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ORIGINAL RESEARCH ARTICLE

Retrospective Observational Study of Outcomes in HER2-Positive Metastatic Breast Cancer (mBC) Patients Treated with Ado-Trastuzumab Emtansine (T-DM1) and Subsequent Treatments After T-DM1 in the United States

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Abstract

Background Limited evidence exists on real-world outcomes with ado-trastuzumab emtansine (T-DM1) treatment and the effectiveness of subsequent therapies.

Objective This study evaluated treatment patterns and outcomes of patients treated with T-DM1 and post-T-DM1 therapy in the United States.

Patients and methods Adult patients with HER2-positive (HER2+) metastatic breast cancer (mBC) initiating treatment with T-DM1 between 1/1/2013 and 9/30/2018 were included and followed through 12/31/2018. Data were obtained from the iKnowMed electronic health record. Demographic, clinical, and pre- and post-T-DM1 treatment characteristics were described. The Kaplan-Meier method was used to estimate time to treatment discontinuation (TTD) and overall survival (OS).

Results Of 318 patients treated with T-DM1, 184 (57.9%) had prior treatment with pertuzumab. The median age was 58 years. Most patients had visceral disease (93.4%), and 62.3% had two or more prior treatments for mBC before T-DM1 (range 0–9). The most common subsequent regimens were trastuzumab + vinorelbine (22.5%), HER2-targeted monotherapy (22.5%), and trastuzumab + other chemotherapy (19.6%). Median TTD with T-DM1 was 5.9 months (95% confidence interval [CI] 4.6–6.9); median OS from the start of T-DM1 therapy was 19.2 months (95% CI 16.8–24.5).

Conclusions Patients treated with T-DM1 in this study appeared to have more advanced disease than patients in clinical trials and were treated in later lines of therapy. Variability was observed across subsequent therapy selections. Treatment patterns and outcomes appeared comparable for patients who received prior pertuzumab. The short treatment durations and survival with T-DM1 therapy in the real-world setting underscore the need for effective post-trastuzumab therapies.

1 Introduction

HER2-positive (HER2+) breast cancer constitutes approximately 15–20% of all breast cancers [1]. Metastatic breast cancer (mBC) management typically includes sequential utilization of HER2-targeted therapies together with chemotherapy. The phase 3 randomized CLEOPATRA and EMILIA trials established trastuzumab + pertuzumab + taxane as first-line (1L) and ado-trastuzumab emtansine (T-DM1) as ≥ 2L treatment options for HER2+ mBC, with reported median overall survival (OS) of 56.5 and 30.9 months, respectively [2, 3]. There is no standard of care after two lines of therapy, and National Comprehensive Cancer Network guidelines recommend several other anti-HER2–based therapies [4]. Until recently, targeted therapy options for patients following T-DM1 treatment were limited to trastuzumab- or lapatinib-based therapies. Newer options for HER2+ mBC have emerged over the past few years: the United States (US) Food and Drug Administration (FDA) approved trastuzumab deruxtecan (T-DXd) in December 2019 (in the US, fam-trastuzumab deruxtecan-nxki) [5],

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Key Points

Patients treated with ado-trastuzumab emtansine (T-DM1) in this study had more advanced breast cancer than patients treated in the clinical trials and received T-DM1 in later lines of therapy.

Patients treated with T-DM1 in this study had shorter treatment periods and survival than in the clinical trials, which suggests the need for additional therapies.

In our study, over half of the patients received pertuzumab prior to T-DM1, and their treatment patterns and outcomes appeared similar for patients who did not receive prior pertuzumab.

These real-world data shed light on treatment patterns and outcomes in patients with HER2-positive metastatic breast cancer who receive treatment post–T-DM1.

neratinib in February 2020 [6], and tucatinib in April 2020 [7].

The optimal sequencing of anti-HER2 therapies is unknown. In EMILIA, patients receiving T-DM1 previously received trastuzumab and a taxane. However, most lacked prior exposure to pertuzumab [3]. Few studies have examined T-DM1 treatment patterns and clinical outcomes outside of clinical trials or in patients previously treated with pertuzumab. Additionally, limited evidence exists on effectiveness of treatments following progression on T-DM1.

This study evaluated how patients receiving T-DM1 in clinical practice are similar to or different from patients treated in clinical trials and evaluated T-DM1 effectiveness in the real-world setting, including patients previously treated with pertuzumab. Additionally, the study explored therapy and outcomes post–T-DM1 given the absence of standard therapy recommendations. These data will help providers understand the real-world benefits of T-DM1 and provide context to evaluate clinical trial data of new treatments approved for HER2+ mBC.

2 Methods

2.1 Study Design and Data Sources

This was a retrospective, observational study of adult patients with HER2+ mBC from US Oncology Network practices utilizing the iKnowMed™ (iKM) electronic health record (EHR). Eligibility criteria included ≥ 18 years old at mBC diagnosis, two or more office visits, HER2+ status documented in iKM as either immunohistochemistry (IHC) 3+ or fluorescence in situ hybridization (FISH)–positive, and T-DM1 initiation for mBC between 1 January 2013 and 30 September 2018. T-DM1 initiation was the index event. Patients were followed through 31 December 2018 until last patient record or end of the study period, whichever occurred first. Patients participating in clinical trials during the study period, patients who received T-DM1 in the neo/adjuvant setting (i.e., those with nonmetastatic disease), and those with other documented primary cancer diagnoses were excluded.

The US Oncology Network is a network of community oncology clinics affiliated with approximately 1400 physicians in over 500 sites of care across 25 states in the US and treats over 1.2 million patients annually [8]. iKM is an integrated web-based, oncology-specific EHR. iKM captures outpatient medical oncology practice encounter history for patients under community-based care, including patient demographics, clinical information (e.g., staging, biomarker testing, performance status), and treatment information (e.g., chemotherapy regimens, lines of therapy). iKM has been implemented across the majority of practices in The US Oncology Network.

Data were extracted via programmatic data queries from structured data fields in the iKM database, along with chart review abstraction to capture unstructured data. Structured data are entered into standardized fields in the EHR: examples include patient demographics, treatment dates and dosages, and laboratory results. Examples of unstructured data from charts include free text in progress notes, scanned documents (e.g., imaging), or other non-standardized fields.

Vital status was supplemented with death data from the US Social Security Administration Limited Access Death Master File. The study was approved by the US Oncology, Inc. Institutional Review Board. Supplementary Table 1 lists variables and data sources in further detail (see the Electronic Supplementary Material).

2.2 Statistical Analysis

Descriptive analyses were performed to describe demographic and clinical characteristics among patients treated with T-DM1 and those treated with pertuzumab before T-DM1, and treatment regimens before and following T-DM1. Treatment regimens included chemotherapy and HER2-based treatments only, while endocrine therapies were excluded. Cycles of T-DM1 were defined as the total number of treatment administrations, with one treatment given every 21 days. The Kaplan-Meier method was used to estimate time to treatment discontinuation (TTD), real-world progression-free survival (rwPFS), and OS from T-DM1 initiation and for post–T-DM1 treatments. TTD was defined as the interval between treatment initiation and discontinuation for any reason. OS was defined as the interval between

T-DM1 initiation and death date. Dates of disease progression for rwPFS were obtained through provider assessments from progress notes. Patients without treatment discontinuation, progression, or death during the study observation period were censored on the earliest of the study end date or the last visit date. Follow-up time was defined as time from index treatment (initiation of T-DM1) to end of the study, last visit to a US Oncology Network clinic, or death, whichever occurred first. Adverse events of special interest consistent with T-DM1 product labeling were collected using Medical Dictionary for Regulatory Activities terms from progress notes during chart review and were also derived from laboratory test results performed throughout the T-DM1 treatment duration. Grading for laboratory values was categorized based on Common Terminology Criteria for Adverse Events laboratory criteria.

3 Results

3.1 Study Population

Over 600,000 patients with breast cancer were identified from iKM, including over 67,000 with documented HER2+ disease; 520 received T-DM1 during the study period, and 318 patients met all eligibility criteria and were included in the analysis (Fig. 1). Median duration offollow-up was 11.7 months (range 0.0–69.5).

Table 1 describes the overall study population. Median age was 58 years (range 25–90+), 68.9% were Caucasian, and all except four patients were female. The highest proportion of patients had three or more organs with metastasis at the time of T-DM1 treatment (40.3%); the most common were bone, liver, and lung (57.9%, 44%, and 39.9%, respectively). Visceral disease was present in 93.4%, and 22.3% had baseline brain metastasis. Performance status was good, with an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 in 13.2% or ECOG PS 1 in 62.6% at the time of treatment. Most (63.8%) had hormone-receptor–positive disease.

There were 184 patients (57.9%) who received trastuzumab and pertuzumab before T-DM1; approximately one third had stage IV disease at initial diagnosis (Table 1). Their patient characteristics were similar to those of the overall study population.

3.2 Treatment Patterns

The 318 patients treated with T-DM1 received a median of seven T-DM1 cycles (range 1–85), and 62.3% received two or more prior treatments for mBC (range 0–9). During the study observation period, 43.4% received a subsequent treatment; the most common were trastuzumab + vinorelbine (22.5%), HER2-targeted–only monotherapy or combination therapy (22.5%), trastuzumab + other chemotherapy (19.6%), or capecitabine + lapatinib (14.5%) (Table 2). The most common reasons for T-DM1 discontinuation were progression (50.3%), patients whose treatment may still be ongoing or who did not return for treatment (17.0%), hospice (9.1%), death (7.9%), and toxicity (5.0%).

Patients with prior pertuzumab (n = 184) received a median of six T-DM1 cycles, 48.4% received a subsequent treatment, and 66.8% had two or more treatments for mBC before T-DM1. The most common were trastuzumab + vinorelbine (28.1%), capecitabine + lapatinib (21.3%), trastuzumab + other chemotherapy (18.0%), and HER2-targeted–only monotherapy or combination therapy (16.9%).

3.3 Clinical Outcomes and Adverse Reactions

Of the 318 patients receiving T-DM1, 252 patients (79.2%) had discontinued treatment and 66 patients (20.8%) had not discontinued T-DM1 at last follow-up and were censored. Among all 318 patients, median TTD was 5.9 months (95% confidence interval [CI] 4.6–6.9), median rwPFS was 5.9 months (95% CI 4.6–7.6), and median OS from T-DM1 initiation was 19.2 months (95% CI 16.8–24.5) (Fig. 2).

Treatment outcomes appeared similar in the 184 patients with pertuzumab exposure before T-DM1. Median TTD was 4.6 months (95% CI 3.5–6.0), median rwPFS was 5.1 months (95% CI 4.0–6.3), and median OS from T-DM1 initiation was 19.9 months (95% CI 14.3–28.2). Among all patients treated with T-DM1, outcome endpoints were observed to be shorter with subsequent therapy. In the 138 patients who received subsequent therapy post T-DM1, median TTD from the start of the subsequent therapy was 3.6 months (95% CI 3.1–4.2), median rwPFS from the start of subsequent therapy was 3.6 months (95% CI 3.2–4.9), and median OS from the start of T-DM1 initiation was 24.5 months (95% CI 19.2–31.4).

Among all 318 patients receiving T-DM1, adverse events were consistent with product labeling: infusion-related reactions in 1.9%, pulmonary toxicity (i.e., interstitial lung disease [ILD] or pneumonitis) in 0.6%, and peripheral neuropathy in 1.6%. Aspartate aminotransferase or alanine aminotransferase $\geq 5 \times$ upper limit of normal (ULN) occurred in up to 1.9% and bilirubin ≥ 3 ULN in 0.3%; 5.3% experienced anemia (hemoglobin < 8 mg/dL), and 7.2% experienced thrombocytopenia (platelets < 50 mm^3). In all patients treated with T-DM1, 4.1% experienced a reduction in left ventricular ejection fraction (LVEF) $< 50\%$, as did 4.3% of those receiving pertuzumab prior to T-DM1 (n = 184).

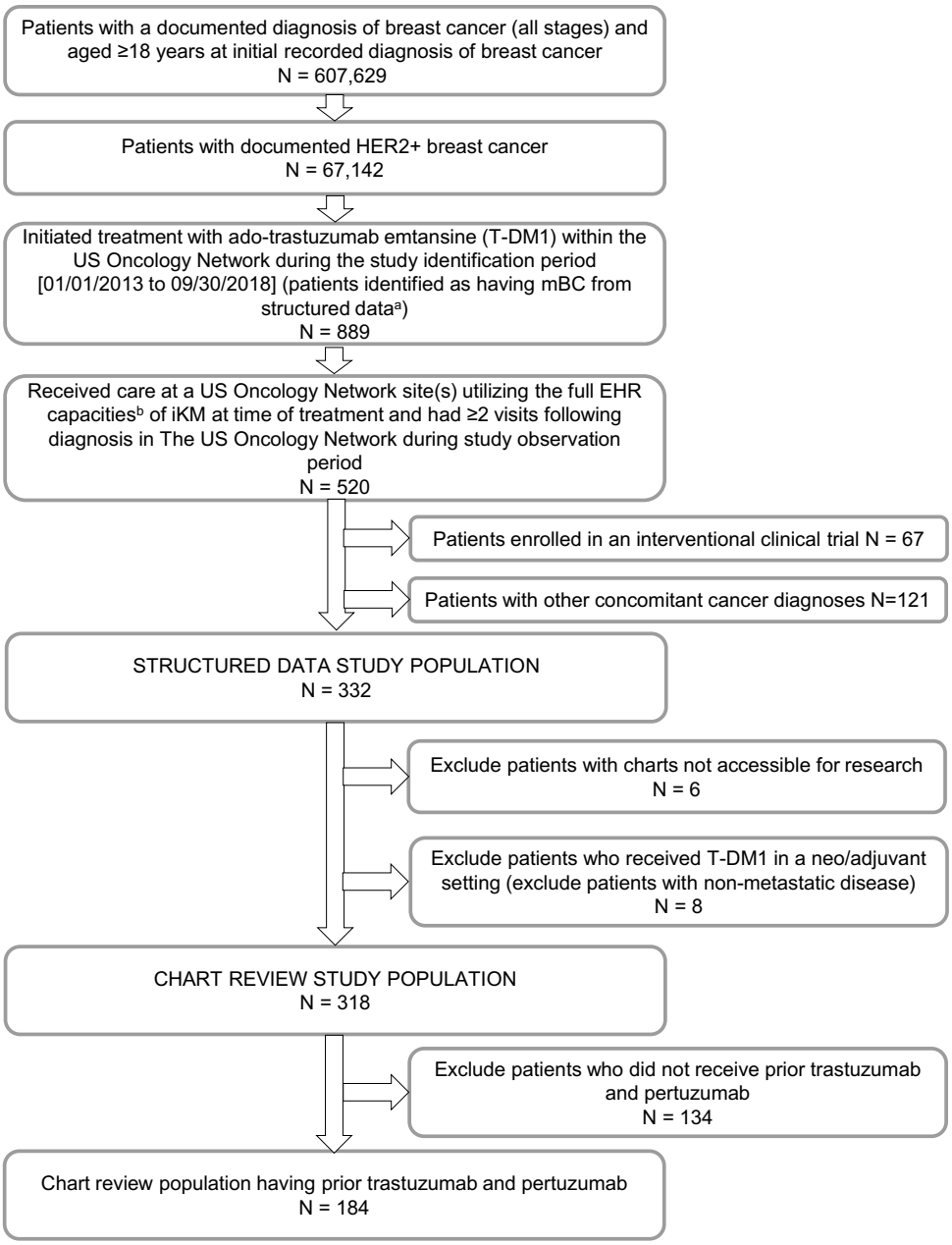

Fig. 1 Study attrition. *EHR* electronic health record, *HER2+* human epidermal growth factor receptor–positive, *iKM* iKnowMed, *mBC* metastatic breast cancer, *T-DM1* ado-trastuzumab emtansine. [a]The use of T-DM1 along with other structured data variables (e.g., stage IV disease, tumor nodal metastasis status, record of metastases location) was first used as a screening step to identify patients presumed to have mBC based on these indicators. Metastatic status was later validated with chart review using pathology reports, progress notes, and scan reports. [b]Utilizing the full EHR capabilities refers to all of a patient's records being available in iKM. Not all sites use iKM. Patients were included in the study if the researchers had full access to the patient records.

4 Discussion

The data from this study help to put clinical trial data of recently approved anti-HER2 regimens into context, as multiple treatments for HER2+ mBC exist and there is no standard of care following T-DM1 therapy. Treatment selection may depend on prior treatment exposure, performance status, and toxicities.

Survival outcomes with T-DM1 in this real-world study were observed to be shorter than those from the EMILIA study of patients who did not receive prior pertuzumab (median rwPFS 5.9 vs progression-free survival [PFS] 9.6 months, median OS 19.2 vs 30.9 months, respectively) [3]. A potential reason is that patients in this study appeared to have more advanced disease at the time of T-DM1 treatment: 62.3% had two or more prior regimens, 93.4% had visceral disease, and 62.6% had an ECOG PS of 1. In EMILIA, 39% had more than one prior regimen for metastatic disease, 67% had visceral disease, and 60% had an ECOG PS of 0.

KAMILLA was a prospective, open-label, phase 3 safety study of 2002 patients treated with T-DM1 [9]. Similar to our study, the majority (66%) had two or more prior metastatic treatments. Median duration of T-DM1 exposure in KAMILLA was 5.6 months, similar to the median TTD of 5.9 months in our study. Median PFS was 6.9 months versus 5.9 months respectively, and median OS was 27.2

Table 1 Baseline demographic and clinical characteristics of patients treated with T-DM1 and patients treated with pertuzumab prior to T-DM1

	Overall population of patients treated with T-DM1 ($n = 318$)		Patients treated with pertuzumab prior to T-DM1 ($n = 184$)	
	N	%	*N*	%
Age at T-DM1 treatment (years)				
Median (min, max)	58	(25, 90+)	57	(25, 90+)
Age group—*n* (%)				
< 65 years	219	68.9	133	72.3
≥ 65 years	99	31.1	51	27.7
Race—*n* (%)				
Black	35	11.0	17	9.2
Asian	17	5.3	10	5.4
Caucasian	219	68.9	128	69.6
Other	7	2.2	3	1.6
Not documented	40	12.6	26	14.1
Practice region—*n* (%)				
Midwest	57	17.9	41	22.3
Northeast	16	5.0	7	3.8
South	94	29.6	46	25.0
West	151	47.5	90	48.9
Stage at initial BC diagnosis—*n* (%)				
Stage I	16	5.0	9	4.9
Stage II	63	19.8	44	23.9
Stage III	76	23.9	48	26.1
Stage IV	115	36.2	60	32.6
Not documented	48	15.1	23	12.5
Distant metastatic site (at T-DM1 initiation)—*n* (%)				
Bone	184	57.9	105	57.1
Brain	71	22.3	38	20.7
Liver	140	44.0	82	44.6
Lung	127	39.9	72	39.1
Lymph node	127	39.9	71	38.6
Other	97	30.5	55	29.9
Not documented	1	0.3	1	0.5
Number of metastatic organ sites (at T-DM1 initiation)—*n* (%)				
Not documented	1	0.3	1	0.5
1	76	23.9	43	23.4
2	113	35.5	68	37.0
3+	128	40.3	72	39.1
Sites of disease involvement (at T-DM1 initiation)—*n* (%)				
Visceral (any metastasis other than bone only)	297	93.4	171	92.9
Non-visceral (bone only metastasis)	20	6.3	12	6.5
Not documented	1	0.3	1	0.5
ECOG PS score (at T-DM1 initiation)—*n* (%)				
0	42	13.2	26	14.1
1	199	62.6	124	67.4
≥ 2	45	14.1	22	12.0
Not documented	32	10.1	12	6.5
Hormone receptor status				
ER-positive, PR-positive or both (HER2+, HR+)	203	63.8	118	64.1
ER-negative AND PR-negative (HER2+, HR−)	113	35.5	65	35.3
Not documented	2	0.6	1	0.5

BC breast cancer, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ER* estrogen receptor, *HER2+* human epidermal growth factor receptor 2+, *HR* hormone receptor, *max* maximum, *min* minimum, *PR* progesterone receptor, *T-DM1* ado-trastuzumab emtansine

Table 2 Subsequent treatment regimens for patients treated with T-DM1 and patients treated with pertuzumab prior to T-DM1

	Treated with T-DM1 and received subsequent treatment ($n = 138$)		Treated with pertuzumab prior to T-DM1 and received subsequent treatment ($n = 89$)	
	N	%	*N*	%
Trastuzumab + vinorelbine	31	22.5	25	28.1
HER2 therapy only	31	22.5	15	16.9
Trastuzumab + chemo	27	19.6	16	18.0
Capecitabine + lapatinib	20	14.5	19	21.3
Chemo only	18	13.0	11	12.4
Pertuzumab + trastuzumab + chemo	9	6.5	3	3.4
Lapatinib + chemo	2	1.4	0	0.0
Total	138	100.0	89	100.0

Chemo chemotherapy, *HER2* human epidermal growth factor receptor, *T-DM1* ado-trastuzumab emtansine

months versus 19.2 months, respectively. Survival estimates decreased with increasing lines of prior therapy (0–1 to 4+), with PFS ranging from 8.3 to 5.6 months and OS from 31.3 to 22.5 months. Visceral disease was present in 78% and baseline brain metastases in 19.9%, similar to the rate of brain metastases within our study (22.3%). The most common grade ≥ 3 laboratory adverse events from KAMILLA were anemia (3%) and thrombocytopenia (2.7%). The rates of these events were higher in our study: 5.3% and 7.2%, respectively.

Limited data exist on T-DM1 effectiveness outside clinical trials. In a single-center retrospective study in Spain ($n = 15$) and a five-center retrospective study in Hong Kong ($n = 37$), median PFS was 10 and 6 months, respectively, and median OS was 34 months and not reached, respectively [10, 11]. A retrospective observational multicenter study in Italy evaluated 250 patients treated with T-DM1, including those with pertuzumab pretreatment [12]. Median age was 56 years, 56% had an ECOG PS of 0, and 59.2% had visceral metastases. T-DM1 was administered as 1L in 5.2%, 2L in 40%, and ≥ 3L in 54.8%; 18.8% received prior taxane + pertuzumab + trastuzumab. In the overall population, median PFS and OS were 6 months and 20 months, respectively. In the pertuzumab-pretreated patients, they were 4 months and 17 months, respectively. These results approximate those of our study (rwPFS of 5.9 months and OS of 19.2 months in the overall population; rwPFS of 5.1 months and OS of 19.9 months in the pertuzumab-pretreated patients, respectively), even though our study sample had worse ECOG PS scores and a higher proportion had visceral disease.

Nearly 60% of all T-DM1–treated patients in our study had prior pertuzumab. Few other real-world studies have examined the effectiveness of T-DM1 in this population. A retrospective multicenter study in Italy ($n = 77$) examined effectiveness of 2L T-DM1 in patients progressing after dual HER2 blockade with 1L taxane + pertuzumab + trastuzumab [13]. Median PFS was 6.3 months (95% CI 4.8–7.7 months), median time to treatment failure (TTF)

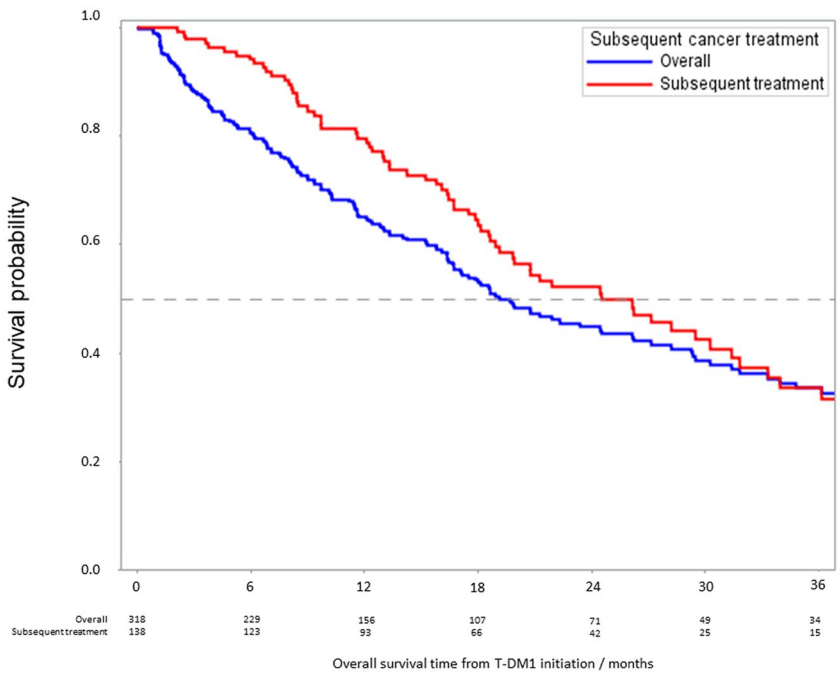

Fig. 2 Kaplan-Meier estimates of overall survival among patients with metastatic breast cancer who received T-DM1 and patients who received post–T-DM1 treatment. *T-DM1* ado-trastuzumab emtansine

was 6.2 months (95% CI 4–8.6 months), and median OS was not reached. In another retrospective study, of patients from several centers in Japan ($n = 34$) who received T-DM1 following pertuzumab, median number of treatment lines was three (range 1–9), median TTF was 6.6 months, and median OS was not reached [14]. Outcomes from our study in pertuzumab-pretreated patients appear similar to these studies. In our study, the median OS in the subgroup treated with prior pertuzumab appeared similar to the overall population, which may be influenced by cross-over and post–T-DM1 treatments. To our knowledge, ours is the largest real-world study.

The differences in clinical characteristics between the real-world studies and the clinical trials suggest that generalizability of trial results to clinical practice settings should be confirmed with post-approval real-world data, particularly if no standard of care exists or when variability exists across the treatment landscape.

In this study, various treatments were utilized after T-DM1; most patients received trastuzumab + chemotherapy, most often with vinorelbine chemotherapy. Short treatment durations and a median rwPFS of less than 4 months were observed with subsequent therapy, demonstrating the need for improved outcomes with newer therapies. The recent approvals of T-DXd, neratinib, and tucatinib now provide additional treatment options, indicated for patients who had received at least one or two prior regimens for mBC.

DESTINY-Breast01 was a single-arm, phase 2 trial of T-DXd monotherapy in 184 patients with HER2+ mBC previously treated with T-DM1 [15]. T-DXd is a humanized anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab, covalently linked to a topoisomerase I inhibitor payload (DXd) via a tetrapeptide-based cleavable linker [5]. Patients received a median of six prior regimens (range 2–17) for locally advanced or metastatic disease. All patients received prior trastuzumab and T-DM1, and 66% received prior pertuzumab. After a median follow-up of 20.5 months, the confirmed objective response rate was 61.4% (95% CI 54.0–68.5), showing durable efficacy, with a median duration of response of 20.8 months (95% CI 15.0–not estimable [NE]). Median PFS was 19.4 months (95% CI 14.1–NE), and estimated median OS was 24.6 months (95% CI 23.1–NE). Grade 3 or higher adverse events were neutropenia in 20.7%, anemia in 8.7%, nausea in 7.6%, and ILD in 2.7% [15, 16].

The randomized, open-label phase 3 NALA trial evaluated the second-generation pan-HER tyrosine kinase inhibitor (TKI) neratinib + capecitabine versus lapatinib + capecitabine in 621 HER2+ patients who had received two or more prior anti-HER2–based regimens for mBC [17, 18]. Median PFS was significantly improved at 5.6 months for patients who received neratinib versus 5.5 months for those receiving lapatinib (hazard ratio 0.76; 95% CI 0.63–0.93; $P = 0.0059$). Median OS was not significantly improved (21 months vs 18.7 months, respectively; hazard ratio 0.88; 95% CI 0.72–1.07; $P = 0.2086$). Sixty-nine percent received two prior anti-HER2–based regimens, 31% received three or more prior anti-HER2–based regimens, and approximately one third received prior treatment with trastuzumab, pertuzumab, and T-DM1. Patients with asymptomatic or stable brain metastases were included (16%). Time to intervention for symptomatic central nervous system disease (overall cumulative incidence 22.8% vs 29.2%; $P = 0.043$) was delayed with neratinib + capecitabine. Grade 3+ diarrhea and palmar-plantar erythrodysesthesia (PPE) syndrome occurred in 24.4% and 9.6% of neratinib-treated patients, respectively, versus 12.5% and 11.3% of lapatinib-treated patients, respectively.

HER2CLIMB was a randomized, double-blind, placebo-controlled phase 3 trial that compared the HER2-selective TKI tucatinib, together with trastuzumab and capecitabine, versus trastuzumab and capecitabine alone in 612 HER2+ patients all previously treated with trastuzumab, pertuzumab, and T-DM1 [19]. Patients with brain metastases were eligible. Patients received a median of three prior treatments for metastatic disease. Median PFS was 7.8 months in the tucatinib-combination group versus 5.6 months with trastuzumab and capecitabine (hazard ratio 0.54; 95% CI 0.42–0.71; $P < 0.001$). The median OS was 21.9 months and 17.4 months, respectively (hazard ratio 0.66; 95% CI 0.50–0.88; $P = 0.005$). Median PFS also improved among patients with brain metastases receiving tucatinib (7.6 months vs 5.4 months). The FDA approved tucatinib in combination with trastuzumab and capecitabine as triplet therapy combining an anti-HER2 monoclonal antibody, TKI, and chemotherapy for treatment of patients with HER2+ mBC, including patients with brain metastases [7]. Grade 3+ diarrhea and PPE occurred in 12.9% and 13.1% of patients receiving tucatinib, respectively, versus 8.6% and 9.1% receiving placebo, respectively. Elevations in liver function tests ≥ grade 3 occurred in approximately 5% in the tucatinib arm versus 0.5% with placebo. Tucatinib is also being evaluated in other studies, including a randomized, double-blind phase 3 trial of tucatinib + T-DM1 compared to T-DM1 alone [20]. DESTINY-Breast03 is an open-label phase 3 trial that will assess the efficacy and safety of T-DXd versus T-DM1 [21].

In our study, 22.3% had brain metastasis at the time of T-DM1 treatment. Antibody–drug conjugates such as T-DM1 and T-DXd have shown activity in patients with asymptomatic brain metastases in post-hoc analyses of KAMILLA [22] and DESTINY-Breast01 [23], which requires further exploration. At the same time, NALA and HER2CLIMB, which evaluated TKIs with neratinib and tucatinib, respectively, have demonstrated a priori clinical benefits in patients enrolled with brain metastasis, and

tucatinib led to improved survival in patients with brain metastases [18, 19, 24].

The toxicity profiles of these newer agents have important implications in clinical practice when selecting subsequent treatments. Cardiotoxicity has been associated with cumulative use of anti-HER2 therapies. In our study, LVEF decreases < 50% occurred in approximately 4% of patients receiving T-DM1. Any-grade LVEF decreases were reported in 1.6% of patients treated with T-DXd in DESTINY-Breast01 [15] and in 4.3% of patients treated with neratinib in NALA [24]. Severe non-hematologic toxicities have been observed with these newer treatment options, including ILD with T-DXd and diarrhea and PPE with neratinib and tucatinib. These may also be important considerations when evaluating the risks and benefits of treatments.

4.1 Strengths and Limitations

This retrospective observational study included a relatively large population of patients receiving T-DM1 and subsequent treatments outside of clinical trials, thus providing insights into treatment utilization and outcomes in US community clinical practices.

Limitations include known methodologic considerations with retrospective analyses, including data completeness. Missing data can result from care or services provided outside of the practice that were not reported to or documented by the treating provider, or from differences in documentation patterns outside of clinical trials. Missing data cannot confirm the absence of a condition or value in a patient's medical history, but only that it was not documented. The frequencies of follow-up assessments in routine care are not standardized outside of clinical trials, and thus progression endpoints cannot be interpreted the same as in clinical trials. Additionally, toxicity assessments for adverse events of special interest were performed with chart review, and attribution and severity were not assessed in the same manner as clinical trials. For the OS outcomes among the patients who received subsequent treatment after T-DM1, immortal time bias could be introduced since the index date was the treatment initiation date of T-DM1, and patients would have to survive from T-DM1 initiation to be able to receive subsequent treatment after T-DM1. Direct comparisons across trials may not be applicable due to trial design and differences in patient characteristics. Further, differences in healthcare systems could preclude generalizability of our results outside of the US.

4.2 Conclusions

Patients with HER2+ mBC who received T-DM1 in this study appeared to have more advanced disease than those treated in the T-DM1 clinical trials and received T-DM1 in later lines of therapy. Overall treatment durations and survival outcomes were shorter compared to clinical trials. Data are lacking on T-DM1 therapy effectiveness among patients with prior pertuzumab exposure, and our results suggest that many patients receive pertuzumab prior to T-DM1 and our survival outcomes appear similar to other studies.

This real-world evidence together with recent clinical trial data help provide context for treatment options and outcomes in patients with HER2+ mBC who receive treatment post–T-DM1. Short treatment durations and survival were observed in this study of T-DM1 therapy, along with treatment variability and limited benefits with subsequent therapy. As newly approved anti-HER2 therapies are utilized, future research is needed to determine the real-world clinical benefits and how best to optimize utilization and sequencing of these agents to improve outcomes for patients with HER2+ mBC.

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Declarations

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Conflicts of Interest/Competing Interests N. Denduluri: consulting or advisory role: Daiichi Sankyo; research funding: Amgen, Novartis, Genentech, Eli Lilly, Pfizer, Daiichi Sankyo, and Immunomedics; travel, accommodations, expenses: Daiichi Sankyo and Seattle Genetics. Michelle D. Hackshaw, Tamy Recchia, and Winghan J. Kwong are employees of Daiichi Sankyo. Janet L. Espirito and Chuck Wentworth are employees of Ontada/McKesson.

Availability of Data and Material The raw data used for this analysis are not publicly available due to privacy or ethical restrictions.

Code Availability Not applicable.

Authors' Contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JLE and CW. All authors reviewed and interpreted the results. The first draft of the manuscript was written by JLE, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval Institutional review board and compliance/privacy approval was gained prior to initiation of the retrospective research. Since this project involved the analysis of existing data and records, study information was analyzed in such a manner that research participants could not be directly identified. Patient informed consent was not required due to the nature of the study design. Thus, exemption status and a waiver of informed consent were approved by The US Oncology, Inc. Institutional Review Board. Data were handled in compliance with *the Health Insurance Portability and Accountability Act of 1996* (HIPAA) and the *Health Information Technology for Economic and Clinical Health (HITECH) Act*.

Consent to Participate Since this project involved the analysis of existing data and records, study information was analyzed in such a manner that research participants could not be directly identified. Patient informed consent was not required due to the nature of the study design.

Consent for Publication Not applicable.

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