

Trastuzumab Use Among Patients With HER2-Positive Metastatic Breast Cancer in an Electronic Health Records Database

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Background

- Breast cancer (BC) is the most common cancer among women in the United States (US), representing an estimated 268,600 new cancer cases in 2019.¹
- Approximately 5.6% of women are initially diagnosed with metastatic BC (MBC),² and an estimated 7% of women progress to metastatic disease within 5 years of diagnosis with early BC (EBC).³
- The human epidermal growth factor receptor 2-positive (HER2+) molecular subtype of BC accounts for around 15% of all female BC diagnosed in the US,⁴ and over one-quarter of de novo MBC.⁵
 - Increased levels of HER2 have been associated with a high likelihood of metastasis and relapse, and poor prognosis.^{3,5,6}
 - Among HER2+ EBC patients, the 5-year progression rate to MBC is 13.0%.³
- Trastuzumab is a commonly used HER2-directed therapy for BC patients in both the early (ie, neo-adjuvant/adjuvant) and metastatic settings. However, real-world data on retreatment with trastuzumab in the metastatic setting, and outcomes associated with retreatment, are lacking.

Objectives

- The primary objective of this study was to describe real-world patterns of trastuzumab use and retreatment among HER2+ MBC patients.
- Among HER2+ MBC patients who completed 2 or more lines of therapy, a secondary study objective was to describe overall survival among those who received trastuzumab in only 1 line vs those who were retreated in multiple lines.

Methods

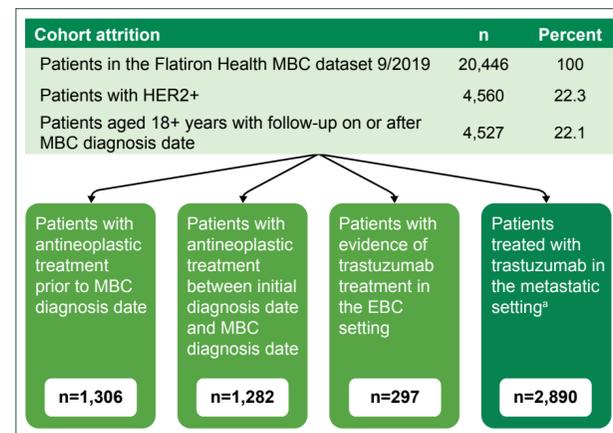
- Patients aged ≥18 years at MBC diagnosis with HER2+ disease, treatment with trastuzumab in the metastatic setting, and follow-up on or after MBC diagnosis were identified in the Flatiron Health MBC database from January 2011 to August 2019.
 - The Flatiron Health database is a nationwide, longitudinal, demographically and geographically diverse, de-identified database derived from electronic health record (EHR) data from over 280 cancer clinics in the US.
- Patient demographic and clinical characteristics (age, stage at diagnosis, Eastern Cooperative Oncology Group [ECOG] score, biomarker status), trastuzumab use (line number and duration of initial and subsequent use), and time to next trastuzumab-containing regimen were described.
- Among patients who received 2 or more lines of therapy, overall survival was described separately for those who received trastuzumab in only 1 line and those who were retreated in multiple lines.

Results

Patient population

- A total of 3,187 HER2+ MBC patients who had evidence of trastuzumab treatment were identified in the Flatiron Health EHR database, including 2,890 who received trastuzumab in the metastatic setting (study population) (Figure 1).

Figure 1. Cohort attrition



*Metastatic setting cohort (ie, study population).
EBC, early breast cancer; HER2+, human epidermal growth factor receptor 2-positive; MBC, metastatic breast cancer.

Baseline demographic and clinical characteristics

- Among patients treated with trastuzumab in the metastatic setting (n=2,890), the median age was 60 years (Table 1).
- 47.0% (n=1,358) were initially diagnosed as stage 0–III, 45.4% (n=1,312) were initially diagnosed as stage IV and 7.6% (n=220) had a missing/unknown stage at initial diagnosis.
- 74.5% (n=2,153) were hormone receptor-positive.
- The first HER2+ tissue collection site was the primary site for 70.1% of patients.
- Median follow-up was 26.2 (range: 12.4–44.9) months.
- The most common initial trastuzumab-containing regimens in the metastatic line were trastuzumab/pertuzumab/chemotherapy (43.7%, n=1,264), trastuzumab/chemotherapy (18.1%, n=522) and trastuzumab/hormone therapy (13.4%, n=387).

Patterns of trastuzumab use and retreatment

- Most (73.4%, n=2,121) patients in the metastatic setting were initially treated with trastuzumab in the first line (Figure 2A).
- Almost half (48.1%, n=1,390) of patients were retreated with trastuzumab; of these, the majority (62.0%, n=862) were retreated with trastuzumab in the second line metastatic setting.
- The majority of retreated patients (89.2%, n=1,240) were retreated in consecutive lines and 30.1% (n=419) in non-consecutive lines (Figure 2B).
- Duration of first and second use of trastuzumab by line of therapy, and median time between end of first trastuzumab use and initiation of retreatment, are shown in Figures 3A and 3B.
 - Across all lines of therapy, the median duration of initial trastuzumab use was 5.1 months and the median duration of second trastuzumab use was 5.3 months.
 - The median time from initial trastuzumab treatment to retreatment (second use) was 5.5 months.
- Among patients who received trastuzumab in the metastatic setting and were retreated in a non-consecutive line (n=419), 62.1% (n=260) received T-DM1-based combination therapy directly after the first trastuzumab use and prior to trastuzumab retreatment.

- Of patients who received trastuzumab only once (n=1,500), 49.7% received only 1 line of therapy, 28.6% received 2 lines of therapy and 21.7% received 3 or more lines of therapy.

- Of patients retreated with trastuzumab in multiple lines (n=1,390), 23.7% received 2 lines of therapy and 76.3% received 3 or more lines of therapy.

Overall survival by treatment with trastuzumab in 1 line only vs treatment in multiple lines

- Among patients who received 2 or more lines of therapy (n=2,114), those who were treated with trastuzumab in only 1 line of therapy had a shorter median overall survival than those who were retreated with trastuzumab in multiple lines (median 29.6 [95% confidence interval (CI), 25.7–33.8] months and 44.1 [95% CI, 41.6–48.3] months, respectively; Figure 4).

Table 1. Demographic and clinical characteristics in the metastatic cohort

Characteristic	Patients, n	Percent
Total	2,890	100
Median age at metastatic diagnosis, years	60.0	
Stage at initial diagnosis		
Stage 0	1	0.0
Stage I	232	8.0
Stage II	555	19.2
Stage III	570	19.7
Stage IV	1,312	45.4
Unknown/missing	220	7.6
ECOG score ^a		
0	365	12.6
1	221	7.7
2+	76	2.6
Missing	2,228	77.1
Biomarker status ^b		
ER+	2,062	71.4
ER–	827	28.6
PR+	1,628	56.3
PR–	1,249	43.2
HR+ (ER+ or PR+)	2,153	74.5
HR– (ER– and PR–)	732	25.3
Median (range) follow-up time, ^c months	26.2	12.4–44.9
Comorbid conditions prior to trastuzumab use (5 most common)		
Hypertension	439	15.2
Pain	369	12.8
Haematologic disorders	362	12.5
Hyperlipidaemia	230	8.0
Diabetes	185	6.4

^aECOG score was identified from closest record within –30 and +7 days from metastatic diagnosis date; if multiple scores occurred on the same day, the higher score was chosen.

^bER and PR statuses were determined using biomarker table: any positive > any negative > unknown.

^cFollow-up time is defined from metastatic diagnosis date to end of follow-up (death or end of activity). ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; HR, hormone receptor; PR, progesterone receptor.

Figure 2. Patterns of trastuzumab use: line of therapy of initial use (n=2,890) and retreatment (n=1,390) (A), and retreatment in consecutive vs non-consecutive lines of therapy (B)

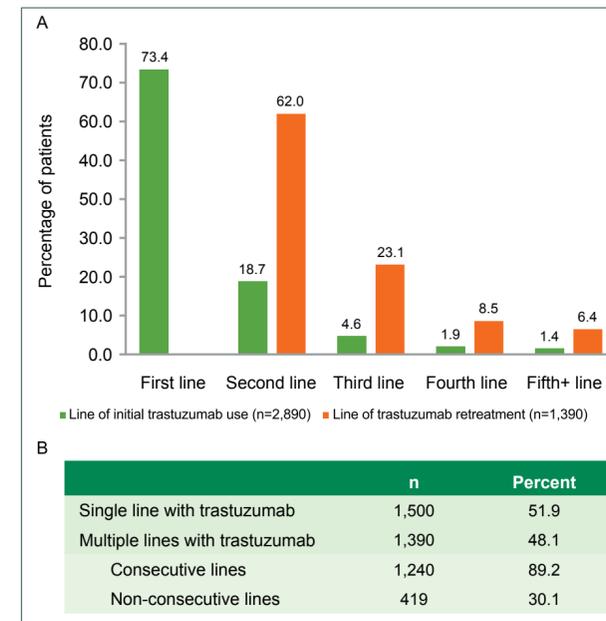


Figure 3. Duration of trastuzumab use by line of therapy (A), and time between first and second trastuzumab use (B)

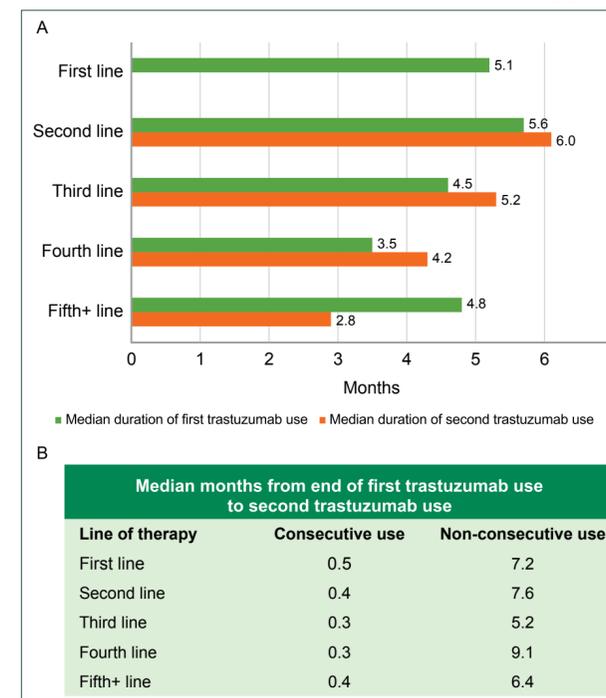
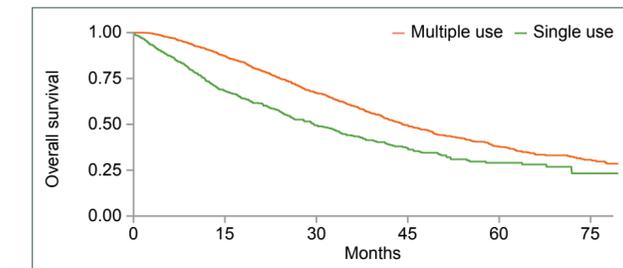


Figure 4. Overall survival by single vs multiple uses of trastuzumab among patients who completed ≥2 lines of therapy



Limitations

- Although the Flatiron database population is nationally and demographically diverse, the use of data from community oncology clinics may limit the generalizability to other treatment settings.
- Standard of care treatment in first- and second-line MBC changed during the course of the study data, such that patients treated at different time points (eg, prior to 2013⁷) may not be directly comparable.
- We cannot eliminate the possibility that patient-level treatment choices may have been influenced by disease-related factors that are associated with overall survival.

Conclusions

- Our study showed that almost half of HER2+ MBC patients in community practice settings who received trastuzumab were treated with trastuzumab in multiple lines of therapy, with most patients retreated in consecutive lines.
- Among patients who received 2 or more lines of therapy, those who were retreated with trastuzumab had longer overall survival than patients treated with trastuzumab in 1 line only.
 - These results are supported by a recent meta-analysis⁹ that found retreatment with trastuzumab results in a statistically significant prolongation of progression-free survival and overall survival among patients with HER2+ MBC.
 - Further research is needed to explore the association of trastuzumab treatment patterns and outcomes in real-world settings.

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