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Patient Characteristics, Treatment Patterns, and Clinical Outcomes Associated With Tucatinib Therapy in HER2+ Metastatic Breast Cancer

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Background

- Tucatinib is an oral tyrosine kinase inhibitor approved in multiple countries in combination with trastuzumab and capecitabine for adult patients with human epidermal growth factor 2 (HER2)+ metastatic breast cancer (MBC), including patients with brain metastases, who have received ≥1 prior anti-HER2–based regimens in the metastatic setting.[1-4]
- In HER2CLIMB, a phase 2, randomized, placebo-controlled trial, tucatinib in combination with trastuzumab and capecitabine demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS) with a tolerable safety profile in 612 patients with HER2+ MBC (including those with previously untreated, treated and stable, or treated and progressing brain metastases).[1,4]
  - For patients receiving tucatinib, trastuzumab, and capecitabine, median OS was 21.9 (95% CI: 18.3–31.0) months and 12-month survival probability was 75.5% (95% CI: 70.4–70.9).[4]
  - Median progression-free survival (PFS) was 7.8 (95% CI: 7.5–9.6) months; the proportion (95% CI) of patients who had not progressed at 6 and 12 months was 62.9% (56.9–68.4) and 33.1% (26.6–39.7), respectively.[4,5]
- To inform clinical decision-making, it is important to understand tucatinib utilization in real-world clinical practice, including patient characteristics and clinical outcomes for tucatinib-treated patients with HER2+ MBC.

Objective

- To describe patient characteristics, treatment patterns, and clinical outcomes for patients treated with tucatinib-based regimens in the real-world setting.

Methods

- This retrospective cohort study included patients with HER2+ MBC diagnosed with metastatic disease between January 2017 and July 2022 in the nationwide de-identified electronic health record–derived Flatiron Health Metastatic Breast Cancer database. Data were collected from patients who received tucatinib-based treatment outside of a clinical trial setting.
- Demographic and clinical characteristics of patients were described during the baseline period prior to tucatinib initiation.
- Key outcomes were measured from the initiation of tucatinib therapy and included median OS (OS), median time to next treatment (TTNT) as a proxy for PFS[6], median time to discontinuation (TTD), and persistence rates (proportion of patients remaining on therapy at 9, 12, and 18 months).
  - Time-to-event analyses were conducted using Kaplan-Meier methodology to account for censoring.

Results

Patient characteristics

- Of 31,059 patients with MBC in the database, 3,115 had evidence of being HER2+. Of these HER2+ patients, 183 received tucatinib-based treatment and met all inclusion criteria (**Table 1**).

Table 1. Patient attrition

Criteria	N (% of prior step)
Were MBC patients in Flatiron (July 2022 data cut)	31,059
Were diagnosed on or after January 1, 2017	15,138 (49%)
Possessed evidence of HER2-receptor positivity prior to or within 90 days of index date[a]	3,115 (21%)
Received tucatinib	211 (6.8%)
Had recorded activity within 90 days; aged ≥18 years at index date[a]	193 (91%)
Received systemic anticancer treatment in the metastatic setting following tucatinib	188 (97%)
Had no evidence of other primary cancers in the 6 months prior to index	184 (98%)
Had ≥1-day supply documented in the EMR	183 (99%)

[a]Defined as the date of first diagnosis of HER2+ MBC.
EMR, electronic medical record; HER2, human epidermal growth factor 2; MBC, metastatic breast cancer.

- Compared with the HER2CLIMB trial population, a higher proportion of patients in this study had brain metastases pre-tucatinib treatment. Patients in this study also had poorer performance status, greater racial diversity, and fewer prior lines of therapy compared with those in the HER2CLIMB trial (**Table 2**).
- Median (interquartile range, IQR) lines of prior therapy were 2 (1–3) among all patients and 1 (1–3) and 3 (2–4) among patients with and without brain metastases pre-tucatinib, respectively, indicating a trend of earlier use of tucatinib-based treatment among patients with brain metastases versus those without brain metastases.
- Median (IQR) follow-up from the start of tucatinib-based treatment was 10 (5–15) months.

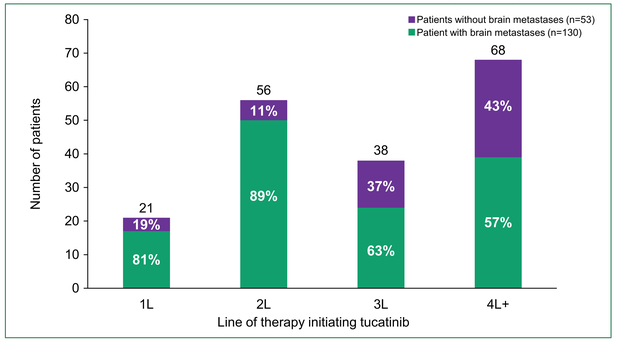
Table 2. Baseline characteristics[a] for patients receiving tucatinib in the Flatiron database and HER2CLIMB trial

Characteristic	Flatiron (N=183)	HER2CLIMB (N=410)
Age (years), median (range)	56 (28–84)	54 (25–80)
Race, n (%)		
White	101 (55)	287 (70)
Black	25 (14)	41 (10)
Asian	6 (3.3)	18 (4.4)
Unknown/Other	51 (28)	64 (16)
De novo at diagnosis, n (%)	75 (41)	143 (35)
ECOG, n (%)		
0	59 (32)	204 (50)
1	67 (37)	161 (50)
2+	17 (9)	n/a
Missing	40 (22)	n/a
Sites of metastasis[b], n (%)		
Brain	130 (71)	198 (48)
Bone	112 (61)	223 (54)
Lung	73 (40)	200 (49)
Liver	81 (44)	137 (33)
Prior lines of therapy, median (range)	2 (0–7)	3 (1–14)

[a]Data for the Flatiron database refer to the period prior to tucatinib treatment initiation. [b]Not mutually exclusive.
ECOG, Eastern Cooperative Oncology Group; n/a, not available.

- Overall, of the 183 patients who received tucatinib-based treatment regimens, 71% had brain metastases prior to treatment initiation. Number and proportion of patients with/without brain metastases in each line of therapy are displayed in **Figure 1**.

Figure 1: Proportion of patients with and without brain metastases[a] receiving tucatinib by line of therapy



[a]Prior to tucatinib-based treatment initiation.
1L, first-line; 2L, second-line; 3L, third-line; 4L+, fourth-line and beyond; BM, brain metastases.

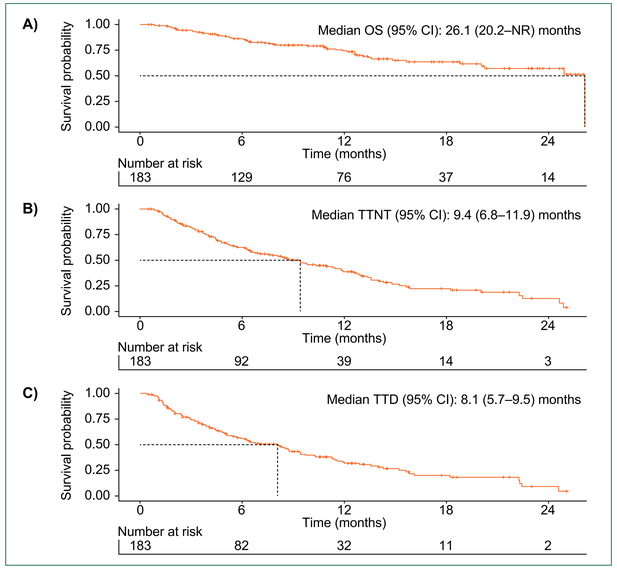
Treatment patterns

- Most patients (n=135; 74%) received tucatinib in combination with trastuzumab and capecitabine.
  - Of the 135 patients initiating triplet therapy, 10 (7.4%) discontinued capecitabine ≥1 month prior to discontinuing tucatinib therapy.
- Of the 48 patients who did not receive tucatinib, trastuzumab, plus capecitabine, 20 (42%) patients received tucatinib with trastuzumab, 14 (29%) tucatinib with capecitabine, 7 (15%) tucatinib monotherapy, and 7 (15%) other tucatinib combinations.
- The most common regimens prior to 2L tucatinib-based treatment were trastuzumab plus pertuzumab-based, and the most common regimens immediately following 2L tucatinib-based treatment were trastuzumab-based and trastuzumab deruxtecan (T-DXd).
- The most common regimens immediately prior to and following 3L tucatinib-based treatment were T-DM1 and T-DXd, respectively.
- Twenty-nine patients received tucatinib immediately following T-DXd therapy (median lines of therapy prior to tucatinib was 3).
  - Median (range) duration of T-DXd was 3.7 (0–21) months.

Real-world OS

- Median OS (95% CI) was 26.1 (20.2–not reached [NR]) months from initiation of tucatinib treatment (**Table 3**, **Figure 2A**).
  - 6- and 12-month survival probability (95% CI) were 86.1% (81.0–91.6), and 74.2% (67.3–81.9), respectively.
- In 2L and 3L, 12-month survival probability (95% CI) was 84.1% (75.6–93.5) for patients receiving any tucatinib regimen and 83.5% (73.3–95.2) for patients receiving the FDA-labeled tucatinib triplet combination (**Table 3**).

Figure 2. Kaplan-Meier curves for (A) OS, (B) TTNT, and (C) TTD among patients with and without brain metastases receiving tucatinib



CI, confidence interval; NR, not reached; OS, overall survival; TTD, time to discontinuation; TTNT, time to next treatment.

Real-world TTNT

- Among all patients, median (95% CI) TTNT was 9.4 (6.8–11.9) months from initiating tucatinib treatment (**Table 3**, **Figure 2B**).

Real-world TTD and persistence rates

- Median (95% CI) TTD was 8.1 (5.7–9.5) months in the overall population and slightly longer in patients receiving tucatinib in 2L or 3L (**Table 3**, **Figure 2C**).
- At 12 months, 32 of the 76 (42%) patients with follow-up in the overall population still were on therapy.

Outcomes for the post-T-DXd tucatinib cohort

- For patients who received tucatinib immediately following T-DXd (n=29), median OS (95% CI) was 12.6 (11.9–NR) months, with a 12-month survival probability (95% CI) of 61.8% (43.2–88.5).
- Median (95% CI) TTNT was 8.1 (4.0–NR) months.
- Median (95% CI) TTD was 8.1 (3.6–11.9) months. Of these patients, 16 had follow-up ≥12 months, and 11 (69%) persisted on tucatinib therapy.

Table 3. Median OS, TTNT, and TTD among patients receiving tucatinib-based regimens

Efficacy outcomes	Flatiron: *Overall* (N=183)	Flatiron 2L+3L: *Any tucatinib regimen* (n=94)	Flatiron 2L+3L: *Approved tucatinib triplet*[a] (n=70)
OS			
Median, months (95% CI)	26.1 (20.2–NR)	NR (NR–NR)	NR (NR–NR)
Survival probability, % (95% CI)			
6 months	86.1 (81.0–91.6)	92.8 (87.4–98.5)	93.5 (87.6–99.9)
9 months	79.8 (73.8–86.4)	90.0 (83.6–96.9)	91.7 (85.0–99.0)
12 months	74.2 (67.3–81.9)	84.1 (75.6–93.5)	83.5 (73.3–95.2)
TTNT			
Median, months (95% CI)	9.4 (6.8–11.9)	9.5 (6.8–13.6)	9.5 (6.5–13.6)
Probability of not starting new therapy, % (95% CI)			
6 months	62.5 (55.5–70.4)	64.3 (54.7–75.5)	66.0 (55.2–79.1)
9 months	50.1 (42.7–58.8)	54.7 (44.7–66.8)	55.1 (43.7–69.4)
12 months	38.9 (31.4–48.3)	42.6 (32.4–56.0)	41.3 (29.7–57.3)
TTD			
Median, months (95% CI)	8.1 (5.7–9.5)	8.8 (6.3–11.3)	8.6 (6.3–11.3)
Persistence rates[b], % (n/N)			
9 months	53 (52/98)	56 (30/54)	54 (22/41)
12 months	42 (32/76)	40 (17/42)	40 (12/30)
18 months	30 (11/37)	27 (6/22)	24 (4/17)

[a]Patients received a minimum of the approved tucatinib triplet of tucatinib in combination with trastuzumab and capecitabine. [b]Proportion of patients with follow-up and still on therapy at 6, 12, and 18 months.
2L, second-line; 3L, third-line; CI, confidence interval; OS, overall survival; NR, not reached; TTD, time to discontinuation; TTNT, time to next treatment.

Limitations

- Study findings may be influenced by the choice of study period.
- These analyses are unadjusted and purely descriptive in nature. We cannot rule out any impact of potentially confounding factors.
- Inherent to all electronic health record–derived data, the analyses were limited by the potential for missing data.
- The median follow-up duration was 10 months; further follow-up is required to better understand clinical outcomes for patients treated with tucatinib-based regimens in the real-world setting.

Conclusions

- The majority (71%) of patients receiving tucatinib-based treatment in clinical practice in the US have brain metastases at treatment initiation, this percentage constitutes a larger proportion of the treated population than in HER2CLIMB (~48% of patients).
- In real-world practice, tucatinib-based treatment was initiated sooner, as an earlier line of therapy, in patients with brain metastases than in those without brain metastases.
- While the populations are not directly comparable, tucatinib-based treatment in the real-world setting is associated with a similar median OS, median TTNT (as a proxy for PFS),[6] and median TTD as observed in HER2CLIMB, reinforcing its durable efficacy in patients with HER2+ MBC with and without brain metastases.
- A potential benefit in OS, TTNT, and TTD was also observed in a subgroup of patients who received tucatinib following T-DXd.

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