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US Real-World Clinical Outcomes of Tucatinib, Trastuzumab, and Capecitabine Following Trastuzumab Deruxtecan for the Treatment of HER2+ Metastatic Breast Cancer

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Objective

- This study aimed to describe real-world outcomes in US patients with HER2+ MBC in the US who were treated with TTC in the 2L, 3L, and 4L settings immediately following T-DXd and who had received at least 1 additional anti-HER2 treatment.

Conclusions

- This real-world retrospective study of patients with HER2+ MBC showed the effectiveness of TTC in a post–T-DXd setting, demonstrating clinically meaningful activity of TTC, indicated by TTNT and OS, in a contemporary treatment landscape.
- The study population reflects patients who are treated with TTC in a real-world clinical setting. These patients typically have a higher frequency of brain metastases and HR- disease.
- The results of this study reinforce the effectiveness of tucatinib in a population that reflects current clinical practice.

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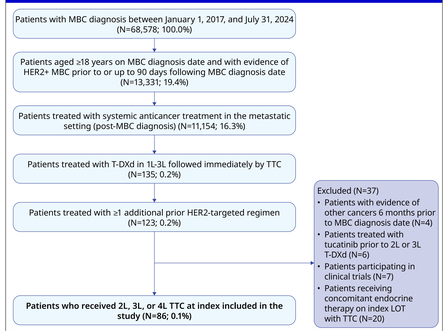
Background

- Current US and EU treatment guidelines recommend tucatinib in combination with trastuzumab and capecitabine (TTC) in the third-line (3L) setting for patients with human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (MBC) and in second-line (2L) for HER2+ MBC patients with brain metastases.[1,2]
- Approval was based on the pivotal phase II HER2CLIMB randomized clinical trial comparing TTC vs placebo + trastuzumab and capecitabine in patients with a median of 3 prior lines of therapy (NCT02614794).[3]
- Trastuzumab deruxtecan (T-DXd) is recommended also as a 2L-treatment option and may be considered as first-line treatment for patients with rapid progression after (neo)adjuvant therapy.[1,2]
- Patients enrolled in the HER2CLIMB trial were not exposed to prior T-DXd,[3] and data on clinical outcomes of TTC given after T-DXd are limited.
- Previous real-world studies in patients with HER2+ MBC receiving TTC after receiving T-DXd have reported median time to next treatment (TTNT) ranging between 5 and 7 months and median overall survival (OS) ranging between 12 and 13 months.[4,5]
- However, the patient populations in those studies included later-line treatment and did not solely include TTC immediately following T-DXd; as such, this study sought to assess the TTNT and OS of TTC immediately following T-DXd in real-world clinical practice.

Methods

- This retrospective cohort analysis (NCT06961331) included adult patients aged ≥18 years with HER2+ MBC receiving TTC from the Flatiron Health electronic health record–derived deidentified longitudinal database.
- Flatiron Health is a US nationwide database containing patient-level structured and unstructured data curated using natural language processing with machine learning and technology-enabled abstraction and includes >720,000 patients with breast cancer.[6,7]
- Patients included in this analysis were diagnosed with HER2+ MBC between January 2017 and July 2024 and treated with TTC in 2L, 3L, or fourth-line (4L) immediately following treatment with T-DXd and at least 1 additional prior anti-HER2 treatment, as per the US Prescribing Information and EU Summary of Product Characteristics. Patients treated with TTC in 2L after T-DXd had all received an additional prior anti-HER2 treatment in the (neo)adjuvant setting.
- Patients were excluded if they had evidence of other cancers 6 months prior to MBC diagnosis date, received tucatinib prior to T-DXd therapy, participated in clinical trials, or received concomitant endocrine therapy during TTC.
- Patients were assessed from the start of TTC (index date) to death, last medical activity, or at data cutoff (January 2025), whichever came first.
- Primary clinical outcomes included TTNT (from index date to start of next systemic therapy or death) and OS in all patients and by index line of therapy (LOT; 2L, 3L, and 4L); exploratory analyses assessed these outcomes by brain metastases status (yes or no), duration of T-DXd treatment (<2 and ≥2 months), and hormone receptor (HR) status (HR-positive [HR+] or HR-negative [HR-]).
- Patient characteristics were described using descriptive statistics, and time-to-event outcomes were evaluated using Kaplan-Meier analyses.

Figure 1. Study attrition



1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; HER2+, human epidermal growth factor receptor 2–positive; LOT, line of therapy; MBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TTC, tucatinib in combination with trastuzumab and capecitabine.

Results

OVERALL PATIENTS

- In total, 86 patients with HER2+ MBC received TTC immediately following T-DXd, with 12 patients in 2L (14.0%), 45 in 3L (52.3%), and 29 in 4L (33.7%) (**Table 1**; **Figure 1**).
  - Median (IQR) age was 55.0 (47.0-62.0) years, and all patients were female; of these patients, 52 (60.5%) had HR- disease and 44 (51.2%) had brain metastases on or before start of index TTC.
  - Patients who received TTC in 2L (n=12) had poor prognostic clinical features compared with patients receiving TTC in 3L or 4L (including higher proportions of patients with recurrent MBC [91.7% vs 37.8% and 41.4%], HR- [83.3% vs 53.3% and 62.1%], Eastern Cooperative Oncology Group Performance Status ≥2 [33.3% vs 13.3% and 13.8%], and brain metastases [66.7% vs 55.6% and 37.9%]).[8]
- As the large majority of patients received T-DXd for ≥2 months (98.8%), analyses by duration of T-DXd were not conducted.
- Overall, patients had a median (95% CI) TTNT of 8.8 (5.8-11.9) months and a median (95% CI) OS of 17.3 (11.9-26.1) months (**Figure 2**).
- In landmark analyses, 61% of patients were still on treatment at 6 months and 36% at 12 months (**Figure 2**). For OS, 85% of patients were still alive at 6 months and 61% at 12 months (**Figure 3**).

TTNT AND OS BY INDEX LINE OF THERAPY

- In patients receiving TTC in 2L, median (95% CI) TTNT was 5.3 (2.7-12.2) months, and OS was 13.1 (3.3-not reached [NR]); these were 9.9 (5.1-13.2) and 21.3 (14.0-31.6) in 3L, and 11.3 (4.5-22.6) and 11.9 (6.7-28.0) in 4L.
- In landmark analyses for patients receiving TTC in 2L, 45% of patients were still on treatment at 6 months and 30% at 12 months; these were 63% and 32% in 3L, and 66% and 43% in 4L.
  - In patients receiving TTC in 2L, 80% were still alive at 6 months and 64% at 12 months; these were 89% and 78% in 3L and 80% and 43% in 4L.

TTNT AND OS BY HORMONE RECEPTOR STATUS AND PRESENCE OF BRAIN METASTASES

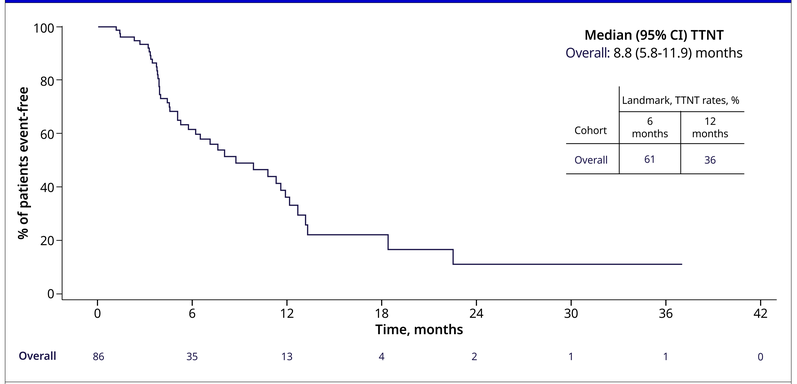
- Median (95% CI) TTNT was 13.2 (4.0-NR) months and OS was 28.8 (28.0-NR) months in patients with HR+ HER2+ MBC; these were 8.1 (4.4-11.9) and 12.7 (10.0-19.9) in patients with HR- HER2+ MBC.
- In landmark analyses for patients with brain metastases, 64% of patients were still on treatment at 6 months and 41% at 12 months; these were 60% and 32% in patients without brain metastases.
  - In patients with brain metastases, 80% were still alive at 6 months and 60% at 12 months; these were 89% and 62% in patients without brain metastases.

Table 1. Baseline characteristics in patients with HER2+ MBC: overall and by index LOT[a]

		Overall (N=86)	Index LOT		
			2L (n=12)	3L (n=45)	4L (n=29)
Age, median (IQR), years		55.0 (47.0-62.0)	55.0 (41.0-65.5)	56.0 (48.0-60.0)	53.0 (45.0-62.0)
Race, n (%)	White	48 (55.8)	7 (58.3)	25 (55.6)	16 (55.2)
	Black	14 (16.3)	0 (0.0)	6 (13.3)	8 (27.6)
	Asian	2 (2.3)	0 (0.0)	2 (4.4)	0 (0.0)
	Hispanic or Latina	5 (5.8)	0 (0.0)	4 (8.9)	1 (3.5)
	Other	10 (11.6)	3 (25.0)	5 (11.1)	2 (6.9)
	Not documented	7 (8.1)	2 (16.7)	3 (6.7)	2 (6.9)
Index treatment year, n (%)	2020	5 (5.8)	0 (0.0)	3 (6.7)	2 (6.9)
	2021	10 (11.6)	1 (8.3)	0 (0.0)	9 (31.0)
	2022	8 (9.3)	3 (25.0)	3 (6.7)	2 (6.9)
	2023	23 (26.7)	3 (25.0)	12 (26.7)	8 (27.6)
	2024	37 (43.0)	4 (33.3)	26 (57.8)	7 (24.1)
	2025	3 (3.5)	1 (8.3)	1 (2.2)	1 (3.5)
ECOG PS, n (%)	0	25 (29.1)	3 (25.0)	12 (26.7)	10 (34.5)
	1	44 (51.2)	5 (41.7)	26 (57.8)	13 (44.8)
	2	12 (14.0)	4 (33.3)	5 (11.1)	3 (10.3)
	3	2 (2.3)	0 (0.0)	1 (2.2)	1 (3.5)
	Unknown	3 (3.5)	0 (0.0)	1 (2.2)	2 (6.9)
De novo vs recurrent at MBC diagnosis, n (%)	De novo	44 (51.2)	0 (0.0)	28 (62.2)	16 (55.2)
	Recurrent	40 (46.5)	11 (91.7)	17 (37.8)	12 (41.4)
	Unknown	2 (2.3)	1 (8.3)	0 (0.0)	1 (3.5)
Stage at initial BC diagnosis, n (%)	Stage I	5 (5.8)	0 (0.0)	3 (6.7)	2 (6.9)
	Stage II	15 (17.4)	4 (33.3)	6 (13.3)	5 (17.2)
	Stage III	20 (23.3)	7 (58.3)	8 (17.8)	5 (17.2)
	Stage IV	44 (51.2)	0 (0.0)	28 (62.2)	16 (55.2)
	Not documented	2 (2.3)	1 (8.3)	0 (0.0)	1 (3.5)
HR status, n (%)	HR+	17 (19.8)	0 (0.0)	11 (24.4)	6 (20.7)
	HR-	52 (60.5)	10 (83.3)	24 (53.3)	18 (62.1)
	Unknown	17 (19.8)	2 (16.7)	10 (22.2)	5 (17.2)
Number of metastatic sites, n (%)	1	19 (22.1)	3 (25.0)	10 (22.2)	6 (20.7)
	2	22 (25.6)	3 (25.0)	9 (20.0)	10 (34.5)
	≥3	40 (46.5)	4 (33.3)	25 (55.6)	11 (37.9)
	Missing	5 (5.8)	2 (16.7)	1 (2.2)	2 (6.9)
Presence of BM on or before index TTC, n (%)	Yes	44 (51.2)	8 (66.7)	25 (55.6)	11 (37.9)
	No	42 (48.8)	4 (33.3)	20 (44.4)	18 (62.1)
Median (IQR) duration of T-DXd treatment, months		13.3 (8.6-17.8)	10.1 (7.5-13.7)	13.4 (8.5-18.4)	13.6 (9.2-20.3)
Median (IQR) follow-up,[b] months		7.5 (3.7-14.0)	5.6 (3.7-13.3)	7.6 (3.8-14.0)	8.5 (3.6-14.8)

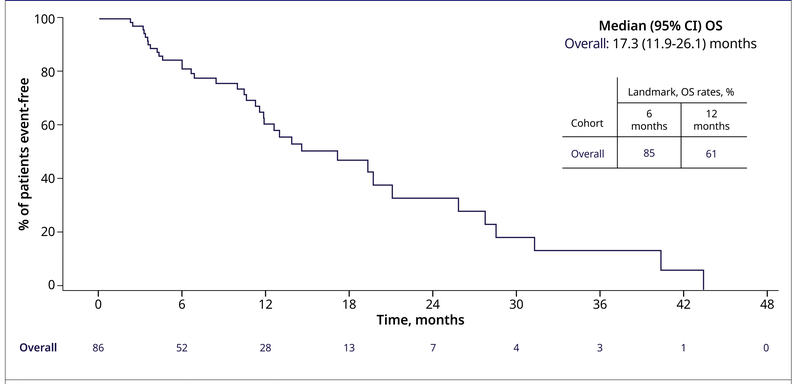
2L, second-line; 3L, third-line; 4L, fourth line; BC, breast cancer; BM, brain metastases; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; LOT, line of therapy; MBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TTC, tucatinib in combination with trastuzumab and capecitabine.
[a]The start of the first treatment within the TTC regimen was the LOT index date. [b]Follow-up duration was calculated as the number of months from index date to death from any cause else censored at earliest of last confirmed activity or data cutoff.

Figure 2. TTNT in patients with HER2+ MBC



HER2+, human epidermal growth factor receptor 2–positive; MBC, metastatic breast cancer; TTNT, time to next treatment.

Figure 3. OS in patients with HER2+ MBC



HER2+, human epidermal growth factor receptor 2–positive; MBC, metastatic breast cancer; OS, overall survival.

STUDY LIMITATIONS

- Limitations of this study include the potential for treatment selection bias, inaccurate or incomplete data capture, and potential inconsistencies in frequency of tumor assessments across sites, which are inherent to retrospective database analyses.
- Additionally, sample sizes in this study were small, with sample sizes and patient characteristics varying across index LOTs, which may limit the interpretability and/or generalizability of findings.
- As Flatiron defines LOT using a rule-based approach, reasons for patients being assigned to a later LOT other than disease progression may exist (such as toxicity switches) due to variation in real-world care.
- Brain metastases are not systematically assessed in the real-world setting, so there may be variability in the capture of events between patients.
- Short follow-up periods (with patients not yet reaching study endpoints) and high amounts of censoring in OS and TTNT curves may affect the interpretation of findings and potentially cause point estimates to be unstable.

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