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ORIGINAL RESEARCH

Real-World Treatment Patterns and Outcomes Following First-Line Pertuzumab and Trastuzumab Among Patients with HER2+ Metastatic Breast Cancer

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ABSTRACT

Introduction: Many patients with human epidermal growth factor receptor-2-positive metastatic breast cancer (HER2+ mBC) require subsequent lines of therapy (LOTs) after being treated with pertuzumab and trastuzumab-based regimens in the first line (1L). Although the efficacy of the second-line (2L) therapies has been demonstrated in clinical trials, the real-world effectiveness of these treatments is understudied. This retrospective cohort study assessed the real-world treatment patterns and outcomes for patients with HER2+ mBC following 1L therapy with pertuzumab and trastuzumab-based regimens in the United States (US) during 2015–2019.

Methods: Adults with HER2+ mBC in the US who initiated 1L pertuzumab and trastuzumab-based regimens between 01/01/2015 and 09/30/2019 and had ≥ 60 days of follow-up after 1L initiation were identified from the IQVIA Oncology Electronic Medical Records database. The regimens utilized in 2L following 1L pertuzumab and trastuzumab-based regimens were described. Median treatment duration and time to treatment failure were reported for 2L based on Kaplan–Meier analyses.

Results: Of the 710 eligible patients who received pertuzumab and trastuzumab-based regimens in 1L (median age: 57.0 years [interquartile range: 48.0–65.0]; median follow-up: 20.3 months; median 1L duration: 15.3 months), 222 (31.3%) initiated 2L. The most common regimens in 2L were ado-trastuzumab emtansine (T-DM1)-based regimens (n = 159 [71.6%]), followed by lapatinib-based (n = 21 [9.5%]) and neratinib-based (n = 18 [8.1%]) regimens. The median treatment duration and time to treatment failure were 5.9 (95% CI: 5.0, 8.7) and 8.6 (7.3, 11.5) months, respectively, among patients initiating 2L, and 5.7 (4.7, 7.8) and 7.9 (6.5, 10.0) months among those receiving 2L T-DM1.

Conclusions: Most patients with HER2+ mBC requiring additional treatments after 1L pertuzumab and trastuzumab-based regimens utilized T-DM1 in 2L during 2015–2019. The short median treatment duration and time to treatment failure highlight an unmet need that can potentially be fulfilled by recently approved treatment options.

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Keywords: HER2+ metastatic breast cancer; First-line pertuzumab and trastuzumab second-line T-DM1; Treatment patterns and outcomes

Key Summary Points

Why carry out the study?

The real-world effectiveness of treatments after first-line (1L) pertuzumab and trastuzumab for patients with human epidermal growth factor receptor-2-positive metastatic breast cancer (HER2+ mBC) is understudied.

What was learned from the study?

This retrospective cohort study assessed the real-world treatment patterns, treatment duration, and time to treatment failure of second-line (2L) therapies for patients with HER2+ mBC following 1L pertuzumab and trastuzumab-based regimens in the United States during 2015–2019. Among patients on 1L trastuzumab and pertuzumab based regimen, about 31% progressed and moved to 2L and about 5% died on 1L.

The most common therapies used in 2L were ado-trastuzumab emtansine (T-DM1)-based regimens, irrespective of a brain metastasis diagnosis prior to the initiation of 2L, while 2L T-DM1 was associated with a short treatment duration (around 6 months) and a short time to treatment failure (8 months).

The short median treatment duration and time to treatment failure highlight an unmet need that can potentially be fulfilled by recently approved treatment options. More recent 2L treatments with better efficacy results will offer the opportunity to improve the outcomes of patients with HER2+ mBC who failed 1L trastuzumab and pertuzumab-based regimen.

INTRODUCTION

Breast cancer (BC) is the most common malignancy among women in the United States (US), accounting for approximately 15% of all new cancer cases and 7% of cancer deaths in 2021 [1]. Approximately 5% of patients with BC have metastatic disease (mBC) at diagnosis, while 30% of patients initially diagnosed with early-stage BC ultimately develop metastases [2, 3].

The prognosis and survival of patients with mBC are influenced by the presence of human epidermal growth factor receptor-2 (HER2), a receptor tyrosine kinase expressed in normal tissues as well as in some cancers [2]. Approximately 14% of US women with mBC have HER2 overexpression (HER2+), which is associated with rapid cell growth, but the advent of anti-HER2 therapies has dramatically improved clinical outcomes of HER2+ mBC [4–7]. In 2011–2017, the 5-year survival rate for HER2+ mBC in the US was estimated at 44.7% for hormonal receptor (HR)-positive disease and 37.9% for HR-negative disease [4]. Despite the improved prognosis, disease recurrence in HER2+ BC still imposes a heavy economic burden on healthcare systems and society; it was estimated to incur $240 million to $1.7 billion in lifetime costs in a systematic literature review [8].

To date, three types of anti-HER2 therapies have been approved by the US Food and Drug Administration (FDA) for the treatment of HER2+ mBC: monoclonal antibodies, including trastuzumab (approved by the FDA in 1998 [9]), pertuzumab (2012 [10]), and margetuximab (2020 [11]); tyrosine kinase inhibitors (TKIs), including lapatinib (2007 [12]), neratinib (2017 [13]), and tucatinib (2020 [14]); and antibody–drug conjugates (ADCs), including ado-trastuzumab emtansine (T-DM1; 2013 [15]), and trastuzumab deruxtecan (2019 [16]). The current guidelines from the National Comprehensive Cancer Network® (NCCN®; v.4.2023) and the American Society for Clinical Oncology (ASCO; 2022) recommend a combination of pertuzumab, trastuzumab, and a taxane as a preferred first-line (1L) regimen option and trastuzumab deruxtecan as a preferred

second-line (2L) regimen option for HER2+ recurrent unresectable or stage IV disease [17, 18].

A recent analysis using a prospective observational registry (SystHERs) showed that 75% of the patients with HER2+ mBC received pertuzumab and trastuzumab combination therapy in 1L, with a median treatment duration of 17.2 months [19]. While T-DM1 and other anti-HER2 therapies have demonstrated efficacy in patients progressing on 1L trastuzumab-based regimens in clinical trials [20–24], data on the real-world outcomes associated with these treatments in a broader US population are limited [25, 26]. Such real-world effectiveness data could complement clinical trial data to assist healthcare decision-makers regarding patient management, resource allocation, and the identification of unmet needs among these patients.

The objective of this study was to assess the real-world treatment patterns and outcomes (i.e., treatment duration and time to treatment failure) for patients with HER2+ mBC following 1L therapy with pertuzumab and trastuzumab in US oncology practices.

METHODS

Data Source

Patients with HER2+ mBC in the US who initiated 1L pertuzumab and trastuzumab-based regimens between January 1, 2015 and September 30, 2019 were identified in the IQVIA Oncology Electronic Medical Records (EMR) database. This database includes EMR records from a representative network of community and academic oncology practices covering at least one million oncology patients from 2012 onward treated by approximately 950 practicing oncologists in over 40 US states. Data elements include patient demographics, oncology and non-oncology therapy administrations and medication orders, diagnoses, and lab test results (including HER2 status). Although vital status was available, data on the date of death were not documented in the database and were imputed using the last encounter in the EMR as a proxy, as suggested by previous literature [27]. Since this study used deidentified pre-existing data in the EMR database, no ethical approval was required. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Study Design

Study Sample

This study used a retrospective cohort design. The study sample included female and male patients with HER2+ mBC who initiated 1L pertuzumab and trastuzumab-based regimens after January 1, 2015 and had ≥ 60 days of follow-up (i.e., at least one clinical activity) after 1L initiation. Patients who died within 60 days of 1L initiation were also included. BC was identified using the International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM) codes of 174.xx and 175.xx, and the International Classification of Diseases, 10th edition, Clinical Modification (ICD-10-CM) codes of C50.x. The mBC diagnosis date was defined as the date of the first secondary malignant neoplasm diagnosis record (ICD-9-CM: 196–198; ICD-10-CM: C77–C79) in the EMR data. Patients with HER2+ status were identified by a positive HER2 test result during the study period. Pertuzumab and trastuzumab-based regimens were defined as those including pertuzumab and trastuzumab ± other systemic treatments not targeting HER2. The date of 1L initiation was defined as the index date.

Identification of Lines of Therapy

The lines of therapy (LOTs) after the HER2+ mBC diagnosis date were defined using an algorithm adapted from Dalal et al. [28]. Treatments for mBC were identified through administration and order records in the EMR and included the following: HER2-targeted agents available during the study period (trastuzumab, pertuzumab, T-DM1, lapatinib, and neratinib); chemotherapy (e.g., taxanes, platinum-based, antimetabolites, and anthracyclines); hormonal therapy; immuno-oncology therapy (nivolumab, pembrolizumab, and atezolizumab); and other targeted therapy

(alpelisib, bevacizumab, cetuximab, everolimus, olaparib, and palbociclib). A treatment regimen was defined as all concomitant anticancer treatments used within 14 days of the initiation of an index intravenous therapy or all anticancer treatments used within 30 days of the initiation of an index oral drug in a LOT.

LOT discontinuation was defined as the initiation of a new LOT, a treatment gap of ≥ 365 days without an anti-HER2 treatment (for regimens including anti-HER2 agents) or without any mBC treatments (for the remaining regimens), or death. A new LOT was initiated when a new anti-HER2 agent was initiated, the patient switched to a different class of chemotherapy, or the same regimen was re-initiated after a gap of at least 365 days.

Outcomes

Baseline Characteristics and Treatment Patterns After a 1L Trastuzumab and Pertuzumab-Based Regimen

Patient demographics as of the index date (age, sex, and US region of residence); HR status (i.e., with estrogen or progesterone receptors); and the Eastern Cooperative Oncology Group (ECOG) functional status score within ± 1 month of the index date were summarized. The median treatment duration of 1L was also reported.

Treatment patterns in 2L were assessed. In addition, treatment patterns for 2L were compared between patients with and without brain metastases (BM) diagnoses (ICD-9-CM: 198.3; ICD-10-CM: C79.31 and C79.32) prior to 2L initiation.

Treatment Outcomes Associated with 2L Therapies

Treatment outcomes, including treatment duration and time to treatment failure, were reported for patients receiving 2L therapies. To be included in this analysis, patients were further required to have ≥ 60 days of follow-up following the initiation of 2L to ensure sufficient time for observation. Patients who died within 60 days of 2L initiation were included. Treatment duration was defined as the time from the initiation to the discontinuation of 2L. Time to treatment failure was defined as the duration from the initiation of 2L until the initiation of the next LOT or death. Patients without a treatment discontinuation or treatment failure event were censored at their last follow-up date.

Statistical Analyses

Baseline patient characteristics and treatment patterns were analyzed using descriptive statistics. For treatment outcomes, the median time to event was reported based on Kaplan–Meier (KM) analyses. Outcomes analyses were also conducted among patients with the most common regimens in 2L.

RESULTS

Baseline Characteristics

A total of 710 patients (median age: 57.0 years [interquartile range: 48.0–65.0]) with HER2+ mBC were treated with 1L pertuzumab and trastuzumab-based regimens (Fig. 1); the median follow-up was 20.3 months from 1L initiation. Of these patients, 47.3% were HR positive, 26.5% were HR negative, and 26.2% had unknown HR status (Table 1). The majority of patients ($n = 656$ [92.4%]) received 1L pertuzumab and trastuzumab in combination with other mBC treatments, including 569 (80.1%) who received pertuzumab and trastuzumab in combination with a taxane and 50 (7.0%) who received pertuzumab and trastuzumab in combination with hormonal therapy. The remaining 54 (7.6%) patients received pertuzumab and trastuzumab only, without other mBC treatments. The median duration of 1L was 15.3 (95% confidence interval [CI]: 13.4, 17.6) months.

2L Treatment Patterns After 1L Pertuzumab and Trastuzumab

Among all 710 patients, 222 (31.3%) discontinued 1L pertuzumab and trastuzumab-based

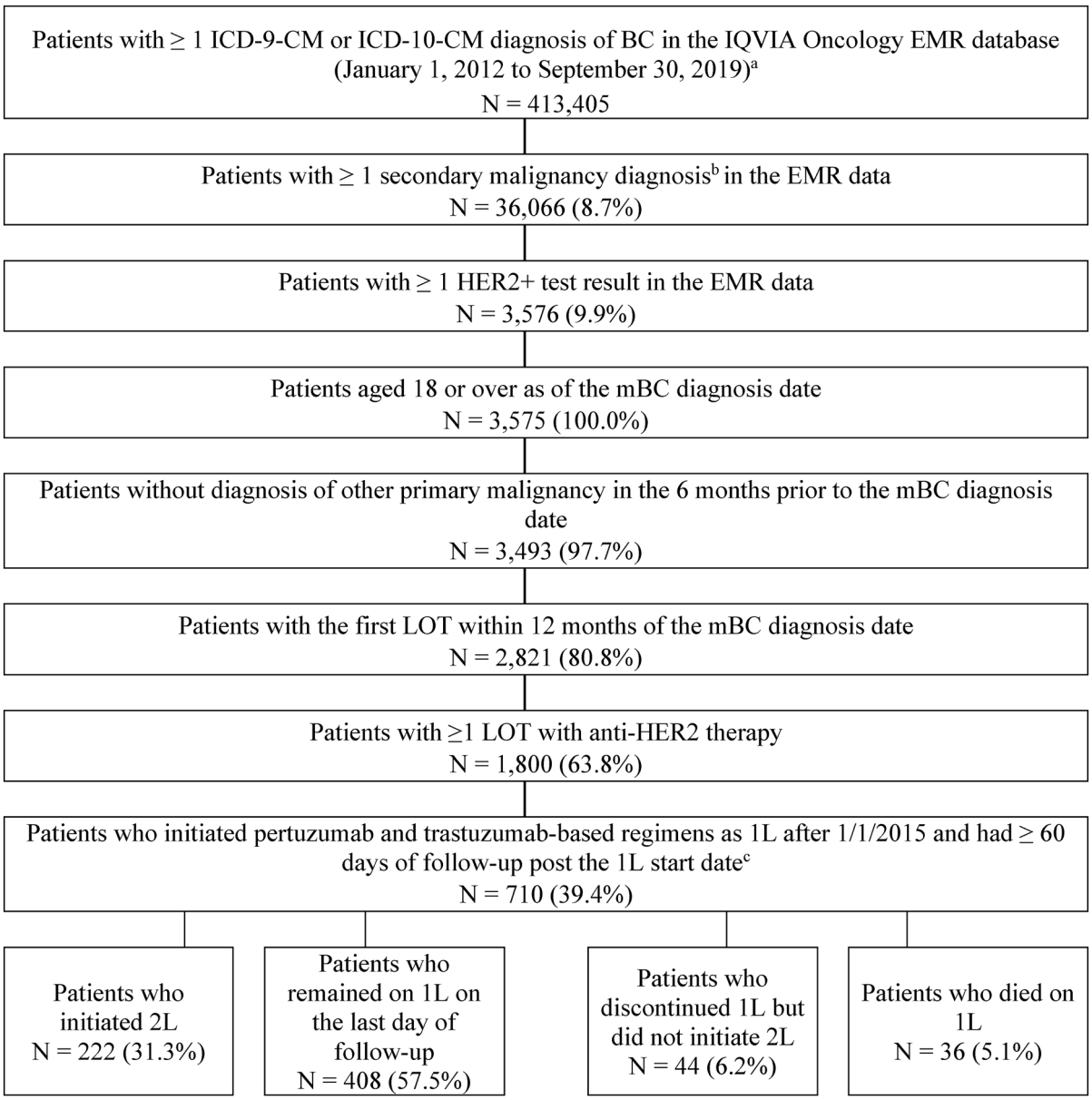

Fig. 1 Sample selection flowchart. *1L* first line, *2L* second line, *BC* breast cancer, *EMR* electronic medical records, *HER2* human epidermal growth factor receptor 2, *ICD-9-CM* International Classification of Diseases, 9th revision, Clinical Modification, *ICD-10-CM* International Classification of Diseases, 10th revision, Clinical Modification, *LOT* line of therapy, *mBC* metastatic breast cancer. [a]BC was identified using ICD-9-CM codes 174.xx and 175.xx and ICD-10-CM codes C50.x (both female and male BC). [b]A primary malignancy other than BC was identified using ICD-9-CM codes 140.0–172.9, 176, 179–195.8, 199.0–199.2, and 200.0–209.36 and ICD-10-CM codes C00.0–C43.9, C4A.0–C49.A9, C51.0–C75.9, C7A.00 - C7B.8, C76.0–C76.8, C80.0–C80.2, and C81.00–C96.Z. [c]Patients who died within 60 days of the 1L start date were also included

Table 1 Baseline characteristics of HER2+ mBC patients who initiated 1L and 2L

	Patients with 1L, *N* = 710	**Patients with 2L, *N* = 222**	**Patients with 2L T-DM1, *N* = 159**	**Patients with 2L regimens other than T-DM1, *N* = 63**
Time from 1L initiation to end of follow-up, median (months)	20.3	23.0	22.9	23.5
Time from 2L initiation to end of follow-up, median (months)	-	9.6	9.9	8.4
Age at index date, median years (Q1, Q3)	57.0 (48.0, 65.0)	59.0 (49.0, 65.0)	59.0 (50.0, 64.0)	59.0 (46.0, 66.0)
Female, *n* (%)	701 (98.7%)	219 (98.7%)	158 (99.4%)	61 (96.8%)
US region, *n* (%)				
Midwest	274 (38.6%)	71 (32.0%)	43 (27.0%)	28 (44.4%)
Northeast	61 (8.6%)	19 (8.6%)	14 (8.8%)	5 (7.9%)
South	264 (37.2%)	92 (41.4%)	74 (46.5%)	18 (28.6%)
West	109 (15.4%)	40 (18.0%)	28 (17.6%)	12 (19.1%)
Unknown	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinical profile, *n* (%)				
ER/PR status measured	524 (73.8%)	152 (68.5%)	110 (69.2%)	42 (66.7%)
ER/PR status				
ER+ /PR+	249 (47.5%)	67 (44.1%)	44 (40.0%)	23 (54.8%)
ER+ /PR−	72 (13.7%)	23 (15.1%)	21 (19.1%)	2 (4.8%)
ER−/PR+	15 (2.9%)	5 (3.3%)	5 (4.5%)	0 (0.0%)
ER−/PR−	188 (35.9%)	57 (37.5%)	40 (36.4%)	17 (40.5%)
ECOG score measured[a]	246 (34.6%)	92 (41.1%)	78 (49.1%)	14 (22.2%)
ECOG score[b]				
0	110 (44.7%)	37 (40.2%)	34 (43.6%)	3 (21.4%)
1	102 (41.5%)	40 (43.5%)	32 (41.0%)	8 (57.1%)
2	31 (12.6%)	15 (16.3%)	12 (15.4%)	3 (21.4%)
3	3 (1.2%)	0 (0%)	0 (0.0%)	0 (0.0%)

1L first line, *2L* second line, *ECOG* Eastern Cooperative Oncology Group, *ER* estrogen receptor, *PR*: progesterone receptor, *Q1* quartile 1, *Q3* quartile 3, *SD* standard deviation, *T-DM1* ado-trastuzumab emtansine, *US* United States
[a]ECOG scores obtained within ± 1 month of the index date were identified; [b] if multiple scores were available, the closest one to the index date was considered

Table 2 Regimens used in 2L following 1L pertuzumab and trastuzumab-based regimens

	Total (*N* = 222)	**Without BM[a] (*n* = 172)**	**With BM[a] (*n* = 50)**
T-DM1-based regimen	159 (71.6%)	124 (72.1%)	35 (70.0%)
T-DM1 only	96 (43.2%)	70 (40.7%)	26 (52.0%)
T-DM1 + chemotherapy ± hormonal therapy	23 (10.4%)	19 (11.0%)	4 (8.0%)
T-DM1 + hormonal therapy	30 (13.5%)	25 (14.5%)	5 (10.0%)
T-DM1 + other[a]	10 (4.5%)	10 (5.8%)	–
Trastuzumab-based regimen	3 (1.4%)	3 (1.7%)	–
Trastuzumab + chemotherapy ± hormonal therapy	2 (0.9%)	2 (1.2%)	–
Trastuzumab + hormonal therapy	1 (0.5%)	1 (0.6%)	–
Trastuzumab + pertuzumab-based regimen	3 (1.4%)	2 (1.2%)	1 (2.0%)
Trastuzumab + pertuzumab	1 (0.5%)	1 (0.6%)	–
Trastuzumab + pertuzumab + chemotherapy ± hormonal therapy	2 (0.9%)	1 (0.6%)	1 (2.0%)
TKI-based regimen	39 (17.6%)	26 (15.1%)	13 (26.0%)
Lapatinib-based regimen	21 (9.5%)	11 (6.4%)	10 (20.0%)
Lapatinib + capecitabine ± hormonal therapy	11 (5.0%)	7 (4.1%)	4 (8.0%)
Lapatinib + trastuzumab + pertuzumab	5 (2.3%)	2 (1.2%)	3 (6.0%)
Trastuzumab + lapatinib + chemotherapy ± hormonal therapy	2 (0.9%)	1 (0.6%)	1 (2.0%)
Trastuzumab + lapatinib	1 (0.5%)	–	1 (2.0%)
Lapatinib only	1 (0.5%)	1 (0.6%)	–
Lapatinib + other[b]	1 (0.5%)	–	1 (2.0%)
Neratinib-based regimen	18 (8.1%)	15 (8.7%)	3 (6.0%)
Neratinib	13 (5.9%)	11 (6.4%)	2 (4.0%)
Neratinib + trastuzumab + pertuzumab	3 (1.4%)	2 (1.2%)	1 (2.0%)
Neratinib + trastuzumab	2 (0.9%)	2 (1.2%)	
Other anti-HER2 regimens	10 (4.5%)	9 (5.2%)	1 (2.0%)
Trastuzumab + pertuzumab + T-DM1	8 (3.6%)	7 (4.1%)	1 (2.0%)
Trastuzumab + T-DM1	2 (0.9%)	2 (1.2%)	–
Other regimens	8 (3.6%)	8 (4.7%)	–
Chemotherapy + hormonal therapy	2 (0.9%)	2 (1.2%)	–
Hormonal therapy only	2 (0.9%)	2 (1.2%)	–

Table 2 continued

	Total (N = 222)	Without BM[a] (n = 172)	With BM[a] (n = 50)
I/O or OTT only	4 (1.8%)	4 (2.3%)	–

1L first line, *2L* second line, *BM* brain metastases, *HER2* human epidermal growth factor receptor 2, *I/O* immuno-oncology therapy, *OTT* other targeted therapy, *T-DM1* ado-trastuzumab emtansine, *TKI* tyrosine kinase inhibitor
[a]BM was identified before 2L initiation; [b]'Other' includes OTT and/or I/O with or without chemotherapy and/or hormonal therapy

therapy and initiated 2L therapy, 408 (57.5%) remained on 1L on the last day of follow-up, 36 (5.1%) died on 1L treatment, and 44 (6.2%) discontinued 1L but did not initiate a next line. The observed characteristics of patients who initiated 2L were similar to the patients in the overall cohort (Table 1). Of the 222 patients with 2L therapy (median follow-up post-2L initiation: 9.6 months), 214 (96.4%) received anti-HER2-based regimens. T-DM1-based regimens were most commonly used in 2L (n = 159 [71.6%]), followed by TKI-based regimens (lapatinib-based regimen: 21 [9.5%]; neratinib-based regimen: 18 [8.1%]) (Table 2).

The distribution of treatments among patients with BM (n = 50 [22.5%]) was similar to that for patients without BM (n = 172 [77.5%]), with T-DM1 remaining a mainstay of treatment for both groups (with BM: 70.0%, without BM: 72.1%) (Table 2). The utilization of TKIs was slightly higher among patients with BM (26.0%) compared to those without BM (15.1%).

Treatment Outcomes

Figure 2 illustrates the KM curves for the treatment outcomes of treatment duration (Fig. 2a) and time to treatment failure (Fig. 2b) for 2L regimens overall (red line) and T-DM1-based regimens (blue line). Overall, the median 2L treatment duration was 5.9 (95% CI 5.0, 8.7) months, and the median time to 2L treatment failure was 8.6 (7.3, 11.5) months. For 2L T-DM1, the median duration of treatment was 5.7 (95% CI: 4.7, 7.8) months, and the median time to treatment failure was 7.9 (6.5, 10.0) months.

DISCUSSION

This study reported the real-world treatment patterns and treatment outcomes of patients with HER2+ mBC following 1L pertuzumab and trastuzumab-based regimens among US oncology practices between 2015 and 2019. The median duration of 1L treatment was estimated to be 15.3 months, which is comparable to that reported in the CLEOPATRA trial for pertuzumab and trastuzumab (24 cycles; 3 weeks per cycle) and is longer than that reported in the French UNICANCER ESME (Epidemiological Strategy and Medical Economics) study (11.3 months) [29, 30]. The treatment patterns analysis suggested that T-DM1-based regimens were the most common 2L therapy after 1L pertuzumab and trastuzumab-based regimens, while approximately 25% of the patients received other anti-HER2 regimens in 2L, predominantly consisting of TKIs in the subgroup of patients with BM. Previous literature has suggested that anti-HER2 TKIs may have higher central nervous system (CNS) exposure than therapeutic antibodies [31]. However, the EMILIA clinical trial showed that T-DM1 was associated with significantly improved overall survival (OS) compared to lapatinib plus capecitabine in patients with treated asymptomatic CNS metastases [32]. A meta-analysis of clinical trials also demonstrated a similar OS benefit from anti-HER2-TKI-containing and non-TKI-containing regimens in patients with stable and asymptomatic BM [33]. It is impossible to ascertain the reasons for selecting particular anti-HER2 agents based on the limited clinical information available in the EMR database. The EMR database utilized for this study does not

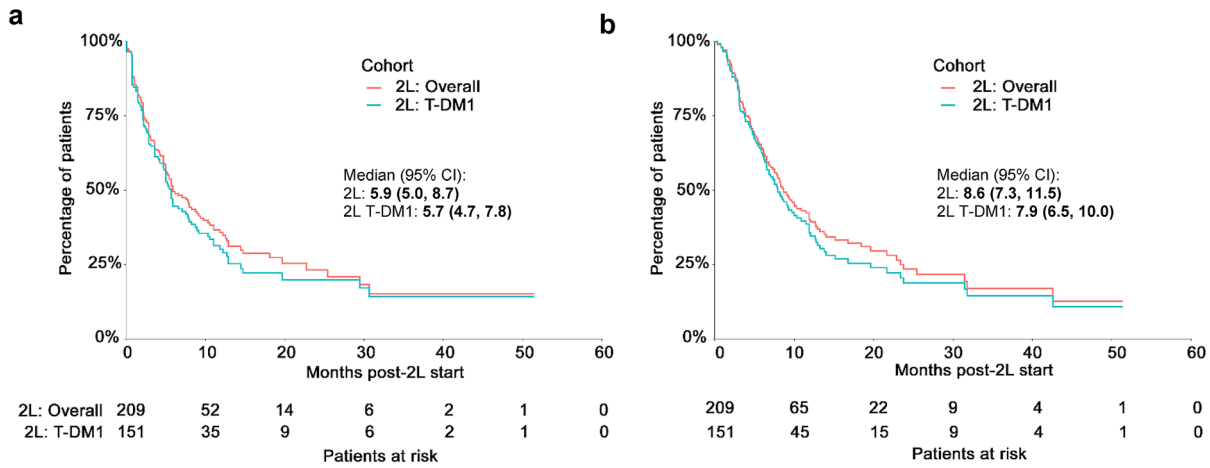

Fig. 2 Treatment duration (**a**) and time to treatment failure (**b**) for patients with 2L therapy and 2L T-DM1 following 1L pertuzumab and trastuzumab-based regimens[a]. *1L* first line, *2L* second line, *CI* confidence interval, *T-DM1* ado-trastuzumab emtansine. [a]Thirteen patients with 2L and eight patients with T-DM1 in 2L were not included in this analysis because they did not have at least 60 days of follow-up from the initiation of 2L. Patients who died within 60 days from 2L initiation were included

offer sufficient clinical details to determine whether the BM were stable or active in our study sample. It is possible that patient preference for an oral therapy such as a lapatinib and capecitabine combination regimen and limited access to infusion clinics for chemotherapy may have played a role in the choice of 2L treatment regimen as well [34, 35]. Further studies to understand the use of regimens other than T-DM1 in patients following 1L pertuzumab and trastuzumab-based regimens are warranted.

The results of this study complement those from clinical trials by providing insights into the real-world treatment outcomes of patients with HER2+ mBC who were treated with T-DM1, lapatinib, and other anti-HER2-based regimens after a 1L pertuzumab and trastuzumab-based regimen in the US. Patients from the US represented only 27% of the patients participating in EMILIA [21]. Compared to patients participating in EMILIA, our study sample of patients receiving 2L treatment was older (median age = 59 years vs. 53 years) [21]. Notwithstanding the differences in study population, design, and follow-up period, the median time to treatment failure for 2L T-DM1 patients in the current study was numerically shorter than that observed in the EMILIA trial [21]. Nevertheless, treatment outcomes for 2L T-DM1 observed in this study were generally similar to results observed in two prior real-world data studies [26, 29]. One US-based study utilized the Flatiron EMR database and reported that the median treatment duration of 2L T-DM1 was 3.5 (95% CI 2.1, 6.5) months in 2015–2016 and 7.0 (95% CI 4.9, 10.4) months in 2017–2018 among patients treated with 1L pertuzumab and trastuzumab [26]. Our estimate of the median treatment duration (5.7 [95% CI 4.7, 7.8]) for 2L T-DM1 between 2015 and 2019 is within the range of the prior study. Another French retrospective study (the UNICANCER ESME mBC cohort) reported a median progression-free survival (PFS) from the initiation of 2L T-DM1 of 7.1 (95% CI 5.7, 8.9) months among patients treated with 1L pertuzumab, trastuzumab, and taxane [29], which is similar to our estimate of the median time to treatment failure (7.9 [95% CI 6.5, 10.0]).

Since the data cut of the current study (2015–2019), several new therapies have been approved by the FDA for patients with HER2+ mBC who have received one or more prior anti-HER2-based regimens. Trastuzumab deruxtecan, an ADC composed of trastuzumab

linked to a topoisomerase I inhibitor, was approved by the FDA in May 2022 for patients with HER2+ mBC who have received a prior anti-HER2-based regimen. In the DESTINY-Breast03 trial, compared to T-DM1, trastuzumab deruxtecan showed a significant improvement in OS (the median was not reached in either arm; hazard ratio: 0.64; $p < 0.01$) and was associated with a significant and clinically meaningful improvement in PFS (median 28.8 vs. 6.8 months; hazard ratio: 0.33; $p < 0.0001$) as well as higher rates of objective response (79% vs. 35%) in patients with HER2+ mBC previously treated with trastuzumab and taxane (median treatment duration: 18.2 vs. 6.9 months) [36]. Another new therapy is tucatinib, a HER2-targeted small-molecule TKI that potently inhibits signal transduction downstream of HER2/HER3 when used in combination with capecitabine and trastuzumab after prior treatment with trastuzumab, pertuzumab, and T-DM1 [14, 37]. In the HER2CLIMB trial, tucatinib demonstrated superior outcomes versus placebo, with a median PFS of 7.8 months and a median OS of 21.9 months [38]. Margetuximab, an anti-HER2-receptor monoclonal antibody used with chemotherapy following two or more prior anti-HER2 regimens, demonstrated prolonged PFS relative to trastuzumab for previously treated patients with HER2+ mBC (median PFS: 5.8 vs. 4.9 months; hazard ratio: 0.76, 95% CI 0.59–0.98), with similar rates of OS [39]. According to NCCN guidelines®, trastuzumab deruxtecan is now a preferred 2L treatment option for HER2+ mBC, whereas T-DM1 and other recently approved treatments (tucatinib and margetuximab) are recommended as 3L and beyond, along with other treatment options based on these clinical trial findings [17]. Considering that patients in real-world clinical practice may have different characteristics from those participating in clinical trials, further research is needed to examine the effectiveness and tolerability of these new treatment options in the future.

The results of this study should be considered in light of its limitations, some of which are common to studies using EMR databases. First, only treatment data received in the practices participating in the EMR networks were captured by the database. Any treatments received by patients outside the participating practices would be missed. Treatment patterns observed in the current study need to be confirmed by future studies. Second, the LOTs were identified using an algorithm that was developed based on the input from clinical experts in breast cancer; however, there may still be some heterogeneous errors impacting the study results. Future studies should consider incorporating a standardized comprehensive framework for defining LOTs, as proposed by Saini and Twelves for solid tumor oncology research [40]. Third, because the median follow-up from 1L initiation in this study was relatively short at 20.3 months, long-term responders to 1L pertuzumab and trastuzumab-based regimens may be underrepresented. The duration of 1L pertuzumab and trastuzumab-based regimens in the real world may also be underestimated. Fourth, date of death was unavailable in the data, so the last follow-up activity date was used as a proxy, which may have resulted in an underestimation of time to treatment failure. Finally, outcomes of 2L treatments, especially T-DM1, may vary with the intensity of HER2 expression, as shown in previous studies [41]. However, we were not able to determine HER2 expression in our study population due to the unavailability of the data. Further research would be helpful to better understand this question. In addition, comorbidities may not be adequately captured in the oncology EMR database, especially if they were diagnosed outside the oncology practices, and ECOG functional status data were missing for the majority of patients. Due to the limited clinical information available in the database, the appropriateness of treatment and dosing and the association between the clinical characteristics and treatment selection could not be assessed.

CONCLUSIONS

This study provides insights into the real-world treatment patterns and outcomes of patients with HER2+ mBC in the US during 2015–2019 and highlights unmet needs that can

potentially be fulfilled by recently approved treatment options. Future real-world studies will be helpful to confirm the generalizability of the clinical trial findings in the diverse patient population receiving treatment for HER2+ mBC in real-world clinical practice.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available, although access to the IQVIA Oncology Electronic Medical Records database can be requested from IQVIA at: https://www.iqvia.com/solutions/real-world-evidence/real-world-data-and-insights.

Declarations

Conflict of Interest. Sandhya Mehta and Winghan J. Kwong are employees of Daiichi Sankyo, Inc. and own stock/stock options. Xiaoyu Nie is an employee of Analysis Group Inc., which has received consultancy fees from Daiichi Sankyo, Inc. and AstraZeneca plc for the conduct of this research; Raluca Ionescu-Ittu and Jipan Xie were employees of Analysis Group, Inc., during the study's conduct.

Ethical Approval. This study used deidentified pre-existing data in the IQVIA Oncology Electronic Medical Records database. Thus, no ethical approval was required. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

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