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C. Courtinard, V. Barbet, R. Schiappa, F. Pilleul, S. Michiels, et al.. Real-world effectiveness of post-trastuzumab emtansine treatment for human epidermal growth factor receptor 2-positive metastatic breast cancer: a multicenter, matched cohort analysis from the Epidemiology Strategy and Medical Economics database (2008-2018). *ESMO Real World Data and Digital Oncology*, 2024, 4, pp.100043. 10.1016/j.esmorw.2024.100043 . inserm-04642250

HAL Id: inserm-04642250

<https://inserm.hal.science/inserm-04642250>

Submitted on 9 Jul 2024

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ORIGINAL ARTICLE

Real-world effectiveness of post-trastuzumab emtansine treatment for human epidermal growth factor receptor 2-positive metastatic breast cancer: a multicenter, matched cohort analysis from the Epidemiology Strategy and Medical Economics database (2008-2018)

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Available online 3 June 2024

Background: Real-world data (RWD) can contextualize clinical trial data. We present real-world evidence that supplemented the single-arm DESTINY-Breast01 trial, which assessed the efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (mBC) previously treated with trastuzumab emtansine (T-DM1).

Patients and methods: Patients from the French Epidemiology Strategy and Medical Economics (ESME) mBC database who initiated treatment for HER2+ mBC between 1 January 2008 and 31 December 2016, and received one or more treatment lines following T-DM1 were propensity score matched 1 : 1 to patients from DESTINY-Breast01 to create an ESME DB-01 matched cohort. Treatment patterns, real-world best overall response, real-world objective response rate (rwORR), real-world disease control rate (rwDCR), real-world progression-free survival (rwPFS), and overall survival (OS) were estimated, including by prior pertuzumab exposure and *de novo*/relapsed mBC status.

Results: A total of 137 patients from the ESME mBC database (78 received prior pertuzumab, 59 did not) were matched to 137 patients from DESTINY-Breast01. In the ESME DB-01 matched cohort, 73.7% received an anti-HER2 drug after T-DM1 treatment. The rwORR was 12.2% (95% confidence interval [CI] 6.2% to 18.2%; only partial responses) and rwDCR was 73.9% (95% CI 65.9% to 81.9%). The median rwPFS was 4.7 months (95% CI 3.8-6.0 months) and similar regardless of prior pertuzumab exposure or *de novo*/relapsed mBC status. The median OS was 24.1 months (95% CI 18.5-26.4 months) and longer in patients naive to versus exposed to pertuzumab and in patients with *de novo* versus relapsed mBC.

Conclusion: These RWD contextualized results of DESTINY-Breast01 and demonstrated an unmet medical need in patients with HER2+ mBC after T-DM1 treatment.

Key words: HER2+, metastatic breast cancer, real-world data, T-DXd, propensity score-matched

INTRODUCTION

Large, real-world datasets, such as the longitudinal Epidemiology Strategy and Medical Economics (ESME) database, allow further characterization and description of clinical effectiveness outcomes of treatment strategies in broad populations outside of clinical trials. Interest in the use of real-world data (RWD) to complement and contextualize data from clinical trials has grown and this use is supported by the United States Food and Drug Administration (FDA)

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and the European Medicines Agency in the evaluation of new drugs, including drugs for oncology and rare diseases.¹⁻³ These data may be generated from electronic health records, patient registries, insurance claims, digital applications, or other sources and can provide information on treatment patterns and effectiveness, including overall survival (OS), in real-world settings.²⁻⁴

The use of RWD to supplement single-arm trial data by providing an external control arm (i.e. data external to trial data) is a subject of growing interest.^{2,5,6} The ideal assessment of new interventions is conducted within randomized controlled trials, with OS as the primary endpoint and with a clinically relevant comparator.⁷ However, in exceptional circumstances, an alternative approach is to conduct single-arm trials that allocate the new intervention to all participants and to measure clinical efficacy using endpoints such as the objective response rate (ORR) or duration of response.⁷ These single-arm trials (that may later be substantiated by confirmatory trials demonstrating clinical benefit) may be considered for accelerated regulatory approval to avoid delay in patient access to treatment before confirmatory trials are completed; however, a major limitation in assessing the efficacy and safety of the intervention being tested is that there is no comparator arm.⁷ Hence, real-world evidence generated from the analysis of RWD can supplement single-arm trials by offering a comparator arm external to the trial that may help inform regulatory or reimbursement decisions.^{2,7,8}

DESTINY-Breast01 is a single-arm, phase II trial that assessed the efficacy and safety of trastuzumab deruxtecan (T-DXd), a human epidermal growth factor receptor 2 (HER2)-directed antibody–drug conjugate, in patients with HER2-positive (HER2+) metastatic breast cancer (mBC) who were previously treated with trastuzumab emtansine (T-DM1).⁹ At the time of study initiation, the established first-line therapy for patients with HER2+ mBC was anti-HER2 therapy with trastuzumab and pertuzumab in combination with a taxane, and the standard second-line therapy was T-DM1.^{10,11} However, there was no approved therapy or defined standard-of-care regimen after T-DM1 treatment. Common third- or greater-line treatments previously included combination chemotherapies in conjunction with HER2-targeting agents, with continued HER2 blockade beyond disease progression being regarded as standard clinical practice.¹⁰ In the post-third-line setting, these treatments had limited benefit on survival [lapatinib plus trastuzumab versus lapatinib alone: median progression-free survival (PFS), 12.0 versus 8.1 weeks; neratinib plus capecitabine versus lapatinib plus capecitabine: median PFS, 5.6 months versus 5.5 months; margetuximab plus chemotherapy versus trastuzumab plus chemotherapy: median PFS, 5.8 months versus 4.9 months].¹²⁻¹⁴ In DESTINY-Breast01, T-DXd demonstrated robust antitumor efficacy, with an ORR of 60.9% (primary endpoint), a median PFS of 16.4 months, and a median duration of response of 14.8 months.⁹ The median OS was not estimable after a median follow-up of 11 months [data cutoff (DCO) date, 1 August 2019; DCO used in approval application].⁹ At the

latest DCO of 26 March 2021, the updated median OS was 29.1 months and the median PFS was 19.4 months.¹⁵

To enrich the clinical data evidence of the single-arm DESTINY-Breast01 trial and to estimate the expected clinical benefit of T-DXd in a comparable patient population, an RWD analysis was conducted using the Unicancer ESME mBC database. Herein, we report the real-world evidence that was intended to contextualize the DESTINY-Breast01 clinical trial data during the initial application for marketing authorization of T-DXd in patients with HER2+ mBC. Real-world patient characteristics, clinical features, treatment patterns, and outcomes during the first subsequent regimen following T-DM1 were assessed in a patient population similar to patients eligible for treatment with T-DXd in DESTINY-Breast01. Based on the results of DESTINY-Breast01, T-DXd was approved in 2019 by the United States FDA for the treatment of adult patients with HER2+ unresectable or mBC who had received two or more previous HER2-directed regimens in the metastatic setting.¹⁶ This approval was later supported by results from the phase III DESTINY-Breast02 trial, which was a confirmatory trial for DESTINY-Breast01.¹⁷ Furthermore, the results of DESTINY-Breast03, a phase III trial of T-DXd in patients with HER2+ mBC previously treated with trastuzumab and a taxane, led to the T-DXd indication being updated to include patients with HER2+ unresectable or mBC who have received a prior anti-HER2-based regimen in the metastatic setting or developed disease recurrence during/within 6 months after neoadjuvant/adjuvant therapy.^{18,19} T-DXd is now approved in >40 countries.²⁰

PATIENTS AND METHODS

Unicancer ESME mBC database

This was a retrospective analysis of data from the Unicancer ESME mBC database, which gathers data regarding all patients with mBC treated in 18 private, nonprofit French comprehensive cancer centers. The ESME database has been fully described previously^{21,22} and is managed by Unicancer in accordance with current best practice guidelines.²¹ The ESME mBC database was authorized by the French data protection authority (initial authorization no. DE-2013-117 and subsequent amendment in accordance with the European general data protection regulation). The ESME mBC cohort is registered on www.clinicaltrials.gov under the number NCT03275311. All data were obtained retrospectively from patient electronic health records, pharmacy records, and inpatient hospitalization records, and all patients approved the reuse of their electronically recorded data. This manuscript is compliant with the ESMO Guidance for Reporting Oncology Real-World (GROW) evidence regarding reporting standards for RWD in oncology.²³

Patient eligibility and matching

Patients with HER2+ mBC who initiated treatment for mBC at any of the 18 French comprehensive cancer centers between 1 January 2008 and 31 December 2016, and who

received one or more treatment lines following T-DM1 were selected from the Unicancer ESME mBC database [ESME DESTINY-Breast01 (ESME DB-01) reference cohort]. This timeframe was selected to capture a sufficient number of patients who received treatment following T-DM1 in the third-line setting. These patients had not received T-DXd as a therapy option as it was not a commercially available therapy at the time of this analysis. The cutoff date for data collection and analysis in the ESME mBC database was 17 September 2018; the enrollment period for DESTINY-Breast01 was October 2017 through September 2018.⁹ A 1 : 1 matching approach was then applied to match patients from the Unicancer ESME mBC database reference cohort to patients from DESTINY-Breast01 (final ESME DB-01 matched cohort). To be selected in this step, patients in the reference cohort were required to have at least two radiological examinations available [at the start date of the first subsequent regimen after the T-DM1-based regimen and at another timepoint(s) during the treatment]. Patients from the ESME database were matched against patients from DESTINY-Breast01 who received a T-DXd dose of 5.4 mg/kg (the recommended dose level). All patients enrolled in the DESTINY-Breast01 trial provided written informed consent.⁹

Outcomes

The primary objective of this analysis was to describe the epidemiology and clinical features of patients in the ESME DB-01 matched cohort who received at least one treatment therapy after T-DM1. The secondary objectives were to describe treatment patterns and estimate effectiveness outcomes, including real-world best overall response (rwBOR), real-world ORR (rwORR), real-world disease control rate (rwDCR), and real-world PFS (rwPFS) during the subsequent line of treatment following T-DM1, and OS using the index date (defined as the date of initiation of the first treatment after T-DM1) as the reference date. These outcomes were also evaluated by prior pertuzumab exposure and by *de novo* versus relapsed mBC status. Additional secondary objectives were to describe treatments received before T-DM1 and after T-DM1 during the first subsequent regimen in the metastatic real-world setting.

rwBOR categories [complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD)], rwORR (CR or PR), and rwDCR (CR, PR, or SD) were evaluated by an independent central review committee. Scans were reviewed by two independent readers and an adjudicator using the Response Evaluation Criteria in Solid Tumors version 1.1 guidelines.

OS was defined as the time (in months) from the index date to the date of death for any cause; for patients without an OS event, OS was censored at the date of last contact or cutoff date, whichever was earlier. rwPFS was defined as the time (in months) from the index date to disease progression or death (PFS events) from any cause before the start of the second subsequent regimen after T-DM1 (i.e. a new treatment was initiated due to progression). Disease progression included the following events: newly diagnosed

lesions, progression in previously diagnosed metastatic organs, diagnosis of local or loco-regional recurrence of primary tumor, death due to any cause, and discontinuation of treatment (chemotherapy, targeted therapy, or endocrine therapy) due to 'progression.' Patients who did not experience a PFS event were censored at the start date of the subsequent regimen or, for patients without a second subsequent regimen after T-DM1, censored at the date of last contact or at the cutoff date, whichever was earlier.

Statistical analysis

A propensity score caliper matching method (or nearest neighbor matching within a caliper) was applied using logistic regression and a caliper width of 0.2 of the standard deviation of the logit of the estimated propensity score.²⁴ The matching algorithm continued until either each DESTINY-Breast01 patient was matched to a patient from the reference cohort or no matching pairs could be found. An inverse probability of treatment weighting approach was also used as a sensitivity analysis. The standardized mortality ratio weighting was used, and patients included in the case group (DESTINY-Breast01) received a weight of 1; control patients (ESME DB-01 matched cohort) received a weight of propensity score/(1 – propensity score).

The propensity score matching method has been previously described.^{25,26} Several prespecified prognostic factors were considered for building the propensity score model but only four factors could be accommodated to ensure there was a sufficient number of patients with data available from the ESME database for the matching exercise. The final factors were chosen based on clinical relevance and included prior treatment with pertuzumab, hormone receptor status, presence of visceral disease, and the number of lines of therapy before T-DM1 treatment. Pertuzumab exposure was selected, as previous reports demonstrated that prior pertuzumab treatment may affect the subsequent response to an anti-HER2 therapy.^{27,28} The balance of the treatment and control groups was checked for each variable included in the propensity score model, before and after applying either method (matching or weighting) by calculating the standardized difference and by displaying the histogram of the propensity score.²⁹ Balance was considered to be achieved if the absolute standardized difference between groups was ≤ 0.10 (threshold commonly used²⁵).

Descriptive analyses were carried out for patient characteristics at the index date, treatment strategies before the index date, and the subsequent line of treatment following T-DM1. rwORRs and associated 95% confidence intervals (95% CIs) were reported for rwBOR categories (CR, PR, SD, and PD) and rwDCR in the matched cohort and by prior pertuzumab exposure and *de novo* mBC. The Kaplan–Meier method was used to estimate the survival distribution of rwPFS and OS. The median rwPFS and median OS, as well as 95% CIs for medians, were reported for the matched cohort and by prior pertuzumab exposure and *de novo* or relapsed mBC. All analyses were reviewed by a multidisciplinary

team that included clinicians, epidemiologists, statisticians, and health economists, among others.

RESULTS

Datasets

Among 19867 patients from the Unicancer ESME mBC database (2008-2018), 721 patients met the predefined inclusion criteria (initiated first-line treatment for mBC between 1 January 2008, and 31 December 2016, received at least one line of treatment after T-DM1 therapy, and were identified as HER2+ at the date of initiation of T-DM1) and formed the ESME DB-01 reference cohort (Figure 1); a total of 222 patients with HER2+ mBC and imaging material were available for matching. Of these, 137 patients from the Unicancer ESME mBC database were matched to 137 patients from DESTINY-Breast01 (enrolled from October 2017 to September 2018) and formed the ESME DB-01 matched cohort.⁹ A total of 78 patients (56.9%) from the matched cohort had prior exposure to pertuzumab, whereas 59 patients (43.1%) did not.

After matching, baseline characteristics of the ESME DB-01 matched cohort and the DESTINY-Breast01 trial population were generally well balanced except for Eastern

Cooperative Oncology Group performance status (ECOG PS) score and age (Supplementary Table S1, available at <https://doi.org/10.1016/j.esmorw.2024.100043>). Most of the matched patients (54.7%) from DESTINY-Breast01 had an ECOG PS score of 0, whereas most matched patients (64.2%) from the Unicancer ESME mBC database had an ECOG PS score of ≥ 1 . Slightly more matched patients from DESTINY-Breast01 were aged <55 years compared with the matched patients from the Unicancer ESME mBC database (48.2% and 40.9%, respectively).

Clinical features and treatment patterns

In the matched ESME DB-01 cohort, the median age at the index date was 56.0 years [interquartile range (IQR) 49-66 years; Table 1]. The median time between primary tumor diagnosis and the index date was 61.9 months (IQR 33.5-106.0 months). In patients stratified by pertuzumab exposure, patients without prior exposure had longer median time since primary tumor diagnosis than patients with prior exposure [74.1 months (IQR 40.7-110.2 months) versus 51.9 months (IQR 26.2-106.0 months)]. The most common type of metastases was 'visceral and not cerebral', and most patients had three or more metastatic sites at the index

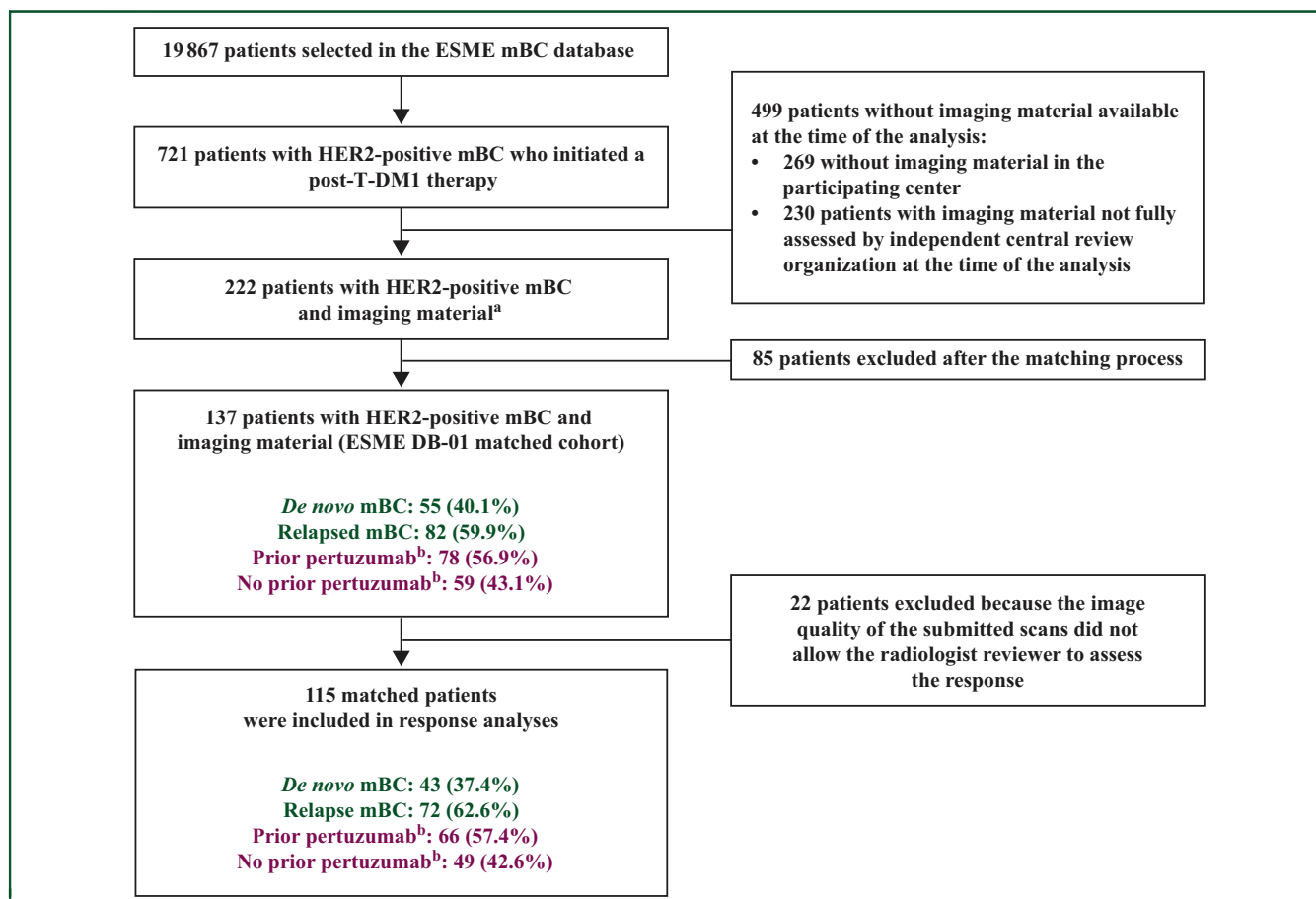


Figure 1. Flow diagram of the ESME DB-01 matched cohort.

DB-01, DESTINY-Breast01; ESME, Epidemiology Strategy and Medical Economics; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine.

^aImaging material available for reading at the time of the analysis at an independent central review organization (non-exhaustive).

^bPertuzumab exposure before the index date.

Characteristics	ESME DB-01 matched cohort (n = 137)	ESME DB-01 matched cohort pertuzumab exposure before the index date	
		Yes (n = 78)	No (n = 59)
Age at the index date (years), median (IQR)	56 (49-66)	56 (48-66)	56 (49-64)
Weight at the selection date (kg), median (IQR)	67 (56-75)	65 (56-74)	68 (58-77)
Time since primary tumor diagnosis (months), median (IQR)	61.9 (33.5-106.0)	51.9 (26.2-106.0)	74.1 (40.7-110.2)
Highest primary tumor size (mm), median (IQR)	25 (15-27)	24 (14-25)	26 (16-38)
Time since metastatic disease diagnosis (months), median (IQR)	31.1 (18.5-43.7)	24.7 (16.6-35.9)	38.3 (26.6-57.3)
Metastatic sites (multiple possible answers), n (%)			
CNS/CSF/brain	44 (32.1)	28 (35.9)	16 (27.1)
Bone	83 (60.6)	44 (56.4)	39 (66.1)
Lung/pleura	68 (49.6)	40 (51.3)	28 (47.5)
Liver	67 (48.9)	39 (50.0)	28 (47.5)
Metastatic nodes	78 (56.9)	49 (62.8)	29 (49.2)
Skin	27 (19.7)	15 (19.2)	12 (20.3)
Other	23 (16.8)	17 (21.8)	6 (10.2)
Metastases type (exclusive), n (%)			
Visceral and cerebral	44 (32.1)	28 (35.9)	16 (27.1)
Visceral and not cerebral	67 (48.9)	38 (48.7)	29 (49.2)
Nonvisceral	26 (19.0)	12 (15.4)	14 (23.7)
Number of metastatic sites at the index date, n (%)			
<3	58 (42.3)	30 (38.5)	28 (47.5)
≥3	79 (57.7)	48 (61.5)	31 (52.5)
ECOG PS at the index date^b, n (%)			
0	29 (35.8)	21 (46.7)	8 (22.2)
1	38 (46.9)	18 (40.0)	20 (55.6)
2	11 (13.6)	4 (8.9)	7 (19.4)
3	3 (3.7)	2 (4.4)	1 (2.8)
Not available	56 (40.9)	33 (42.3)	23 (39.0)

CNS, central nervous system; CSF, cerebrospinal fluid; DB-01, DESTINY-Breast01; ECOG PS, Eastern Cooperative Oncology Group performance status; ESME, Epidemiology Strategy and Medical Economics; IQR, interquartile range; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine.

^aIndex date is the date of initiation of the first treatment after T-DM1.

^bAmong patients with an available ECOG PS score.

date in the matched cohort regardless of prior pertuzumab exposure. A total of 127 patients (92.7%) in the matched ESME DB-01 cohort had received ≥ 1 prior lines of treatment in the metastatic setting before initiating treatment with T-DM1 and a median of 3 lines of treatment, including T-DM1 (IQR 3-5 lines) before the index date. The therapies that patients received before the index date (including in the adjuvant setting) were trastuzumab (94.9%), taxanes (89.8%), anthracyclines (48.9%), and oral chemotherapy (40.9%; [Table 2](#)). T-DXd was not a commercially available therapy at the time of this study. The median duration of T-DM1 treatment was 5.6 months (95% CI 2.3-12.0 months); >80% of patients discontinued treatment due to disease progression.

Effectiveness of treatment strategy in the ESME DB-01 matched cohort

For the first regimen following T-DM1 therapy, 73.7% of patients in the ESME DB-01 matched cohort received an anti-HER2 therapy, whereas 35% received an oral chemotherapy and 37.2% received an intravenous chemotherapy ([Supplementary Table S2](#), available at <https://doi.org/10.1016/j.esmorw.2024.100043>). Disease progression was the primary reason for discontinuing the first treatment regimen after T-DM1, followed by physician's choice/protocol-driven choice and toxicity.

Tumor responses in the ESME DB-01 matched cohort could only be assessed in 115 patients, as the radiographic scans for 22 of 137 patients were of insufficient quality to

Treatments received	ESME DB-01 matched cohort (n = 137)
Prior number of treatment regimens in the metastatic setting, median (IQR)	3 (3-5)
Oral chemotherapy, n (%)	56 (40.9)
Anthracyclines, n (%)	67 (48.9)
Taxanes, n (%)	123 (89.8)
Anti-HER2 drugs, n (%)	137 (100)
Trastuzumab, n (%)	130 (94.9)
Pertuzumab, n (%)	78 (56.9)
Other anti-HER2 drugs ^d , n (%)	137 (100)
Other IV chemotherapy/targeted therapy, n (%)	64 (46.7)
Antiestrogen, n (%)	45 (32.8)
Aromatase inhibitors, n (%)	45 (32.8)
LHRH analogs, n (%)	6 (4.4)
Other endocrine therapies (not including aromatase inhibitors, LHRH analogs, and antiestrogen), n (%)	1 (0.7)

DB-01, DESTINY-Breast01; ESME, Epidemiology Strategy and Medical Economics; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; IV, intravenous; LHRH, luteinizing hormone-releasing hormone; T-DM1, trastuzumab emtansine.

^aIncludes treatments received in the adjuvant setting and includes T-DM1.

^bIndex date: the date of initiation of the first treatment after T-DM1.

^cPatients could have received more than one type of therapy.

^dIncludes T-DM1 treatment but excludes trastuzumab treatment.

enable radiologist assessment. For rwBOR among these 115 patients, PR, SD, and PD were observed in 14 (12.2%), 42 (36.5%), and 30 (26.1%) patients, respectively; no patient had a CR and more patients who previously received pertuzumab had a PR than patients without prior pertuzumab exposure (16.7% versus 6.1%, respectively; Table 3). The rwORR was 12.2% (95% CI 6.2% to 18.2%; only PRs) and rwDCR was 73.9% (95% CI 65.9% to 81.9%). In patients with relapsed and *de novo* mBC, the rwORR was 13.9% (95% CI 5.9% to 21.9%) and 9.3% (95% CI 2.6% to 22.1%), respectively (Supplementary Table S3, available at <https://doi.org/10.1016/j.esmorw.2024.100043>).

In the matched cohort, the median rwPFS during the first subsequent regimen following T-DM1 therapy was 4.7 months (95% CI 3.8-6.0 months; Figure 2A, Table 3); this did not differ in patients with and without prior pertuzumab treatment [5.1 months (95% CI 3.8-6.7 months) and 4.4 months (95% CI 2.8-6.0 months), respectively; Figure 2B]. The median rwPFS in the matched cohort was also similar in patients with *de novo* mBC and relapsed mBC [4.2 months (95% CI 2.6-6.7 months) and 4.8 months (95% CI 3.8-6.6 months), respectively] (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmorw.2024.100043>).

The median OS from the index date for patients in the matched cohort was 24.1 months (95% CI 18.5-26.4 months; Figure 2C, Table 3) and was numerically longer in patients without prior pertuzumab treatment than patients with prior pertuzumab exposure [29.7 months (95% CI 20.1-47.7 months) and 21.1 months (95% CI 17.0-25.4 months); Figure 2D]. The median OS in the matched cohort was also numerically longer in patients with *de novo* mBC compared with patients with relapsed mBC [26.5 months (95% CI 14.4

months-not estimable) and 22.1 months (95% CI 18.5-25.4 months); Supplementary Figure S2, available at <https://doi.org/10.1016/j.esmorw.2024.100043>].

The standardized mortality ratio weighting sensitivity analysis results for survival endpoints were also similar to those of the main analysis in the ESME DB-01 matched cohort (Supplementary Table S4, available at <https://doi.org/10.1016/j.esmorw.2024.100043>), indicating that the results of the propensity score caliper matching method may be robust.

DISCUSSION

From a real-world dataset of 137 patients from the Unicancer ESME mBC database matched to 137 patients enrolled in DESTINY-Breast01, real-world effectiveness outcomes were estimated in patients with HER2+ mBC who received treatment following T-DM1. Most patients in the ESME DB-01 matched cohort (73%) received an HER2-directed therapy and about one-third received oral or intravenous chemotherapy as part of their first regimen following T-DM1. Patients in the matched cohort had not received T-DXd as it was not a commercially available therapy at the time of the study. In the ESME DB-01 matched cohort, the ORR was 12.2%, with all responses being PRs, and the DCR was 73.9%. The median rwPFS during the first regimen after T-DM1 was 4.7 months and was similar regardless of prior pertuzumab exposure or *de novo* or relapsed mBC. The median OS from the index date was 24.1 months, with a longer OS observed in patients without prior pertuzumab exposure than patients with prior exposure and in patients with *de novo* than relapsed mBC. Prior treatment with pertuzumab was selected as a

Table 3. Real-world overall response rate, rwDCR, rwPFS, and OS during the first regimen following T-DM1 therapy			
	ESME DB-01 matched cohort (n = 115 ^a)	ESME DB-01 matched cohort pertuzumab exposure before the index date ^b	
		Yes (n = 66)	No (n = 49)
rwBOR, n (%)			
CR	0 (0)	0 (0)	0 (0)
PR	14 (12.2)	11 (16.7)	3 (6.1)
SD	42 (36.5)	27 (40.9)	15 (30.6)
PD	30 (26.1)	16 (24.2)	14 (28.6)
Non-CR/non-PD	29 (25.2)	12 (18.2)	17 (34.7)
rwORR (CR + PR), n (%); 95% CI	14 (12.2); 6.2% to 18.2% ^c	11 (16.7); 7.7% to 25.7% ^c	3 (6.1); 1.3% to 16.9% ^d
rwDCR (CR + PR + SD + non-CR/non-PD), n (%); 95% CI	85 (73.9); 65.9% to 81.9% ^c	50 (75.8); 65.4% to 86.1% ^c	35 (71.4); 58.8% to 84.1% ^c
	ESME DB-01 matched cohort (n = 137)	ESME DB-01 matched cohort pertuzumab exposure before the index date ^b	
		(n = 78)	(n = 59)
rwPFS (months), median (95% CI)	4.7 (3.8-6.0)	5.1 (3.8-6.7)	4.4 (2.8-6.0)
OS ^e (months), median (95% CI)	24.1 (18.5-26.4)	21.1 (17.0-25.4)	29.7 (20.1-47.7)

CI, confidence interval; CR, complete response; DB-01, DESTINY-Breast01; ESME, Epidemiology Strategy and Medical Economics; OS, overall survival; PD, progressive disease; PR, partial response; rwBOR, real-world best overall response; rwDCR, real-world disease control rate; rwORR, real-world objective response rate; rwPFS, real-world progression-free survival; SD, stable disease; T-DM1, trastuzumab emtansine.

^a22 of 137 patients in the ESME DB-01 matched cohort were excluded from the response analysis because the image quality of their radiographic scans was insufficient for response assessment.

^bIndex date: the date of initiation of the first treatment after T-DM1.

^c95% normal CI.

^dExact binomial CI.

^eOverall survival calculated from the index date.

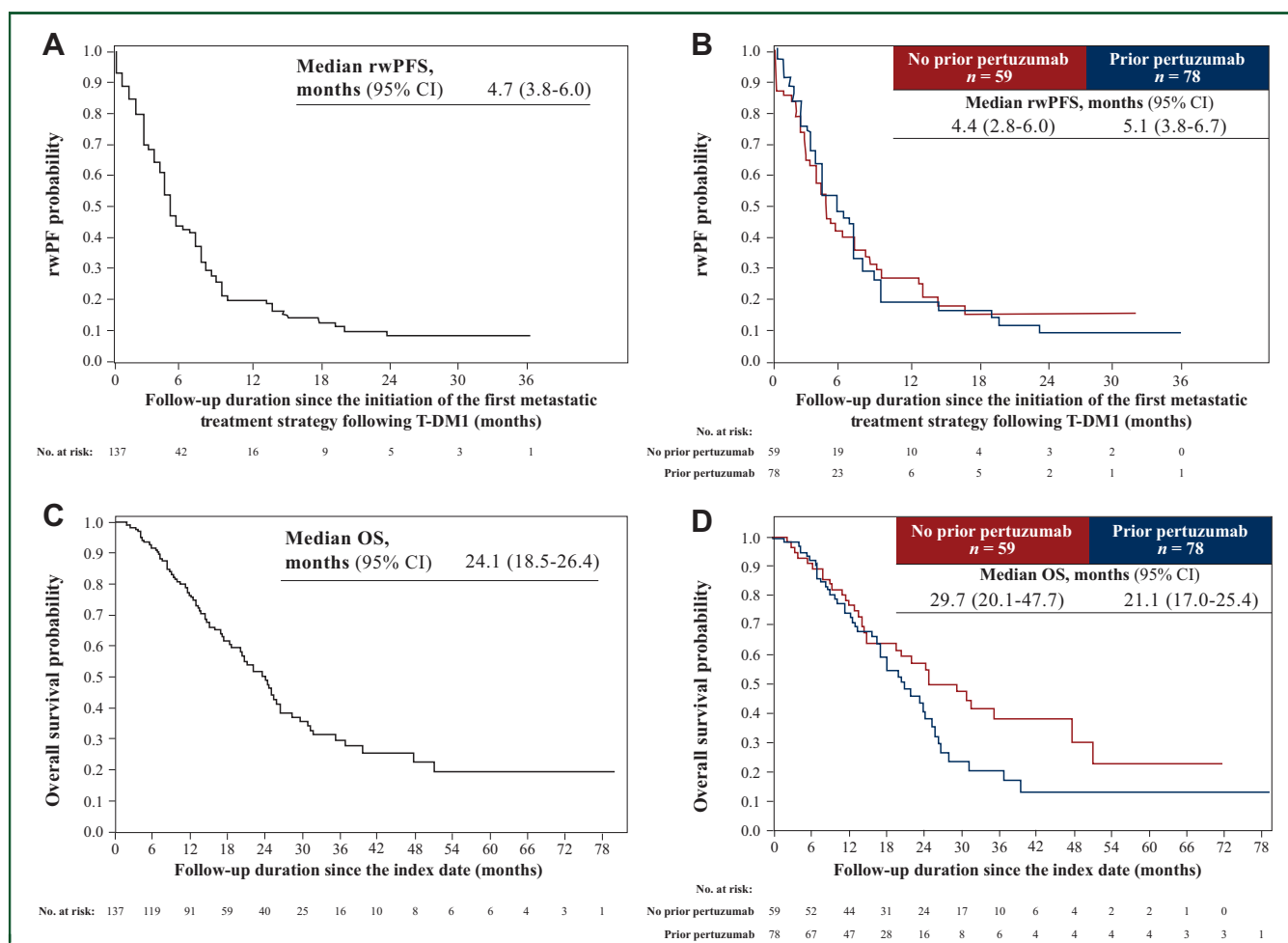


Figure 2. Kaplan–Meier survival curves for the ESME DB-01 matched cohort.

rwPFS during the first regimen following T-DM1 therapy in the (A) matched cohort and (B) the matched cohort according to pertuzumab exposure before the index date^a. Overall survival from the index date^a in the (C) matched cohort and (D) the matched cohort according to pertuzumab exposure before the index date^a. CI, confidence interval; DB-01, DESTINY-Breast01; ESME, Epidemiology Strategy and Medical Economics; mOS, median overall survival; rwPFS, real-world progression-free survival; T-DM1, trastuzumab emtansine.

^aIndex date is the date of initiation of the first treatment after T-DM1.

propensity score matching factor due to a previous report that suggested that exposure to pertuzumab may affect the efficacy of subsequent HER2-targeted therapy.²⁸ Although the median PFS in the matched cohort did not differ depending on pertuzumab exposure, patients without prior pertuzumab treatment demonstrated a numerically longer OS than those with prior exposure; further investigations would be needed to confirm this difference.

This real-world evidence demonstrated the unmet medical need at the time of the study for an effective therapy in patients with HER2+ mBC after treatment with T-DM1. This type of evidence generation is useful to contextualize clinical trial results in regulatory submissions and for comparative effectiveness estimates during reimbursement processes, particularly when assessing phase II, single-arm trial data. At the time of the Biologics Licensing Application submission for T-DXd, the standard of care for the first-line treatment of patients with HER2+ mBC included combination therapy of trastuzumab, pertuzumab, and a taxane followed by T-DM1 in the second-line setting, with no standard of care established following

T-DM1.^{10,11} Ultimately, results from DESTINY-Breast01 led to the approval of T-DXd and established this drug as the new standard of care following T-DM1. The results from the phase III DESTINY-Breast03 study have since then led to T-DXd replacing T-DM1 as the second-line standard-of-care therapy for patients with HER2+ unresectable cancer or mBC previously treated with an anti-HER2-based regimen.¹⁰

Results from DESTINY-Breast01 were further supported by the results of DESTINY-Breast02, a phase III, open-label confirmatory trial for DESTINY-Breast01, which enrolled patients previously treated with T-DM1 who were then randomized to receive either T-DXd or treatment of physician's choice (capecitabine plus trastuzumab or capecitabine plus lapatinib). The results of DESTINY-Breast02 demonstrated an ORR of 70%, a median PFS of 17.8 months, and a median OS of 39.2 months in the T-DXd treatment group versus an ORR of 29%, a median PFS of 6.9 months, and a median OS of 26.5 months in the treatment of physician's choice group.¹⁷ Of note, there were differences in patient therapy history between DESTINY-Breast01 and

DESTINY-Breast02, with a median of six prior regimens in patients enrolled in DESTINY-Breast01 compared with a median of two prior lines of therapy in the locally advanced/metastatic setting for patients enrolled in DESTINY-Breast02. In addition, patients who had been previously treated with capecitabine were ineligible for enrollment into DESTINY-Breast02.^{9,17} A direct comparison of effectiveness outcomes in the ESME DB-01 matched cohort cannot be made with the efficacy outcomes observed in DESTINY-Breast01 and DESTINY-Breast02 due to differences in study design and data collection as well as differences in therapies used following T-DM1 in the comparator arm of DESTINY-Breast02.¹⁷

A strength of this analysis is that the Unicancer ESME database pools data gathered from patient electronic health records, pharmacy records, and hospital databases from several centers that specialize in oncology. These abundant clinical data allowed the creation of an observational cohort that was similar to patients enrolled in DESTINY-Breast01. Thus, RWD were used in this analysis to leverage and contextualize clinical trial data from the DESTINY-Breast01 clinical trial. In addition, propensity scores were used to balance potential differences in background variables, which enhanced the evaluation of treatment effects on survival outcomes by removing any association between measured confounders and treatment.^{26,30}

Some limitations of this study are the potential selection bias when matching cohorts and differences in the follow-up and treatment times of patients in the ESME DB-01 matched cohort. Propensity score matching was carried out to minimize overall confounding, but a potential exists for residual confounding. Furthermore, although a sensitivity analysis was conducted to assess the robustness of the matching method, it was not exhaustive in assessing the impact of all possible variables. In addition, not all patients from the DESTINY-Breast01 trial could be matched; only 30.8% of patients in the reference cohort from the Unicancer ESME mBC database met the required criteria for matching. About one-fourth of patients in the ESME DB-01 matched cohort also did not receive an anti-HER2 treatment as the first subsequent regimen following T-DM1, whereas all patients in the DESTINY-Breast01 cohort did. Patients from the matched cohort were also followed up and treated according to the guidelines and practices current to the institution at their time of treatment, resulting in inherent differences across the treatment institutions comprising the French comprehensive cancer centers as well as the times of treatment. In addition, the patient data source was restricted to only the 18 cancer centers that comprise the ESME network. Finally, these analyses present descriptive results; no direct statistical comparisons were made between the matched cohort and patients from DESTINY-Breast01. Therefore interpretations of these data in context with DESTINY-Breast01 should be made with caution.

This study characterized third-line treatment strategies and responses in a real-world patient population with advanced HER2+ mBC who were previously treated with

T-DM1, which was the common second-line treatment at the time of this analysis. In the absence of a comparator arm in the DESTINY-Breast01 trial, this RWE demonstrated an unmet medical need in the third-line and later setting at the time that DESTINY-Breast01 was initiated.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, no generative AI or AI-assisted technologies were used in the writing process. The authors take full responsibility for the content of the publication.

ACKNOWLEDGEMENTS

We thank the patients who participated in this study, as well as their families and caregivers. We deeply thank all patients who participated in the ESME mBC database for granting access to their data, thus allowing this work to be carried out. We thank the 18 sites involved in the ESME Research program and each ESME local coordinator for managing the project at the local level. We also thank the ESME central coordinating staff from Unicancer, the mBC Scientific Group, and the ESME Strategic Committee for their ongoing support. Under the guidance of the authors, assistance in medical writing and editorial support was provided by Vishal Gor, PhD, and Jill Shults, PhD, of ApotheCom, and was funded by Daiichi Sankyo.

FUNDING

This work was supported by Daiichi Sankyo and designed by Unicancer and Daiichi Sankyo, Inc., in collaboration with AstraZeneca (no grant number). AstraZeneca entered into a collaboration agreement with Daiichi Sankyo Co., Ltd., for T-DXd in March 2019. Unicancer independently manages ESME databases (i.e. data collection, analysis, and publication) and is the sole data controller for data processing. The ESME MBC database receives financial support from industrial partners.

DISCLOSURE

CC reports an executive partnership between Unicancer and Daiichi Sankyo. RS is an employee of Unicancer. LB is a full-time employee of Unicancer. SM is a scientific committee study member for Roche; a data and safety monitoring member of clinical trials for Sensorion, Biophytis, Servier, IQVIA, Yuhan, and Kedrion; and reports consulting fees for Amaris. BA is an advisory board member for Daiichi Sankyo and AstraZeneca; and reports consulting fees for Daiichi Sankyo, AstraZeneca, Servier, BMS, Roche, and Gilead. SDe reports clinical research grants for her institution from Pfizer, Novartis, AstraZeneca, Roche Genentech, Lilly, Orion, Amgen, Sanofi, Genomic Health/Exact Sciences, Servier, BMS, Pierre Fabre, Taiho, the European Commission, and the French Government; has received travel support for attending meetings from Novartis, Roche, and Seagen; is on a scientific board for Sanofi, Elsan, Rappta, Besins, DeciBio, and AstraZeneca; is on the advisory board for Gilead; and is

on the IDMC of a trial sponsored by the BIG International Group and Pfizer. KD, ZL, and JC are employees of Daiichi Sankyo. MR is an employee of Daiichi Sankyo; an unpaid associate professor at Karolinska Institute; and reports stock for GSK and stock options for Daiichi Sankyo. All other authors have declared no conflicts of interest.

DATA SHARING

Anonymized individual participant data (IPD) on completed studies and applicable supporting clinical study documents may be available upon request at <https://vivli.org/>. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of the company and our clinical study patients. Details on Daiichi Sankyo's data-sharing criteria and the procedure for requesting access can be found at <https://vivli.org/ourmember/daiichi-sankyo/>. However, real-world datasets analyzed for this study are from the ESME mBC database. In accordance with ethical and legal requirements related to the ESME data warehouse, individual data from the ESME databases cannot be made available. For any specific demand, please contact Unicancer (valorisation-esme@unicancer.fr). Each demand will be examined on a case-by-case basis by the ESME mBC scientific committee.

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