



Eligibility Criteria:

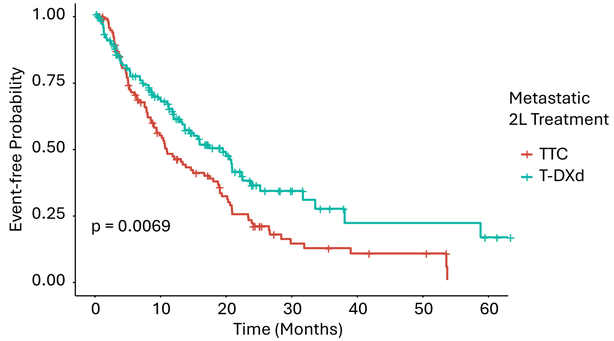
1. Documented BrM prior to initiating second-line (2L) therapy
2. Determined HER2+ status based on receipt of at least one HER2-targeted therapy during first-line (1L) metastatic treatment
3. The index date was defined as the start of 2L treatment with either TTC or T-DXd

Exclusionary Criteria:

1. Individuals who received T-DXd as 1L metastatic therapy

Characteristic	Overall N=255	TTC n=117	T-DXd n=138	*P* value
Age at Index Start	57 (50, 64)	55 (49, 62)	58 (51, 65)	0.026
Race				0.4
Black or African American	23 (9.0%)	11 (9.4%)	12 (8.7%)	
Other	64 (25%)	25 (21%)	39 (28%)	
White	168 (66%)	81 (69%)	87 (63%)	
Ethnicity				0.4
Hispanic or Latino	21 (8.2%)	10 (8.5%)	11 (8.0%)	
Not Hispanic or Latino	194 (76%)	85 (73%)	109 (79%)	
Other	40 (16%)	22 (19%)	18 (13%)	
Payer				0.2
Commercial	44 (17%)	17 (15%)	27 (20%)	
Medicare/Medicaid	88 (35%)	44 (38%)	44 (32%)	
Other	112 (44%)	54 (46%)	58 (42%)	
Self Pay	11 (4.3%)	2 (1.7%)	9 (6.5%)	
BMI Category				0.026
Normal (BMI 18.5-24.9)	92 (36%)	35 (30%)	57 (41%)	
Obese (BMI 30+)	76 (30%)	37 (32%)	39 (28%)	
Overweight (BMI 25-29.9)	58 (23%)	34 (29%)	24 (17%)	
Underweight (BMI <18.5)	15 (5.9%)	3 (2.6%)	12 (8.7%)	
Unknown	14 (5.5%)	8 (6.8%)	6 (4.3%)	

Figure: Metastatic 2L Therapy: Time to Next Treatment or Death



Characteristic	Overall N = 255	TTC N = 117	T-Dxd N = 138	*P* value
ECOG PS				0.094
0	74 (29%)	38 (32%)	36 (26%)	
1	98 (38%)	41 (35%)	57 (41%)	
2+	50 (20%)	18 (15%)	32 (23%)	
Unknown	33 (13%)	20 (17%)	13 (9.4%)	
Liver Metastases				0.7
Absent	214 (84%)	97 (83%)	117 (85%)	
Present	41 (16%)	20 (17%)	21 (15%)	
Bone Metastases				0.4
Absent	191 (75%)	85 (73%)	106 (77%)	
Present	64 (25%)	32 (27%)	32 (23%)	
Lung Metastases				>0.9
Absent	233 (91%)	107 (91%)	126 (91%)	
Present	22 (8.6%)	10 (8.5%)	12 (8.7%)	
ER Status				0.053
Negative	108 (42%)	59 (50%)	49 (36%)	
Positive	111 (44%)	43 (37%)	68 (49%)	
Unknown	36 (14%)	15 (13%)	21 (15%)	
1L Treatment				0.2
ET ± HP	72 (28%)	31 (26%)	41 (30%)	
HP + T	101 (40%)	54 (46%)	47 (34%)	
T-DM1	35 (14%)	16 (14%)	19 (14%)	
Other	47 (18%)	16 (14%)	31 (22%)	

Table: Multivariable Cox Proportional Hazards Model: Time to Next Treatment or Death

Characteristic	HR	95% CI	*P* value
Treatment Group			
TTC	—	—	—
T-DXd	0.52	0.37, 0.74	<0.001

Abbreviations

1L, first-line; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HP, trastuzumab + pertuzumab; T, taxane; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTC, tucatinib, trastuzumab, and capecitabine

Results

- A total of 255 pts met study eligibility, of whom 138 (54%) received 2L T-DXd.
- Pts treated with T-DXd were slightly older than those who received TTC (median age: 58 vs. 55 years; Wilcoxon *P*=0.026).
- A lower proportion of pts in the T-DXd group were classified as overweight (BMI 25–30) compared to the TTC group (17% vs. 29%; chi-square *P*=0.026).
- No other significant differences in demographic or clinical characteristics were observed between treatment groups.
- Median TTNT was significantly longer among pts who received T-DXd compared to TTC (17 vs. 11 months; log-rank *P*=0.006).
- This difference remained significant after adjustment for demographic and clinical covariates, with T-DXd associated with a 48% reduced likelihood of requiring subsequent therapy (HR: 0.52; 95% CI: 0.37–0.74; *P*<0.001).

Conclusion

- **In this real-world analysis of pts with prior HER2+ therapy and documented BrM, 2L treatment with T-DXd was associated with significantly longer TTNT compared to TTC among pts with BrM.**
- **These findings may help inform treatment decisions in this high-risk population.**
- **However, interpretation is limited by the retrospective design, potential selection bias, and the use of treatment patterns to infer HER2 status.**
- **Most importantly, granular clinical data on BrM, including prior local therapies (radiation and/or surgery) and CNS-specific outcomes, were unavailable.**
- **Further prospective studies are needed to validate these findings.**

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