

Real-world evidence corroborates the clinical trial results for management of HER2-positive metastatic breast cancer with T-DM1: a systematic review

Bivek Shah¹, Kunal Jain^{2*}, Oluwasola Lawal³, Amit Kishore^{1*}, Rajinder Chawla¹

¹AccuScript Consultancy, Ludhiana, India

²Dayanand Medical College and Hospital, Ludhiana, India

³AccuScript Consultancy, Reading, UK

*Author for correspondence:
Email: drkunaljain1@gmail.com,
amit.kishore@accuscript.org

Received date: September 13, 2025

Accepted date: February 11, 2026

Copyright: © 2025 Kishore A, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Purpose: Trastuzumab emtansine (T-DM1), an antibody-drug conjugate consisting of the humanized monoclonal antibody trastuzumab covalently linked to the cytotoxic agent DM1, is utilized for the management of human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer (mBC), after progression on prior trastuzumab. Its regulatory approval preceded the era before pertuzumab approval. In the contemporary era, pertuzumab and/or trastuzumab is employed in routine clinical practice in the first-line (1L) setting. It is therefore relevant to consider currently utilized regimens to confirm their role in current clinical practice. The current study evaluated real-world evidence (RWE) for the efficacy and safety of T-DM1 in HER2-positive mBC and compare with evidence from the clinical trial program.

Methods: Searches were performed in PubMed, Embase, and Cochrane for eligible studies from inception until May 22, 2024. Screening was performed using AccuScreener module of SymproAI online software. Variables of interest included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and grade ≥ 3 adverse events (AEs).

Results: Fifty-five publications were identified; 19 from 12 clinical trials and 36 from 34 real-world studies. ORR ranged between 25.0–50.4% (clinical trials) and 14.3–80.0% (real-world studies). Corresponding median PFS was 4.3–9.6 months and 2.8–12.0 months while the median OS was 22.7–34.3 and 12.0–45.0 months, respectively. Furthermore, real-world data suggest the benefit of T-DM1 is more marked in patients without prior pertuzumab. Evidence from both trials and real-world studies support the use of T-DM1 in patients with brain/central nervous system (CNS) metastasis. Safety data from the studies demonstrated a consistent safety profile in terms of AEs (\geq grade 3), with thrombocytopenia being the most frequent.

Conclusion: This review demonstrated T-DM1 as an effective treatment for HER2-positive mBC in the second-line (2L) or later setting and has an acceptable safety profile.

Keywords: Breast Cancer, *HER2* Gene, Trastuzumab emtansine, Treatment outcome, Brain metastasis

Introduction

Human epidermal growth factor receptor-2 (HER2)-directed therapies have transformed the management of HER2-positive breast cancer (BC), a subtype previously associated with poor prognosis [1]. These therapies currently constitute part of recommended regimens for most lines of therapy for recurrent or metastatic HER2-positive BC [2,3]. There are three classes of approved HER2-directed therapies: anti-HER2 monoclonal antibodies (e.g., trastuzumab and pertuzumab) [4–6]; antibody-drug conjugates (ADC) (e.g., trastuzumab emtansine [T-DM1] and trastuzumab deruxtecan [T-DXd]) [7,8]; and tyrosine kinase inhibitors (TKIs; e.g., lapatinib, tucatinib and neratinib)

[9]. In the contemporary era, the dual blockage of HER2 using trastuzumab and pertuzumab in combination with chemotherapy (CT) constitutes the standard first-line (1L) treatment regimen [10], while T-DM1 is used for the management of metastatic BC (mBC), and is indicated for use after disease progression on prior treatment with trastuzumab and a taxane [7].

Although the European Society for Medical Oncology (ESMO; and Pan Asian adapted ESMO clinical guidelines) and National Comprehensive Cancer Network clinical guidelines provide recommendations on the sequencing of HER2-directed therapies up to the third-line (3L) [2,3,11], some therapies may be unavailable in some regions or inappropriate for certain patients due to cost and safety profile.

The treatment landscape for HER2-positive metastatic breast cancer (mBC) has shifted significantly over the past five years with the introduction of newer therapies, such as pertuzumab. As a result, clinical trial data for agents like T-DM1, approved more than five years ago, may no longer align with the current clinical practices. These trials, conducted before pertuzumab's approval, typically enrolled heavily pretreated patients who had progressed on one or more prior HER2-directed therapies. Today's patient populations and treatment approaches differ, raising questions about whether the efficacy and safety outcomes from those historical trials still apply in modern real-world settings [12–14].

The clinical efficacy and safety of T-DM1, reported among clinical trials in the treatment of HER2-positive BC, have been systematically reviewed and meta-analyzed [15–17], however, limited reports have reviewed the findings from observational or real-world settings [18] or, have compared the findings of clinical trials with that of observational studies [19]. The growing integration of real-world evidence (RWE) in clinical practice is becoming crucial for complementing findings from randomized controlled trials (RCTs). In this context, T-DM1 has been established as an effective treatment for HER2-positive mBC. However, RWE on T-DM1's effectiveness and safety in comparison to observations from clinical trials remains limited. To address the gap, this systematic literature review (SLR) aims to corroborate clinical trial results with RWE, with a specific focus on studies comparing the efficacy/effectiveness and safety of T-DM1 in patients with HER2-positive mBC.

Methods

This SLR was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocol (PRISMA-P) [20] and was registered on PROSPERO (ID: CRD42023410972). The PubMed, Embase, and Cochrane search strategies were designed to identify relevant publications on T-DM1 efficacy and safety. Searches were performed on 22nd May 2024, without geographic or time restrictions. The search strategies and outputs are detailed in **Table S1**.

Publications were screened to identify relevant evidence as per the eligibility for inclusion and exclusion criteria (**Table S2**). Studies incongruent with the protocol were excluded. The titles and abstracts of publications from the searches were screened using AccuScreener, a screening module [21] within SymproAI, an online Artificial Intelligence based Systematic Literature Management and Processing software for end-to-end automation of systematic reviews [22]. The AccuScreener output was cross-checked manually by a team of two expert researchers. The full-text of included publications

were reviewed by two researchers. A senior systematic reviewer authenticated the results and resolved any uncertainties at both the title/abstract and full-text screening steps. Data from the included publications were extracted by one researcher and reviewed by a second researcher. Extracted efficacy data included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety data included grade 3 or worse adverse events (AEs). The substantial methodological heterogeneity between included studies precluded formal meta-analysis, therefore, a robust descriptive approach was employed.

Quality appraisal with the risk of bias (RoB) analysis for all the included full-text publications were performed using validated Cochrane RoB tools in ROB Master module of SymproAI [22]. Quality assessment of randomized controlled trials (RCTs) was performed using the Cochrane Collaboration RoB 2.0 tool [23]. The RoB 2.0 assessed bias across five domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. An overall RoB judgment was assigned to each study based on domain-specific assessments. The Cochrane ROBINS-I tool was used for non-randomized trials and real-world studies [23,24]. The ROBINS-I evaluated seven domains of potential bias: (1) bias due to confounding, (2) bias in participant selection, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in outcome measurement, and (7) bias in selection of reported results. Each study was assigned an overall RoB rating based on the highest risk level identified across all domains.

Results

Overview of identified studies

Overall, 55 publications (42 full-text articles and 13 congress abstracts) (**Figure 1**) that explored T-DM1 efficacy and safety were identified. Of these, 19 publications were from 12 different clinical trials. This included multiple publications from DESTINY-Breast03 (four publications) [25–28], EMILIA (four publications) [29–32], and KAMILLA (two publications) [33,34] while the remaining nine trials each described distinct studies [35–43]. A total of 36 publications were reported from real-world studies, of which a “field practice study” had three publications [44–46] and the remaining 33 studies each contributed a single publication [47–79]. The median age of patients ranged from 42 to 64.5 years across RWE studies and clinical trials. Where reported, ECOG performance status ranged from 0 to ≤ 2 (**Tables 2–7**). An overview of studies with multiple publications (primary and secondary) summarizing the overlapping cohorts across clinical trials (DESTINY Breast03, EMILIA, and KAMILLA) and real-world study (FIELD PRACTICE) has been presented as **Table 1**.

Among the 19 publications from clinical trials, 15 investigated HER2 positive mBC patients with/without brain metastasis [25,26,28–30,32,34–40,42,43], three reported subgroup analysis on brain metastasis [27,31,33] while one reported only safety outcomes [41].

Efficacy

Clinical trials

Fifteen publications from 11 clinical trials (including five phase 2, five phase 3 clinical trials, and one T-PAS expanded-access study)

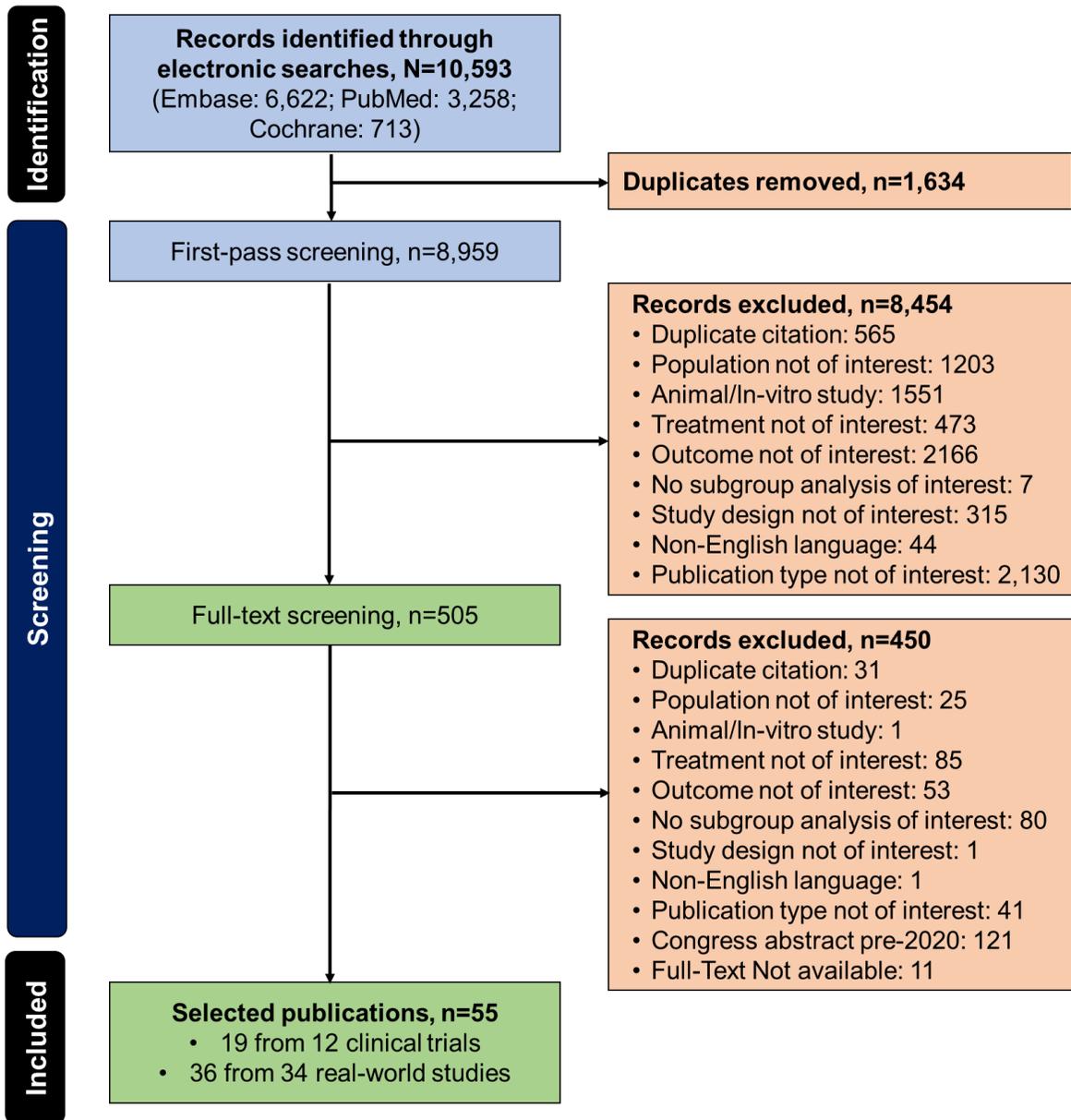


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

Table 1. Patient demographics and baseline clinical characteristics in patients with UC and CD.

Acronym	Trial identifier	Total publications	Study design	Primary publication details	Secondary publications and its details	Outcomes (details presented in tables)
A. Clinical trials						
DESTINY Breast03	NCT03529110	Four	Randomized, open-label, multi-center, active-controlled, phase 3	<ul style="list-style-type: none"> Cortés <i>et al.</i> 2022 [80] Global N=524 First interim analysis Data cut-off: May 21, 2021 	<ul style="list-style-type: none"> Hurvitz <i>et al.</i> 2023 [26] Global N=524 Second interim analysis Data cutoff: July 25, 2022 Hurvitz <i>et al.</i> 2024 [27] Global N=82 Subgroup analysis of patients with brain metastasis Data cut-off: May 21, 2021 Im <i>et al.</i> 2022 [28] Asian subpopulation N=309 	<ul style="list-style-type: none"> Efficacy (Table 2) Cortés <i>et al.</i> 2022 [80] Hurvitz <i>et al.</i> 2023 [26] Im <i>et al.</i> 2022 [28] Brain metastases (Table 5) Hurvitz <i>et al.</i> 2023 [26] Hurvitz <i>et al.</i> 2024 [27] Safety (grade ≥ 3) (Table 6) Cortés <i>et al.</i> 2022 [80] Hurvitz <i>et al.</i> 2023 [26] Im <i>et al.</i> 2022 [28] Safety (Any grade) (Table S3) Cortés <i>et al.</i> 2022 [80] Hurvitz <i>et al.</i> 2023 [26] Im <i>et al.</i> 2022 [28]
EMILIA	NCT00829166	Four	Randomized, open-label, multi-centre, phase 3	<ul style="list-style-type: none"> Verma <i>et al.</i> 2012 [32] Global N=991 Follow-up: 13-19 months First data cut-off date: Jan 14, 2012 Second data cut-off date: July 31, 2012 	<ul style="list-style-type: none"> Diéras <i>et al.</i> 2017 [29] Global N=991 Follow-up: 41.9-47.8 months First data cut-off date: Dec 31, 2014 Krop <i>et al.</i> 2015 [31] Global N=95 Subgroup analysis of patients with Brain metastasis Im <i>et al.</i> 2021 [30] Asian subpopulation N=158 	<ul style="list-style-type: none"> Efficacy (Table 2) Verma <i>et al.</i> 2012 [32] Diéras <i>et al.</i> 2017 [29] Im <i>et al.</i> 2021 [30] Brain metastases (Table 5) Krop <i>et al.</i> 2015 [31] Safety (grade ≥ 3) (Table 6) Verma <i>et al.</i> 2012 [32] Diéras <i>et al.</i> 2017 [29] Krop <i>et al.</i> 2015 [31] Im <i>et al.</i> 2021 [30] Safety (Any grade) (Table S3) Verma <i>et al.</i> 2012 [32] Diéras <i>et al.</i> 2017 [29] Krop <i>et al.</i> 2015 [31] Im <i>et al.</i> 2021 [30]

Acronym	Trial Identifier	Total publications	Study design	Primary publication details	Secondary publications and its details	Outcomes (details presented in tables)
KAMILLA	NCT01702571	Two	Single-arm, On-going, phase 3b	<ul style="list-style-type: none"> Wuerstlein <i>et al.</i> 2022 [34] <ul style="list-style-type: none"> Global (Cohort 1) and Asia (Cohort 2) N, Cohort 1: 2002; Cohort 2: 181 Follow-up: 20.6 months (Cohort 1); 15.1 months (Cohort 2) Data cut-off date: Jan 31, 2017 (Cohort 1); July 31, 2019 (Cohort 2) 	<ul style="list-style-type: none"> Montemurro <i>et al.</i> 2020 [33] <ul style="list-style-type: none"> Global N=358 Subgroup analysis of patients with Brain metastasis 	<ul style="list-style-type: none"> Efficacy (Table 2) <ul style="list-style-type: none"> Wuerstlein <i>et al.</i> 2022 [34] Brain metastases (Table 5) <ul style="list-style-type: none"> Montemurro <i>et al.</i> 2020 [33] Safety (grade ≥ 3) (Table 6) <ul style="list-style-type: none"> Wuerstlein <i>et al.</i> 2022 [34] Montemurro <i>et al.</i> 2020 [33] Safety (Any grade) (Table S3) <ul style="list-style-type: none"> Wuerstlein <i>et al.</i> 2022 [34] Montemurro <i>et al.</i> 2020 [33]
B. Real-world study						
Field-practice study	NR	Three	Retrospective analysis	<ul style="list-style-type: none"> Fabi <i>et al.</i> 2017 [45] <ul style="list-style-type: none"> Italy N=303 Follow-up: 10 months Outcome focused on treatment line, previous lapatinib treatment and patterns of metastasis. 	<ul style="list-style-type: none"> Fabi <i>et al.</i> 2017 [46] <ul style="list-style-type: none"> Italy N=107 Follow-up: NR Population prior treated with 1L pertuzumab / trastuzumab vs trastuzumab-only-based regimen. Fabi <i>et al.</i> 2018 [44] <ul style="list-style-type: none"> Italy N=87 Follow-up: 16 months Subgroup analysis of patients with Brain metastasis 	<ul style="list-style-type: none"> Efficacy as per prior LoT (Table 3) <ul style="list-style-type: none"> Fabi <i>et al.</i> 2017 [46] Efficacy as per prior pertuzumab regimens (Table 4) <ul style="list-style-type: none"> Fabi <i>et al.</i> 2017 [45] Brain metastases (Table 5) <ul style="list-style-type: none"> Fabi <i>et al.</i> 2018 [44] Fabi <i>et al.</i> 2017 [45] Safety (grade ≥ 3) (Table 7) <ul style="list-style-type: none"> Fabi <i>et al.</i> 2017 [45] Fabi <i>et al.</i> 2017 [46] Safety (Any grade) (Table S4) <ul style="list-style-type: none"> Fabi <i>et al.</i> 2017 [45] Fabi <i>et al.</i> 2017 [46]

Abbreviations: 1L: First line of treatment; LoT: Line of Treatment.

reported efficacy outcomes for T-DM1 utilized as second-line (2L) therapy in patients who had progressed on prior treatment with ≥ 1 taxane and trastuzumab or other anti-HER2 regimen (**Table 2**).

The single-arm phase 2 trials involved heavily pre-treated patients who previously received HER2-directed therapies; across the studies, the median number of prior lines of therapy (LoT) ranged between 3.0–8.5 in the metastatic setting [35–37,39]. The randomized two-arm phase 3 trials and an expanded access study evaluated patients that previously received HER2-directed therapies: trastuzumab plus taxane in EMILIA, DESTINY and ELAINA [25–32,40], and trastuzumab plus lapatinib in TH3RESA and T-PAS [38,43]. An additional phase 3b safety trial (KAMILLA) only included patients with prior anti-HER2 treatment [33,34].

The ORR with T-DM1 in phase 3 studies ranged between 29.3–50.4% [26,30,34,40] and between 25.0–38.4% in phase 2 studies [35–37,39,42]. In the T-PAS expanded access study involving patients with measurable disease, ORR was 25.6% [43]. In comparison, T-DXd treatment was associated with a higher ORR of 79.0% in patients pre-treated with a taxane and trastuzumab with consistent rates observed in subgroups (79.6% and 79.8% in de-novo and recurrent populations, respectively) [25,26].

Median progression-free survival (mPFS) observed in clinical trials of T-DM1 ranged between 4.3–9.6 months [26,32,34–37,39,40,43]. In the phase 3 trials, mPFS was 9.6 months (versus 6.4 months for lapatinib plus capecitabine; 9.3 months in the Asian subgroup) in EMILIA [30,32] and 6.8 months in KAMILLA [34], the latter being consistent with DESTINY and T-PAS (each 6.8 months; versus not reached for T-DXd in DESTINY) [43,80]. Further subgroup analysis of KAMILLA revealed that the Asian cohort had a lower mPFS (5.7 months) compared with the global cohort (6.8 months) [34]. The phase 2 trials reported a mPFS that ranged between 4.3–6.9 months [36,39].

Median overall survival (mOS) observed in the phase 3 trials [26,29,30,34,38,40], ranged between 22.7–34.3 months and was not reached in DESTINY-BREAST03 trial [26]. T-DM1 mOS was 34.3 months (versus 22.7 months for lapatinib plus capecitabine) in EMILIA [30], 22.7 months (versus 15.8 months for physician's choice) in TH3RESA [38], 27.2 months in KAMILLA [34], and was not reached (versus not reached for T-DXd) in DESTINY [26]. Only one phase 2 trial reported a mOS of 30.5 months in patients treated with T-DM1 [37].

Real-world studies

Thirty-six publications (34 real-world studies) reported data on T-DM1 therapy in patients who had progressed after ≥ 1 prior anti-HER2 regimen.

T-DM1 efficacy in pertuzumab pre-treated patients

The ORR ranged between 14.3–57.1% in six studies [46,48,54,56,66,78]. This appeared to be lower in pertuzumab-pretreated patients (14.3–40.2%) compared to pertuzumab-naïve patients (30.0–57.1%) [46,48,78]. A study by Fabi *et al.* (2020) also showed significantly lower ORR in pertuzumab pre-treated compared with naïve patients (33.3% vs. 57.1%; $p=0.03$) [46].

In patients who received T-DM1 as 2L therapy following 1L pertuzumab, mPFS ranged between 2.8–10.5 months (**Table 3**) [46,48,54,56,66,70–74,78], with one study suggested a potential

association between longer 1L treatment duration and better mPFS (5.4 versus 10.8 months for <12 versus ≥ 12 months of 1L therapy, respectively; $p=0.003$) [71]. Compared with pertuzumab-naïve patients, 2L T-DM1 was generally associated with significantly shorter mPFS in pertuzumab pre-treated patients (7.8–12.0 versus 2.8–7.0 months, respectively; $p<0.05$) [46,72,74,78]. Seven studies demonstrated considerable variability in mOS (12.0–45.0 months) [48,55,65,66,71,74,78]. A trend towards a shorter mOS in pertuzumab pre-treated compared to pertuzumab-naïve patients (12.0–24.0 versus 14.4–45.0 months, respectively) was a consistent finding [48,65,74,78], although only one study (PANHER) reported a significant difference (24.0 vs. 45.0 months, $p=0.002$) [74]. Only two studies reported that prior pertuzumab treatment did not significantly impact mPFS (8.7 vs 8.3 months [51] and 6.18 vs 5.98 months [61]; $p>0.05$) or mOS (18.5 vs 20.6 months, $p=0.86$) [51].

T-DM1 efficacy in early versus later lines of therapy

Ten studies described T-DM1 efficacy in patients with HER2-positive mBC in early vs. later lines of therapy [45,50,53,59,62,64,68–70,77].

Where reported, most studies showed a decline in ORR, mPFS, and mOS in more heavily pre-treated patients versus those receiving T-DM1 as 2L therapy (**Table 4**). Early T-DM1 treatment showed better ORR (2L: 20.0–44.4%) [45,50,64,77] compared with heavily treated patients (≥ 4 L: 17.1–20.3%) [50,68] which was also reflected in mPFS (2L: 7.7–12.0 months) compared with later lines (≥ 4 L: 2.7–8.0 months) [45,50,59,69]. A similar pattern was also reported in studies that compared 1–4L versus 5–8L (12.9 vs. 6.6 months) [68] or 1–3L versus 4–10L (9.21 vs. 7.29 months) [70]. Consistently, one study reported a mOS of 41 months (2L) versus 17 months (5L) [50]. One-year OS rates were reported in two studies; this was 80% (2L) compared with 39% (≥ 4 L) in one study [69], and 91% (1–4L) compared with 64% (5–8L) in another [68].

Seven other studies reported ORR (21.9–73.3%), mPFS (4.0–10.0 months) and mOS (17.3–not reached) with T-DM1 therapy in any LoT (**Table 4**) [49,52,57,60,63,67,79].

Efficacy with or without brain/central nervous system metastasis

HER2-positive disease may progress and metastasize to the brain/central nervous system (CNS), which may impact treatment efficacy. In fact, evidence from trials that included patients with HER2-positive mBC with and without brain metastasis (BM) suggest mPFS and mOS are longer in the latter patient subgroup (**Table 5**) [26,27,33]. In patients with BM/CNS metastasis, mPFS and mOS ranged from 3.0–6.9 months and 18.9–26.8 months, respectively [26,27,31,33,43], which increased to 7.1 months and 30.0 months, respectively, in patients without BM [27,33]. Considering other 2L therapeutic options, T-DM1 was associated with prolonged mOS compared with capecitabine–lapatinib (26.8 vs. 12.9 months) although mPFS was similar (5.9 vs. 5.7 months) [31], while T-DXd yielded a better 1-year PFS rate of 72.0% (vs. 20.9% for T-DM1) [27]. Additionally, among patients with BM treated with T-DM1 ($n=39$), mPFS was longer in those without prior therapy for BM (5.6 months, $n=19$) compared to those with prior therapy for BMs (radiotherapy alone, surgery alone or both) (2.8 months, $n=20$) [27].

Similarly, evidence from six real-world studies also indicate a better mPFS and mOS in response to T-DM1 in patients without BM, although patients with BM also benefited from T-DM1 (**Table 5**) [44,45,60,61,71,75,77]. In patients with and without BM/CNS

Table 2. T-DM1 efficacy in pivotal HER2-positive advance/metastatic breast cancer clinical trials.

Study (Primary / Secondary Publication)	Study details (Country, Study name, design)	Population; N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
A. DESTINY-Breast03 (three publications)						
Cortés <i>et al.</i> 2022 [80] (Primary)	Global DESTINY-Breast03 (NCT03529110)	N=524; prior taxane + trastuzumab T-DM1, n: 263	· T-DXd: 16.2 · T-DM1: 15.3	T-DM1 · De novo: 33.7 (24.7–43.6) · Recurrent: 34.6 (27.2–42.5)	T-DM1: 6.8 (5.6–8.2) T-DXd: NE (18.5–NE) HR: 0.28 (95% CI, 0.22–0.37)	NR
	Randomized, open-label, multi-centre, active-controlled, phase 3	prior anti-HER2 therapy ◦ Prior 1L: 197 ◦ Prior >2L: 63		T-DXd · De novo: 79.6 (69.9–87.2) · Recurrent: 79.8 (72.9–85.6)	TDM1 vs T-DXd · Prior 0 or 1L: 8.0 (5.7–9.7) vs 22.2 (16.8–NE); HR: 0.33 (95% CI, 0.24–0.45) · Prior ≥2L: 5.6 (4.2–7.1) vs NE (16.8–NE); HR: 0.28 (95% CI, 0.19–0.41); <i>p</i> <0.05	
		Patient subgroups ◦ De novo: 104 ◦ Recurrent: 159				
Hurvitz <i>et al.</i> 2023 [26] (Secondary)		T-DXd, n: 261 prior anti-HER2 therapy ◦ Prior 1L: 193 ◦ Prior >2L: 66	· T-DXd: 28.4 · T-DM1: 26.5	· T-DM1: 35.0 (29.2–41.1) · T-DXd: 79.0 (73.1–83.4)	· T-DM1: 6.8 (5.6–8.2) · T-DXd: 28.8 (22.4–37.9) · HR: 0.33 (95% CI, 0.26–0.43); <i>p</i> <0.0001	· T-DM1: Not reached (34.0–NE) · T-DXd: Not reached (40.5–NE) · HR: 0.64 (95% CI, 0.47–0.87); <i>p</i> =0.0037
		Patient subgroups ◦ De novo: 93 ◦ Recurrent: 168				
		Median age, years ◦ T-DM1: 54.2 ◦ T-DXd: 54.3				
		ECOG 0, n (%) ◦ T-DM1: 175 (66.5) ◦ T-DXd: 154 (59.0)				
		ECOG 1, n (%) ◦ T-DM1: 87 (33.1) ◦ T-DXd: 106 (40.6)				
Im <i>et al.</i> 2022 [28] (Secondary)	Asia	Asians, n: 309 ◦ T-DM1, n: 160 ◦ T-DXd, n: 149	NR	NR	Asians · T-DM1: 5.6 · T-DXd: Not reached · HR: 0.27 (95% CI, 0.20–0.38); <i>p</i> <0.05	NR

Study (Primary / Secondary Publication)	Study details (Country, Study name, design)	Population: N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
B. EMILIA (three publications)						
Verma <i>et al.</i> 2012 [32] (Primary)	Global EMILIA (NCT00829166) Randomized, open-label, multi-centre, phase 3	N=991; prior taxane + trastuzumab ◦ T-DM1, n: 495 ◦ Lapatinib plus capecitabine, n: 496	First interim analysis (for all parameter): 13 Second interim analysis (Only for OS): 19	◦ T-DM1: 43.6 (38.6–48.6) ◦ Lapatinib plus capecitabine: 30.8 (26.3–35.7)	◦ T-DM1: 9.6 ◦ Lapatinib plus capecitabine: 6.4 ◦ Stratified HR: 0.65 (95% CI, 0.55–0.77); $p < 0.001$	◦ T-DM1: 30.9 ◦ Lapatinib plus capecitabine: 25.1 ◦ Stratified HR: 0.68 (95% CI, 0.55–0.85); $p < 0.001$
Diéras <i>et al.</i> 2017 [29] (Secondary)		Median age, years ◦ T-DM1: 53 ◦ Lapatinib plus capecitabine: 53 ECOG 0, n (%) ◦ T-DM1: 299 (60) ◦ Lapatinib plus capecitabine: 312 (63) ECOG 1, n (%) ◦ T-DM1: 194 (39) ◦ Lapatinib plus capecitabine: 176 (35) ECOG NA, n (%) ◦ T-DM1: 2 (<1) ◦ Lapatinib plus capecitabine: 8 (2)	◦ T-DM1: 47.8 ◦ Lapatinib plus capecitabine: 41.9	NR	NR	◦ T-DM1: 29.9 (26.32–34.10) ◦ Lapatinib plus capecitabine: 25.9 (22.74–28.32) ◦ HR: 0.75 (95% CI, 0.64–0.88); $p < 0.05$
Im <i>et al.</i> 2021 [30] (Secondary)	Asia	N=158; Asians with prior taxane + trastuzumab ◦ T-DM1, n: 82 ◦ Lapatinib plus capecitabine, n: 76	◦ For ORR and PFS: 13 ◦ For OS: 19	◦ T-DM1: 44.4 (31.9–57.5) ◦ Lapatinib plus capecitabine: 38.7 (26.7–51.9)	◦ T-DM1: 9.3 ◦ Lapatinib plus capecitabine: 6.9 ◦ HR: 0.72 (95% CI: 0.48–1.06)	◦ T-DM1: 34.3 ◦ Lapatinib plus capecitabine: 22.7 ◦ HR: 0.43 (95% CI: 0.24–0.77); $p < 0.05$

Study (Primary / Secondary Publication)	Study details (Country, Study name, design)	Population: N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)	
C. Other trials							
Wang <i>et al.</i> 2023 [40] (Primary)	China ELAINA (NCT03084939) Randomized, open-label bridging, multi-centre, phase 3	N=200; prior taxane + trastuzumab · T-DM1, n: 151 · Lapatinib plus capecitabine, n: 49 Median age, years ◦ T-DM1: 51 ◦ Lapatinib plus capecitabine: 52 ECOG 0, n (%) ◦ T-DM1: 83 (55.0) ◦ Lapatinib plus capecitabine: 26 (53.1) ECOG 1, n (%) ◦ T-DM1: 68 (45.0) ◦ Lapatinib plus capecitabine: 23 (46.9)	Overall · T-DM1: 8.6 · Lapatinib plus capecitabine: 9.7 For OS · T-DM1: 27.6 · Lapatinib plus capecitabine: 34.0	· T-DM1: 50.4 (41.0–59.8) · Lapatinib plus capecitabine: 55.8 (39.9–70.9)	· T-DM1: 7.0 (6.0–9.8) · Lapatinib plus capecitabine: 6.8 (5.6–9.7) · Stratified HR: 0.85 (95% CI, 0.56–1.29)	· T-DM1: 33.2 (27.6–43.9) · Lapatinib plus capecitabine: 40.0 (23.6–NE) · HR: 1.08 (95% CI, 0.69–1.69)	
Wildiers <i>et al.</i> 2022 [42] (Primary)	Europe EORTC 75111-10114 ETF/BCG Randomized, open-label, multi-centre, investigator-initiated, phase 2	N=40; prior trastuzumab + pertuzumab without or with metronomic oral cyclophosphamide Median age, years ◦ TP: 76.2 ◦ TPM: 77.3 WHO PS 0, n (%) ◦ TP: 10 (25.6) ◦ TPM: 17 (41.5) WHO PS 1, n (%) ◦ TP: 17 (43.6) ◦ TPM: 17 (41.5) WHO PS 2, n (%) ◦ TP: 8 (20.5) ◦ TPM: 7 (17.1) WHO PS 3, n (%) ◦ TP: 4 (10.3) ◦ TPM: 0 (0.0)	33.7	25.0	NR	NR	NR

Study (Primary / Secondary Publication)	Study details (Country, Study name, design)	Population; N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Wuerstein <i>et al.</i> 2022 [34] (Primary)	Global and Asian KAMILLA (NCT0170257) Single-arm, multi-centre, phase 3b	N=2,183; prior anti-HER2 + CT <ul style="list-style-type: none"> · Cohort 1 (Global), n: 2,002 · Cohort 2 (Asia), n: 181 Median age, years <ul style="list-style-type: none"> ◦ Cohort 1: 55 ◦ Cohort 2: 51 ECOG PS 0, n (%) <ul style="list-style-type: none"> ◦ Cohort 1: 1110 (55.4) ◦ Cohort 2: 76 (42.0) ECOG PS 1, n (%) <ul style="list-style-type: none"> ◦ Cohort 1: 775 (38.7) ◦ Cohort 2: 101 (55.8) ECOG PS 2, n (%) <ul style="list-style-type: none"> ◦ Cohort 1: 115 (5.7) ◦ Cohort 2: 4 (2.2) ECOG PS missing, n (%) <ul style="list-style-type: none"> ◦ Cohort 1: 2 (0.1) ◦ Cohort 2: 0 (0.0) Total (by prior LoT) <ul style="list-style-type: none"> · 0-1, n: 656 · 2, n: 496 · 3, n: 386 · 4+, n: 550 · Missing, n: 95 	<ul style="list-style-type: none"> · Cohort 1: 20.6 · Cohort 2: 15.1 	<ul style="list-style-type: none"> · Cohort 1 (Among 1613 patients with measurable disease): 29.3 (27.1–31.6) · Cohort 2 (Among 169 patients with measurable disease): 29.6 (22.8–37.1) 	<ul style="list-style-type: none"> · Cohort 1: 6.8 (5.8–7.6) · Cohort 2: 5.7 (5.5–7.0) Total (by prior LoT) <ul style="list-style-type: none"> · 0-1: 8.2 (7.7–8.6) · 2: 6.2 (5.6–7.7) · 3: 6.0 (5.5–8.0) · 4+: 5.5 (5.3–5.7) · Missing: 8.6 (5.7–13.1) 	<ul style="list-style-type: none"> · Cohort 1: 27.2 (25.5–28.7) · Cohort 2: 29.5 (21.1–NE) Total (by prior LoT) <ul style="list-style-type: none"> · 0-1: 31.3 (28.5–34.5) · 2: 28.8 (24.9–31.2) · 3: 24.5 (21.2–27.9) · 4+: 22.0 (19.9–24.1) · Missing: NE (26.3–NE)

Study (Primary / Secondary Publication)	Study details (Country, Study name, design)	Population: N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Krop <i>et al.</i> 2017 [38] (Primary)	Global TH3RESA (NCT01419197) Randomized, open-label, multi-centre, phase 3	N=602; ≤2 prior HER2-directed therapy (trastuzumab and lapatinib and a taxane) · T-DM1, n: 404 · Physician's choice, n: 198 Median age, years ◦ T-DM1: 53 ◦ Physician's choice: 54 ECOG PS 0, n (%) ◦ T-DM1: 180 (45) ◦ Physician's choice: 82 (41) ECOG PS 1, n (%) ◦ T-DM1: 200 (50) ◦ Physician's choice: 101 (51) ECOG PS 2, n (%) ◦ T-DM1: 22 (5) ◦ Physician's choice: 15 (8)	30.5	NR	NR	· T-DM1: 22.7 (19.4–27.5) · Physician's choice: 15.8 (13.5–18.7) Stratified HR: 0.68 (95% CI, 0.54–0.85); p=0.0007
Kashiwaba <i>et al.</i> 2016 [37] (Primary)	Japan JO22997 Single-arm, multi-centre, phase 2	N=73; ≥1 prior CT + trastuzumab Median age, years: 58 n (%) ◦ ECOG PS 0: 61 (84) ◦ ECOG PS 1: 10 (14) ◦ ECOG PS 2: 2 (3)	· For ORR and PFS: 6.5 · For OS: 28.9	38.4 (28.8–48.6)	5.6 (4.6–8.2)	30.5 (25.2–not reached)

Study (Primary / Secondary Publication)	Study details (Country, Study name, design)	Population; N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Yardley et al. 2015 [43] (Primary)	USA T-PAS (TDM4884g/ NCT01120561) Single-arm, multi- centre, expanded access	N=215; ≤2 prior HER2- directed therapy (trastuzumab and lapatinib) Median age, years: 53 n (%) ◦ ECOG PS 0: 99 (46.3) ◦ ECOG PS 1: 91 (42.5) ◦ ECOG PS 2: 24 (11.2)	5.9	Among the 172 patients with measurable disease: 25.6 (19.2–32.8)	Of the 202 patients with available efficacy data: 6.8 (5.7–7.6)	NR
Gupta et al. 2013 [36] (Primary)	NR TDM4688g/ NCT00943670 Single-arm, multi- centre, phase 2	N=51; prior trastuzumab Single-agent T-DM1 with HER2-positive disease, n: 38 Median age, years: 53.5 n (%) ◦ ECOG PS 0: 28 (54.9) ◦ ECOG PS 1: 23 (45.1)	NR	· Single-agent T-DM1: 25.5 (15.2–38.5) · Single-agent T-DM1 with HER2-positive disease: 34.2 (20.1–51.4)	4.3 (4.0–6.7)	NR
Krop et al. 2012 [39] (Primary)	NR TDM437g Single-arm, phase 2	N=110; ≤2 prior HER2- directed therapy (trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine) Median age, years: 52.5 n (%) ◦ ECOG PS 0: 54 (49.1) ◦ ECOG PS 1: 53 (48.2) ◦ ECOG PS 2: 3 (2.7)	17.4	34.5 (26.1–43.9)	6.9 (4.2–8.4)	NR
Burriss et al. 2011 [35] (Primary)	USA TDM4258g Single-arm, phase 2	N=112; ≥1 prior HER2- targeted therapy Median age, years: 54.5 n (%) ◦ ECOG PS 0: 60 (53.6) ◦ ECOG PS 1: 43 (38.4) ◦ ECOG PS 2: 8 (7.1) ◦ ECOG PS 3: 1 (0.9)	≥12	25.9 (18.4–34.4)	4.6 (3.9–8.6)	NR

Abbreviations: CI: Confidence Interval; CT: Chemotherapy; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hazard Ratio; ITT: Intent-to-Treat; LoT: Line of Therapy; mOS: Median Overall Survival; mPFS: Median Progression-Free Survival; NE: Not Estimable; NR: Not Reported; ORR: Overall Response Rate; T-DM1: Trastuzumab Emtansine; T-DXd: Trastuzumab Deruxtecan; TKI: Tyrosine Kinase Inhibitor; TP: Trastuzumab; TPM: Trastuzumab; Metronomic Cyclophosphamide

Table 3. T-DM1 efficacy after first-line pertuzumab-containing regimen in real-world studies.

Study details (Country, study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
He <i>et al.</i> 2024 [61]	N=101	NR	NR	Prior pertuzumab	NR
China	Previous treatment, n (%)			· Yes: 6.18 (5.87–6.50)	
Multicentric, observational	· Trastuzumab: 101 (100.00)			· No: 5.98 (4.06–7.91); p=0.92	
March 2023–June 2023	· Paclitaxel: 101 (100.00)			Prior pyrotinib	
	· Pertuzumab: 35 (34.65)			· Yes: 6.18 (58.4–6.52)	
	· Pyrotinib: 19 (18.81)			· No: 4.24 (1.92–6.56); p=0.49	
	Median age, years: 51				
	n (%)				
	◦ ECOG PS 0–1: 101 (100)				
	Prior LoTs, n (%)				
	· Early, N=31				
	◦ Pertuzumab: 22 (70.97)				
	◦ Pyrotinib: 0				
	◦ Advanced, N=70				
	◦ Pertuzumab: 13 (18.57)				
	◦ Pyrotinib: 19 (27.14)				
Peters <i>et al.</i> 2023 [73]	N=85; 1L pertuzumab	NR	NR	6.5	NR
UK	Median age, years: 58				
Real-world analysis					
2016–2021					
Moinard-Butot <i>et al.</i> 2022 [71]	N=233; 1L taxane + pertuzumab + trastuzumab	20.8	NR	Overall: 7.1 (5.7–9.0)	· Overall: 36.7 (28.3–not reached)
France	Median age:			1L treatment duration:	· Without BM: 36.7 (28.3–not reached)
Retrospective study	◦ Cohort A (2L T-DM1): 52			· <12 months: 5.4 (4.1–7.1)	· With BM: 19.1 (10.9–not reached)
2008–2016	◦ Cohort B (2L T-DM1 and 3L/4L lapatinib plus capecitabine): 48			· ≥12 months: 10.8 (7.5–13.9); p=0.003	
Al Rabadi <i>et al.</i> 2021 [48]	N=33, 1L pertuzumab	17	· Pertuzumab-pretreated: 14.3 (3.0–36.3)	Pertuzumab-pretreated vs. naive: 9.5 (2.9–not reached) vs. 7.3; HR: 0.66 (95% CI: 0.30–1.47), p=0.310	Pertuzumab-pretreated vs. naive: Not reached vs. 14.4; HR: 0.56 (95% CI: 0.22–1.46), p=0.230
USA	Median age, years		· Pertuzumab-naïve: 30.0 (6.7–65.2)		
Retrospective study	◦ Pertuzumab-pretreated: 58				
2013–2018	◦ Pertuzumab-naïve: 52				

Study details (Country, Study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Daniels <i>et al.</i> 2021 [55] Australia Population-based retrospective study 2015–2019	N=309; 1L pertuzumab /trastuzumab Median age, years: 58	30.7	NR	NR	18.9 (IQR: 7.9–29.5)
Migeotte <i>et al.</i> 2021 [70] Belgium Multi-centre observational retrospective study 2009–2016	N=51; Prior pertuzumab Median age, years ◦ 2L: 52.4 ◦ 3L: 50 ◦ ≥4L: 52.9	NR	NR	Pts receiving T-DM1 with vs without prior taxane-trastuzumab-pertuzumab: 3.55 (2.27–11.38) vs 9.50 (6.15–12.26); p=0.144	NR
Pizzuti <i>et al.</i> 2021 [74] Italy PANHER – multi-centre, observational study with retrospective design 2000–2020	N=1,328; 1L pertuzumab / trastuzumab; non-pertuzumab regimens Median age, years: 52 ECOG PS, median (range): 1 (1-3)	52	NR	Overall: 8.0 1L pertuzumab: 7 (5.1–8.9) 1L trastuzumab or pertuzumab-naïve: 12.0 (5.8–18.2), p=0.01	1L pertuzumab: 24.0 (19.0–29.0) 1L pertuzumab naïve: 45.0 (36.0–54.0); p=0.002
Battisti <i>et al.</i> 2020 [51] UK Retrospective review 2014–2018	· N=128; 1L-2L+ ◦ 1L: 15 ◦ 2L+: 113 Median age, years: 55 n (%) ◦ ECOG PS 0: 35 (27.3) ◦ ECOG PS 1: 80 (62.5) ◦ ECOG PS 2: 10 (7.8) ◦ ECOG PS 3: 3 (2.4) · Prior pertuzumab, n ◦ Curative: 2 (1.6) ◦ Palliative: 37 (28.9) ◦ Total: 39 (30.5) · Prior trastuzumab, n ◦ Curative: 63 (49.2) ◦ Palliative: 113 (88.3) ◦ Total: 128 (100.0)	NR	64.1	Overall: 8.7 (7.0–10.1) · Prior curative pertuzumab ◦ No (n=124): 8.6 (7.0–10.1) ◦ Yes (n=2): 6.4 (6.4–not reached); p=0.658 · Prior palliative pertuzumab ◦ No (n=89): 8.3 (6.1–10.1) ◦ Yes (n=37): 8.7 (6.6–11.3); p=0.610 · Prior curative trastuzumab ◦ No (n=64): 9.2 (7.7–11.5) ◦ Yes (n=62): 7.4 (5.3–10.1); p=0.582 · Prior palliative trastuzumab ◦ No (n=14): 5.3 (1.3–15.8) ◦ Yes (n=112): 8.7 (7.5–10.1); p=0.138	Overall: 20.4 (17.0–22.1) · Prior curative pertuzumab ◦ No (n=124): 20.4 (16.6–22.1) ◦ Yes (n=2): 17.0 (17.0–NR); p=0.580 · Prior palliative pertuzumab ◦ No (n=89): 20.6 (17.5–22.9) ◦ Yes (n=37): 18.5 (13.2–37.4); p=0.859 · Prior curative trastuzumab ◦ No (n=64): 22.1 (20.2–35.4) ◦ Yes (n=62): 16.6 (13.7–20.4); p=0.025 · Prior palliative trastuzumab ◦ No (n=14): 17.0 (2.5–43.0) ◦ Yes (n=112): 21.1 (16.6–22.9); p=0.367

Study details (Country, Study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Conte <i>et al.</i> 2020 [54] Italy Retrospective/prospective observational multi-centre study 2000–2018	N=77; 1L taxane + pertuzumab / trastuzumab Median age, years: 50	7	27.1	6.3 (4.8–7.7)	Not reached
del Prete <i>et al.</i> 2020 [56] Italy Multi-centre, retrospective study	N=135; 1L taxane + pertuzumab / trastuzumab Median age, years: 56	10.3	20.7	10.5 (8.6–12.7)	NR
Martinez-Garcia <i>et al.</i> 2020 [66] Spain TDM1RM – retrospective observational study 2015–2020	N=52; 1L taxane + pertuzumab / trastuzumab Median age, years: 52 % ◦ ECOG PS 0: 15 ◦ ECOG PS 1: 61 ◦ ECOG PS 2: 23	33	42	8.4 (6.9–9.9)	23.6 (17.5–29.7)
Lupichuk <i>et al.</i> 2019 [65] Canada Retrospective study 2013–2016	N=104, 1L pertuzumab; pertuzumab-naïve Median age, years ◦ Adjuvant trastuzumab: 56 ◦ No prior Adjuvant trastuzumab: 57	29.7 (14.0–57.5)	NR	NR	Pertuzumab naïve vs. pretreated: 23.2 vs. 14.1; aHR: 0.60 (95% CI: 0.35–1.03), p=0.065
Noda-Narita <i>et al.</i> 2019 [72] Japan Retrospective study 2014–2017	N=42; 1L pertuzumab / trastuzumab or trastuzumab alone Median age, years ◦ Trastuzumab/Pertuzumab: 53 ◦ Trastuzumab: 60 ECOG 0, n (%) ◦ Trastuzumab/Pertuzumab: 13 (72) ◦ Trastuzumab: 13 (54) ECOG 1, n (%) ◦ Trastuzumab/Pertuzumab: 5 (28) ◦ Trastuzumab: 10 (42) ECOG 2, n (%) ◦ Trastuzumab/Pertuzumab: 0 (0) ◦ Trastuzumab: 1 (4)	4.8	NR	· Pertuzumab/trastuzumab: 2.8 (1.7–4.8) · Trastuzumab alone: 7.8 (5.5–15.9); p=0.003	NR

Study details (Country, Study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Fabi <i>et al.</i> 2017 [46] Italy Multi-centre field-practice retrospective study 2012–2016	N=107; 1L taxane + pertuzumab/trastuzumab Median age, years ◦ Trastuzumab/Pertuzumab: 43 ◦ Trastuzumab: 51	NR	1L pertuzumab: 33.3 1L trastuzumab: 57.1; $p=0.03$	1L pertuzumab vs. naive: 5.0 (4.3–5.7) vs. 11.0 (7.8–14.2); HR: 2.02 (95% CI: 1.14–3.58), $p=0.01$	NR
Vici <i>et al.</i> 2017 [78] Italy Retrospective observational study 2013–2016	N=245; 1L pertuzumab-trastuzumab-taxane Median age, years: 56 % ◦ ECOG PS 0: 140 (56) ◦ ECOG PS 1: 91 (36.4) ◦ ECOG PS 2: 19 (7.6)	15	• T-DM1 LoT2: 44.5 (38.3–50.7) • 1L pertuzumab vs naive: 40.2 (26.4–54.4) vs. 44.3 (37.5–51.2); $p=0.75$	• T-DM1 LoT2: 6.0 (5.0–7.0) • 1L pertuzumab vs naive: 3.0 (2.0–4.0) vs. 8.0 (4.0–12.0); $p=0.0001$	• T-DM1 LoT2: 26.0 (15.6–36.3) • 1L pertuzumab vs naive: 12.0 (9.0–15.0) vs. 26.0 (16.0–36.0); $p=0.06$

Abbreviations: 1L: First-line; aHR: adjusted Hazard Ratio; BM: Bone Metastasis; CI: Confidence Interval; HER2: Human Epidermal Growth Factor Receptor 2; IQR: Interquartile Range; Lot: Line of Therapy; mOS: Median Overall Survival; mPFS: Median Progression-Free Survival; NR: Not Reported; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression Free Survival; pts: Patients; T-DM1: Trastuzumab Emtansine; UK: United Kingdom.

Table 4. T-DM1 efficacy in different lines and combined line (2L+) of therapy in real-world studies.

Study details (Country, Study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI), unless stated otherwise	mOS, months (95% CI), unless stated otherwise
A. Different line of therapy (LoT)					
Bahceci <i>et al.</i> 2021 [50] Turkey Retrospective multi-centre study	N=414; prior trastuzumab / trastuzumab + pertuzumab / trastuzumab + lapatinib /CT Median age, years: 47 T-DM1 lines, n · 1L: 20 · 2L: 156 · 3L: 111 · 4L: 78 · ≥5L: 49	67.3±42.6 Post-T-DM1: 13.7±7.9	Last status at response · 2L: 34.1 · 3L: 15.8 · 4L: 20.2 · ≥5L: 17.0 · Total: 25.2	· 2L: 12.0 · 3L: 8.0 · 4L: 8.0 · ≥5: 8.0	· 2L: 41.0 · 3L: 46.0 · 4L: 23.0 · ≥5: 17.0
Migeotte <i>et al.</i> 2021 [70] Belgium Retrospective multi-centre study 2009–2016	N=51; Prior T-DM1 treated T-DM1 lines, n · 1L: 4 · 2L: 20 · 3L: 1 · 4L+: 6 Median age, years ◦ 2L: 52.4 ◦ 3L: 50 ◦ ≥4L: 52.9	NR	NR	Overall: 9.01 (4.87–11.41) · Pts with T-DM1 in LoT 1–3 vs 4–10: 9.21 (4.87–12.14) vs 7.29 (2.73–12.30) · Pts with T-DM1 in LoT 1–2 vs 3–10: 9.41 (3.59–18.88) vs 6.41 (2.80–11.74) · Pts with T-DM1 with vs without prior capecitabine and lapatinib: 5.56 (2.70–28.96) vs 9.17 (5.42–12.10)	NR
Tataroglu Ozyukseler <i>et al.</i> 2021 [77] Turkey Single-centre retrospective, observational study 2016–2019	N=78; 1L trastuzumab-based regimens Median age, years: 52 % ◦ ECOG PS 0: 32 (41.0) ◦ ECOG PS 1: 38 (48.7) ◦ ECOG PS 2: 8 (10.3)	12.9 (7.4–19.8)	Objective response rate: 25.6	7.8 (IQR, 3.7–19.5)	21.1 (IQR, 8.7–30.9)

Study details (Country, Study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI), unless stated otherwise	mOS, months (95% CI), unless stated otherwise
Michel <i>et al.</i> 2020 [69] Germany PRAEGNANT – Ongoing prospective study	N=76; 1L: pertuzumab Median age, years: 54.6 % ◦ ECOG PS 0: 37 (55.2) ◦ ECOG PS 1: 25 (37.3) ◦ ECOG PS 2: 3 (4.5) ◦ ECOG PS 3: 2 (3.0) T-DM1 lines, n · 2L: 39 · 3L: 25 · ≥4L: 12	3.1	NR	Overall: 3.5 (2.8–7.8) · 2L: 7.7 (2.8–11.0) · 3L: 3.4 (2.3–not reached) · ≥4L: 2.7 (1.2–not reached)	Overall: 22.5 (16.9–not reached) · 3L: 18.3 (12.6–not reached) · ≥4L: 9.1 (4.7–not reached)
Fabi <i>et al.</i> 2017 [45] Italy FIELD-PRACTICE – multi-centre study 2012–2016	N=282; Prior CT / hormonal therapies / anti-HER2 therapy Median age, years: 51 T-DM1 lines, n · 1L: 6 · 2L: 117 · 3L: 64 · >3L: 95	Overall: 10 For OS: 8	· Total: 102 (36.2) ◦ 2L: 52 (44.4) ◦ 3L: 26 (40.6) ◦ >3L: 23 (24.2)	· 2L: 9.0 (6.4–11.6) · 3L: 12.0 (9.7–16.3) · >3L: 5.0 (4.0–5.9)	Not reached
Michel <i>et al.</i> 2015 [68] Germany Retrospective chart review 2010–2014	N=23; Prior trastuzumab / lapatinib / pertuzumab Median age, years: 54.6 % ◦ ECOG PS 0: 37 (55.2) ◦ ECOG PS 1: 25 (37.3) ◦ ECOG PS 2: 3 (4.5) ◦ ECOG PS 3: 2 (3.0) Prior therapies, n (%) · Trastuzumab: 21 (91.3) · Lapatinib: 14 (60.9) · Pertuzumab: 8 (34.8) T-DM1 lines, n (%): · 1L: 4 (17) · 2L: 3 (13) · 3L: 6 (26) · ≥4L: 10 (43.5)	285 (21–1016) days	All: 26.0 · ≥2L: 21.0 · ≥4L: 20.0	Overall: 8.4 (5.7–12.9) · 1L-4L: 12.9 (5.7–31.5) · 5-8L: 6.6 (0.7–7.4)	NR

Study details (Country, Study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI), unless stated otherwise	mOS, months (95% CI), unless stated otherwise
B. Second and further LoT (2L+)					
Baek <i>et al.</i> 2024 [49] Korea	· N=824; Prior trastuzumab and taxane Median age, years: 58 n (%) · ECOG PS 0-1: 695 (84) · ECOG PS 2: 74 (9) · Unknown: 54 (7) Prior therapy, % · Pertuzumab: 21.7	16.8 with advanced line of TD-M1 (2L+)	35	6.6 (6.1–7.3) aHR for prior pertuzumab use: 1.204 (95% CI: 0.936–1.55), p=0.149	Not reached aHR for prior pertuzumab use: 1.623 (95% CI: 1.022–2.578), p=0.040
Bian <i>et al.</i> 2023 [52] China	· N=213; Prior TKI · T-DM1, n: 71 · ADC, n: 73 · HP (combination CT), n: 69 Median age, years: 47	NR	· T-DM1: 22.5 · ADC: 54.8 · HP: 27.5	· T-DM1: 4.0 · ADC: 7.0 · HP: 6.6	NR
Retrospective study 2013–2022					
Blotta <i>et al.</i> 2023 [53] Brazil	N=73, Pts with T-DM1 (1L, 2L, 3L/3L+) Median age, years: 57	NR	82.6	12.7	53.9
Retrospective, medical records 2013–2023					
Hsieh <i>et al.</i> 2023 [62] Taiwan	N=32 (any LoT) Prior pertuzumab + trastuzumab, n: 12 Median age, years: 60	NR	NR	NR	· Dual-blockade: 68.2 · Trastuzumab only: 73.2
Retrospective cohort study 2013–2022					

Study details (Country, Study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI), unless stated otherwise	mOS, months (95% CI), unless stated otherwise
Ji et al. 2023 [63]	N=144; Prior TKI, trastuzumab · Anti-HER2 ADC, n: 73 · T-DM1, n: 71	NR	Objective response rate: · Anti-HER2 ADC: 54.8 · T-DM1: 22.5	For pts who reached endpoint- · Anti-HER2 ADC: 7.0 (6.1-7.9) · T-DM1: 4.0 (3.4-4.6); HR: 0.43 (95% CI: 0.29-0.65)	NR
China	Subgroup analysis				
Real-world retrospectively study 2013-2022	· Anti-HER2 ADC, n: 43 · T-Dxd, n: 30 · T-DM1, n: 71			For all pts- · Anti-HER2 ADC: 7.0 (6.2-9.8) · T-Dxd: 13.0 (8.1-12.5) · T-DM1: 4.0 (4.4-6.8)	
	Median age, years · Anti-HER2 ADCs: 48 · T-DM1: 42				
Martins et al. 2023 [67]	N=32; Prior Pertuzumab/trastuzumab plus taxane	NR	Objective response rate: 21.9 (9.3-40.0)	4.4 (1.54-7.26)	17.3 (10.6-24.54)
Portugal	Median age, years: 53				
Retrospective study 2017-2023					
Drago et al. 2022 [57]	· T-DM1 (LoT unknown), N=164 · Statins with T-DM1, n: 21	NR	NR	· T-DM1: 5.5 · Statins with T-DM1: 14 · No statins: 5.4	NR
USA	Median age, years · With Statin: 58 · No Statin: 50				
Retrospective study					
Gogia et al. 2022 [59]	N=80; 1L anti HER2 therapy or relapse within 6 months of adjuvant trastuzumab	18	80	10	27
India	Median age, years: 49				
Retrospective study 2015-2021	ECOG PS 0-1: 80% Prior therapy, % · Trastuzumab monotherapy: 100 · Pertuzumab + trastuzumab: 22.5				
	T-DM1 line, n 2L: 80 (100%)				

Study details (Country, Study name, design, data source and study duration)	Population, N; eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI), unless stated otherwise	mOS, months (95% CI), unless stated otherwise
Li <i>et al.</i> 2021 [64] China Real-world study 2013–2019	N=105; prior trastuzumab and lapatinib (any LoT) · Pyrotinib, n: 55 · T-DM1, n: 50 Median age, years · Pyrotinib, n: 47 · T-DM1, n: 46	NR	Objective response rate, n (%) · Pyrotinib: 9 (16.3) · T-DM1: 10 (20.0)	Overall · Pyrotinib: 6.0 (4.7–7.3) · T-DM1: 4.2 (3.6–4.8), p=0.044 · Patients who have benefited from · prior therapy · Lapatinib ◦ Pyrotinib: 8.1 (4.8–11.4) ◦ T-DM1: 4.4 (3.8–5.0), p=0.013 · Trastuzumab ◦ Pyrotinib: 5.1 (3.7–6.5) ◦ T-DM1: 4.4 (3.8–5.0), p=0.251 · Lapatinib and Trastuzumab ◦ Pyrotinib: 6.9 (4.3–9.5) ◦ T-DM1: 4.4 (3.8–5.0), p=0.053	NR
Hardy-Werbin <i>et al.</i> 2019 [60] Spain Retrospective 2012–2016	N=15; Prior trastuzumab Median age, years: 48 N (%) · ECOG PS 0: 3 (20) · ECOG PS 1: 11 (73.3) · ECOG PS 2: 1 (6.7)	NR	Objective response rate: 73.3	10 (3.47–16.52)	34 (16.96–51.04)
Yeo <i>et al.</i> 2018 [79] Hong Kong Retrospective study 2013–2015	N=37; Prior anti-HER2 (trastuzumab, lapatinib or pertuzumab), CT or endocrine therapy Median age, years: 52 N (%) · ECOG PS 0: 4 (10.8) · ECOG PS 1: 29 (78.4) · ECOG PS 2: 4 (10.8)	· Overall: 15.6 · For PFS: 5.0	29.7	6.0 (3.3–9.8)	Not reached

Abbreviations: 1L: First-line; 2L: Second-line; 3L: Third-line; 4L: Fourth line; 5L: Fifth line; ADC: Antibody-Drug Conjugate; aHR: Adjusted Hazard Ratio; CI: Confidence Interval; CT: Chemotherapy; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hazard Ratio; IQR: Interquartile Range; LoT: Line of Therapy; mBC: Metastatic Breast Cancer; mOS: Median Overall Survival; mPFS: Median Progression-Free Survival; NR: Not Reported; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression Free Survival; pts: Patients; T-DM1: Trastuzumab Emtansine; T-Dxd: Trastuzumab Deruxtecan; TKI: Tyrosine Kinase Inhibitor; UK: United Kingdom; US: United States

Table 5. T-DM1 efficacy outcomes of HER2-positive mBC patients with or without brain metastasis (BM)/CNS metastasis.

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N (%); eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
A. Clinical studies						
I. DESTINY-Breast03 (two publications)						
Hurvitz <i>et al.</i> 2024 [27] (Secondary)	Global DESTINY-Breast03 (NCT03529110) Randomized, open-label, multi-centre, phase 3	N=524; prior anti-HER2 (trastuzumab and pertuzumab) <ul style="list-style-type: none"> • T-DXd, n: 261 ◦ Patients with BM, n: 43 (16.5) ◦ Patients without BM, n: 218 (83.5) • T-DM1, n: 263 ◦ Patients with BM, n: 39 (14.8) ◦ Patients without BM, n: 224 (85.2) Median age, years <ul style="list-style-type: none"> ◦ T-DM1: 54.2 ◦ T-DXd: 54.3 ECOG 0, n (%) <ul style="list-style-type: none"> ◦ T-DM1: 175 (66.5) ◦ T-DXd: 154 (59.0) ECOG 1, n (%) <ul style="list-style-type: none"> ◦ T-DM1: 87 (33.1) ◦ T-DXd: 106 (40.6) 	NR	T-DXd <ul style="list-style-type: none"> • Overall: 79.7 (74.3–84.4) • Patients with BMs: 67.4 (51.5–80.9) • Patients without BMs: 82.1 (76.4–87.0) T-DM1 <ul style="list-style-type: none"> • Overall: 34.2 (28.5–40.3) • Patients with BMs: 20.5 (9.3–36.5) • Patients without BMs: 36.6 (30.3–43.3) 	Patients with BM at baseline <ul style="list-style-type: none"> • T-DXd: 15.0 (12.5–22.2) • T-DM1: 3.0 (2.8–5.8); HR 0.25, (95% CI 0.13–0.45) Patients without BM at baseline <ul style="list-style-type: none"> • T-DXd: NR (22.4–NE) • T-DM1: 7.1 (5.6–9.7); HR 0.30 (95% CI 0.22–0.40) Patients with prior BM therapy <ul style="list-style-type: none"> • T-DXd: 14.1 (8.5–18.5) • T-DM1: 2.8 (2.6–NE); HR 0.35 (95% CI 0.15–0.79) Patients without prior BM therapy <ul style="list-style-type: none"> • T-DXd: 16.8 (12.4–NE) • T-DM1: 5.6 (2.8–5.8); HR 0.16 (95% CI 0.06–0.44) 	Patients with BM <ul style="list-style-type: none"> • T-DXd: NR (23.8–NE) • T-DM1: 25.1 (12.6–NE) HR: 0.54 (95% CI, 0.29–1.03) Patients without BM <ul style="list-style-type: none"> • T-DXd: NR (40.5–NE) • T-DM1: NR (37.7–NE) HR: 0.66 (95% CI, 0.47–0.94)

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N (%); eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
II. Other trials						
Fabi <i>et al.</i> 2017 [45] (Primary)	Italy FIELD-PRACTICE – multi-centre study	N=303; prior brain loco-regional treatment · BM group, 87 (28.7) · Non-BM group: 216 (71.2)	16 (1–55)	BM: 35.1 Non-BM: 38.3	Overall population · BM: 7.0 (5.4–8.6) · Non-BM: 8.0 (5.7–10.3)	Overall population · BM: 14 (12.2–15.8) · Non-BM: 32 (24.4–39.6)
Fabi <i>et al.</i> 2018 [44] (Secondary)	2012–2016 Median age, years: 51				2 LoT · BM: 5.0 (3.1–6.9) · Non-BM: 11 (7.1–14.9)	2 LoT · BM: 13 (9.1–16.9) · Non-BM: 31 (21.1–40.8)
					3 LoT · BM: 12.0 (4.9–19.8) · Non-BM: 13 (8.0–18.0)	3 LoT · BM: 14 (5.6–22.4) · Non-BM: 35 (32.2–37.8)
					4 LoT · BM: 6.0 (2.8–9.2) · Non-BM: 5.0 (4.1–5.9)	
Montemurro <i>et al.</i> 2020 [33] (Secondary)	Global KAMILLA (NCT01702571) Single-arm, ongoing, phase 3b	N=2002; prior taxane, Trastuzumab, pertuzumab, Lapatinib, Endocrine therapy, Anthracyclines · Patients with BM at baseline, n: 398 (19.8) · Patients without BM at baseline, n: 1604 (80.1)	20.6	Patients with measurable BM at baseline (n=126) BOR: 21.4 (14.6–29.6)	Patients with BM at baseline: 5.5 (5.3–5.6) Patients without BM at baseline: 7.7 (6.8–8.1)	Patients with BM at baseline: 18.9 (17.1–21.3) Patients without BM at baseline: 30.0 (27.6–31.2)
	Median age, years · Patients with BM at baseline: 52 · Patients without BM at baseline: 55					
	ECOG PS 0 · Patients with BM at baseline: 192 (48.2) · Patients without BM at baseline: 918 (57.2)					
	ECOG PS 1 · Patients with BM at baseline: 174 (43.7) · Patients without BM at baseline: 601 (37.5)					
	ECOG PS 2 · Patients with BM at baseline: 32 (8.0) · Patients without BM at baseline: 83 (5.2)					

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N (%); eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Krop et al. 2015 [31] (Secondary)	Global EMILIA (NCT00829166) Randomized, open-label, multi-centre, phase 3	N=991; prior taxane + trastuzumab stable CNS metastasis at baseline · T-DM1, n: 45 (4.5) · Lapatinib plus capecitabine, n: 50 (5.0) Median age, years · T-DM1: 51 · Lapatinib plus capecitabine: 53 n (%) ECOG PS 0 · T-DM1: 22 (48.9) · Lapatinib plus capecitabine: 24 (49.0) ECOG PS 1 · T-DM1: 23 (51.1) · Lapatinib plus capecitabine: 25 (51.0)	· For ITT pop · T-DM1: 19.1 · Lapatinib plus pectabine: 18.6	NR	· T-DM1: 5.9 · Lapatinib plus capecitabine: 5.7 Stratified HR: 1.000 (95% CI, 0.542–1.844); p=0.9998	· T-DM1: 26.8 · Lapatinib plus capecitabine: 12.9 Stratified HR=0.696 (95% CI, 0.328–1.476); p=0.3378
Yardley et al. 2015 [43] (Primary)	USA T-PAS (TDM4884g / NCT01120561) Single-arm, multi-centre, expanded access	N=215; ≤2 prior HER2-directed therapy Patients with BM, n: 26 (9.4) Median age, years: 53 n (%) ◦ ECOG PS 0: 99 (46.3) ◦ ECOG PS 1: 91 (42.5) ◦ ECOG PS 2: 24 (11.2)	5.9	Measurable, N=22 27.3 (10.7–50.2)	6.9 (2.7–12.3)	NR
B. Real-world studies						
He et al. 2024 [61] (Primary)	China Multicentric, observational March 2023–June 2023	N=101; prior trastuzumab and taxane · BM: 10 (26.3) · Non-BM: 28 (73.7) Median age, years: 51 n (%) ◦ ECOG PS 0-1: 101 (100)	7	NR	BM: 6.1 (5.9–6.3) Non-BM: 4	NR

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N (%); eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Sangler <i>et al.</i> 2023 [75] (Primary)	USA Retrospective, observational study Jan 1, 2011–Dec 31, 2020	N=214; no prior T-DM1 or LC treatment BM cohort treated with · T-DM1: 161 (75.2) · LC: 53 (24.8) Before weighting Median age, years · T-DM1: 56 · LC: 54 ECOG PS 0 · T-DM1: 32 (19.9) · LC: 13 (24.5) ECOG PS 1 · T-DM1: 60 (37.3) · LC: 16 (30.2) ECOG PS ≥2 · T-DM1: 30 (18.6) · LC: 9 (17.0) ECOG PS missing · T-DM1: 39 (24.2) · LC: 15 (28.3) After weighting Median age, years · T-DM1: 56 · LC: 53.7 ECOG PS 0 · T-DM1: 32.4 (20.4) · LC: 8.1 (15.0) ECOG PS 1 · T-DM1: 55.5 (35.0) · LC: 21.6 (40.0) ECOG PS ≥2 · T-DM1: 30.1 (18.9) · LC: 9.5 (17.6) ECOG PS missing · T-DM1: 40.7 (25.6) · LC: 14.8 (27.5)	Prior to weighting: 30.7 After weighting: 28.8	NR	Prior to weighting · T-DM1: 6.2 (4.7–8.0) · LC: 3.9 (3.2–5.1) HR: 0.57 (95% CI 0.42–0.78); $p < 0.001$ After weighting · T-DM1: 6.0 (4.6–7.2) · LC: 4.0 (2.8–5.1) HR: 0.50 (95% CI 0.36–0.69); $p < 0.001$	Prior to weighting · T-DM1: 18.3 (16.5–23.7) · LC: 10.7 (8.7–16.6) · HR: 0.69 (95% CI 0.46–1.03), $p = 0.046$ After weighting · T-DM1: 17.7 (16.0–23.7) · LC: 9.6 (7.9–14.5) · HR: 0.55 (95% CI 0.34–0.89); $p = 0.013$

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N (%); eligibility criteria	Median follow-up (months)	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)
Moinard-Butot <i>et al.</i> 2022 [71] (Primary)	France Retrospective, 18 French Comprehensive Cancer Centre's 2008–2016	Cohort A treated with T-DM1 N=233; taxane-based CT and dual HER2-blockage by trastuzumab + pertuzumab · BM: 18 (7.7) · Non-BM: 215 (92.3) Median age: ◦ Cohort A (2L T-DM1): 52 ◦ Cohort B (2L T-DM1 and 3L/4L lapatinib plus capecitabine): 48	20.8 (0–61)	NR	NR	Cohort A · BM: 19.1 (10.9–NA) · Non-BM: 36.7 (28.3–NA)
Tataroglu Ozyukseler <i>et al.</i> 2021 [77] (Primary)	Turkey Single-centre retrospective, observational study 2016–2019	N=78; ≥1 trastuzumab-based regimens · BM: 36 (46.2) · Non-BM: 42 (53.8) Median age, years: 52 % ◦ ECOG PS 0: 32 (41.0) ◦ ECOG PS 1: 38 (48.7) ◦ ECOG PS 2: 8 (10.3)	12.9 (7.4–19.8)	NR	· BM: 8.5 (4.0–not reached) · Non-BM: 6.2 (3.6–19.5)	· BM: 17.5 (9.6–NR) · Non-BM: 29.5 (8.3–30.9)
Hardy-Werbin <i>et al.</i> 2019 [60] (Primary)	Spain Retrospective 2012–2016	N=15; prior trastuzumab and taxane · BM: 5 (33.3) · Non-BM: 10 (66.7) Median age, years: 48 n (%) · ECOG PS 0: 3 (20) · ECOG PS 1: 11 (73.3) · ECOG PS 2: 1 (6.7)	NR	80.0	BM: 6.0 (3.85–8.14) Non-BM: 13 (8.6–17.93)	Not reached

Abbreviations: BM: Brain Metastasis; BOR: Best Overall Response; CI: Confidence Interval; CNS: Central Nervous System; CT: Chemotherapy; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hazard Ratio; ITT: Intent-to-Treat; LC: Lapatinib plus Capecitabine; LoT: Line of Therapy; mOS: Median Overall Survival; mPFS: Median Progression-Free Survival; NA: Not Applicable; NE: Not Evaluable; NR: Not Reported; ORR: Overall Response Rate; PFS: Progression Free Survival; T-DM1: Trastuzumab Deruxtecan; US: United States.

metastasis, mPFS ranged from 6–7 months and 8–13 months, respectively [44,45,60]; and mOS was 14–not reached and 32 months, respectively [44,60].

Safety

Clinical trials

The pivotal phase 3 trials (DESTINY-Breast03, ELAINA, KAMILLA, EMILIA and TH3RESA), phase 2 studies, and the expanded-access study demonstrated a consistent T-DM1 safety profile in terms of types of grades 3 or worse AEs (**Table 6**). Thrombocytopenia emerged as one of the most common grade ≥ 3 AEs, occurring in 2.3%–10.2% of patients in most of the included trials [33,34,36,38,39,42,43]. Three trials reported higher grade ≥ 3 AE rates (14.0–29.7%) [26,29,41], while a notably higher (40.4%) incidence of thrombocytopenia was observed in the ELAINA trial [40].

Liver toxicity/dysfunction was reported in 5.0–11.2% of patients in four studies [26,36,40,41], although lower incidences ($\leq 5\%$) were observed in other studies [29,33,38,39,42,43]. Anemia in 2.7% to 7.0% of patients [26,29,33,35,38,43], grade 3 or worse anorexia (5%) [42], hypokalemia (8.9%) [35] and lymphopenia (15%) [42] were also reported. The incidence of other grade 3/4 AEs including neutropenia, fatigue, liver toxicity/dysfunction, vomiting, diarrhea, dyspnea, epistaxis, asthenia, hyperglycemia, pneumonia, headache, cellulitis and cardiac toxicity was consistently below $<5\%$ [26,29,33–36,38,39,42,43]. Other grade AEs reported among clinical trials are presented as supplemental **Table S3**.

AEs most commonly led to dose reductions (≈ 5 –30% in most studies; up to $\sim 60\%$ in a large phase IIIB safety cohort) while permanent treatment discontinuation (≈ 2 –15% in most studies, and up to 25% in a small pertuzumab+T-DM1 cohort) and protocol-defined dose delays/interruptions were also reported [77–82]. In the updated DESTINY-Breast03 trial, treatment modifications occurred more often with T-DXd than with T-DM1, including drug-related discontinuation (20% vs 7%), dose reduction (25% vs 15%), and interruption (42% vs 17%), with pneumonitis/interstitial lung disease (ILD) among the most common causes of discontinuation on T-DXd [75]. In the DESTINY-Breast03 brain metastases subgroup (data cut-off 21 May 2021), overall treatment discontinuation was 48.6% with T-DXd and 82.0% with T-DM1 [76].

Real-world studies

Consistent with trial data, several real-world studies identified thrombocytopenia, liver toxicity/dysfunction, neutropenia, anemia, fatigue, and nausea as the most frequently reported grade 3 or worse AEs (**Table 7**).

Almost half of the included real-world publications reported incidences of grade 3 or worse thrombocytopenia [45,46,49–52,59,61,63,64,66,68,77–79], with considerable variation ranging between 1.2–29.0%. Grade 3/4 neutropenia and anemia were less frequent compared to thrombocytopenia; about 25% of the included real-world studies highlighted low immune cells/infection and low red blood cell counts as grade 3/4 AEs [45,49–51,56,59,61,63,64,66,77,79]. Of note, the frequency of neutropenia across studies ranged between 0.7–6.5% [45,49–51,56,61,63,64,66] and between 1.2–6.2% for anemia [49–51,59,61,63,66,77,79].

Four studies [50,61,63,77] reported leukopenia (0.4–6.5%) and one study [68] reported grade 3/4 infection (4.3%).

Grade 3/4 liver toxicity or dysfunction was the most frequently reported grade ≥ 3 non-hematological toxicity, reported in one third of studies [45,46,49–51,59,63,64,67,68,77–79]. Grade 3/4 elevations in liver enzymes including transaminases, aminotransferase, and gamma-glutamyl transferase along with bilirubin, alanine, and aspartate were also described, with incidence ranging between 0.4–12.5% [45,46,49,50,59,63,64,68,77–79]. Notably, one study reported that 19.5% of patients experienced liver toxicity [51]. Other non-hematological grade 3 or worse AEs included fatigue and nausea. The frequency of fatigue was less frequent (1.3–2.8%) in six studies [49–51,63,77,78], was 8.0%–12.5% in two other studies [59,64]; and one study reported fatigue in 21.7% of patients [68]. The incidence of nausea was observed to be between 0.6–6% as described in five studies [49,51,64,77,78]. Other less common grade 3/4 AEs ($<5\%$) included diarrhea [49–51,77], alopecia [45,46], peripheral neuropathy [51,59], hypokalemia [50,79], asthenia [45,66], and mucositis [51]. Additionally, three studies linked minimal cardiotoxicity with T-DM1 treatment [47,50,67]. Other grade AEs reported in real-world studies are presented as supplemental **Table S4**.

Three studies reported T-DM1 discontinuation, primarily due to disease progression or AEs. Dzimitrowicz *et al.* (2016) [58] reported disease progression as predominant cause of treatment discontinuation (84.3%, 59/70 of cases), while 10% discontinued due to toxicity or poor tolerance. Similarly, Silva *et al.* (2023) [76] reported T-DM1 discontinuation majorly due to disease progression (90%, 36/40), specifically progression in bone, brain, and liver, and the remaining due to toxic side effects (10%, 4/40). Blotta *et al.* (2023) [53] reported T-DM1 discontinuation majorly due to AEs that included peripheral neuropathy (40%), pneumonitis (20%), and hepatic pseudocirrhosis (20%) (data not shown in the table).

Corroboration of clinical trial findings with real-world outcomes

Across pivotal trials and heterogeneous RWE cohorts, T-DM1 demonstrated concordant effectiveness and tolerability in HER2-positive mBC, supporting the corroboration of findings from clinical trials and routine clinical practice. ORR were comparable, with trials reporting ORRs of ~ 29 –50% (29.3–29.6% in KAMILLA [34]; 34–35% in DESTINY-Breast03 [26,80]; 43.6–47.8% in EMILIA [29,32]; 50.4% in ELAINA [40]). In routine clinical practice, ORRs ranged from ~ 20 –64%, including 20.7–44.5% in multiple post-pertuzumab/second-line datasets [51,54,56,66,78,79]. Similarly, mPFS ranged 6.8–9.6 months in key trials (6.8 months in Breast03 [26,80] and KAMILLA [34]; 7.0 months in ELAINA [40]; 9.6/9.3 months in EMILIA [30,32]) which was consistent with RWE estimates of ~ 6.0 –10.5 months in similar settings [51,54,56,66,74,78,79]. The mOS in trials was ~ 30 months (29.9–34.3 months in EMILIA [29,30,32]; 27.2–29.5 months in KAMILLA [34]; 33.2 months in ELAINA [40]) while RWE cohorts reported a broad but overlapping range (~ 17 months to not reached), with several studies reported outcomes within the ~ 23 –36+ month range [51,54,55,59,60,66,67,71,78,79]. For subgroups, brain/CNS metastases were consistently prognostic (shorter outcomes than non-CNS cohorts) while T-DM1 demonstrated measurable activity in the clinical trials and RWE [27,31,33,44,71,75,77].

Table 6. T-DM1 safety (grade ≥ 3) in pivotal HER2-positive advance/metastatic breast cancer in clinical trials.

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥ 3 AEs, n (%)
A. Breast-03 Trial Cortés <i>et al.</i> 2022 [80] (Primary)	Global DESTINY-Breast03 (NCT03529110) Randomized, open-label, multi-centre, active-controlled, phase 3	N=524; prior taxane + trastuzumab T-DM1, n: 263 prior anti-HER2 therapy ◦ Prior 1L: 197 ◦ Prior >2L: 63 Patient subgroups ◦ De novo: 104 ◦ Recurrent: 159 T-DXd, n: 261 prior anti-HER2 therapy ◦ Prior 1L: 193 ◦ Prior >2L: 66 Patient subgroups ◦ De novo: 93 Recurrent: 168 Median age, years ◦ T-DM1: 54.2 ◦ T-DXd: 54.3 ECOG 0, n (%) ◦ T-DM1: 175 (66.5) ◦ T-DXd: 154 (59.0) ECOG 1, n (%) ◦ T-DM1: 87 (33.1) T-DXd: 106 (40.6)	· T-DXd: 16.2 · T-DM1: 15.3	NR	NR	T-DXd (N = 257) vs T-DM1 (N = 261) Haematologic toxicities · Neutropenia: 49 (19.1) vs 8 (3.1) · Thrombocytopenia: 18 (7.0) vs 65 (24.9) · Leukopenia: 17 (6.6) vs 1 (0.4) · Anemia: 15 (5.8) vs 11 (4.2) Non-haematologic toxicities · Nausea: 17 (6.6) vs 1 (0.4) · Fatigue 13 (5.1) vs 2 (0.8) · AST increased: 2 (0.8) vs 13 (5.0) · ALT increased: 4 (1.6) vs 12 (4.6) · Vomiting: 4 (1.6) vs 1 (0.4) · Decreased appetite 3 (1.2) vs 0 · Diarrhoea: 1 (0.4) vs 1 (0.4) · ILD/pneumonitis: 2 (0.8) vs 0 · Any grade ≥ 3 AE: 52.1% vs 48.3% · Drug-related grade 3/4 AE: 45.1% vs 39.8% Grade ≥ 3 TEAEs leading to discontinuation: 13.6% vs 7.3%

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Hurvitz et al. 2023 [26] (Secondary)			<ul style="list-style-type: none"> · T-DXd: 28.4 · T-DM1: 26.5 	<ul style="list-style-type: none"> · T-DXd (N=257) vs. T-DM1 (N=261) · Hematologic toxicities · Anemia: 24 (9) vs. 15 (6) · Platelet count decreased: 18 (7) vs. 45 (17) · WBC count decreased: 16 (6) vs. 2 (<1) · Non-hematologic toxicities · Nausea: 18 (7) vs. 1 (<1) · Vomiting: 3 (1) vs. 2 (<1) · Diarrhoea: 3 (1) vs. 2 (<1) · Fatigue: 15 (6) vs. 2 (<1) · Neutrophil count decreased: 38 (15) vs. 8 (3) · AST increased: 2 (<1) vs. 14 (5) · ALT increased: 4 (2) vs. 12 (5) · Decreased appetite: 4 (2) vs. 1 (<1) · Weight decreased: 6 (2) vs. 2 (<1) 	<ul style="list-style-type: none"> · T-DXd (N=257) vs. T-DM1 (N=261) · Hematologic toxicities · Platelet count decreased: 2 (<1) vs. 7 (3) · Non-hematologic toxicities · Neutrophil count decreased: 3 (1) vs. 0 	<ul style="list-style-type: none"> · T-DXd (N=257) vs. T-DM1 (N=261) · Hematologic toxicities · Anemia: 24 (9) vs. 17 (7) · Platelet count decreased: 20 (8) vs. 52 (20) · WBC count decreased: 16 (6) vs. 2 (<1) · Non-hematologic toxicities · Neutrophil count decreased: 3 (1) vs. 0 · Nausea: 18 (7) vs. 1 (<1) · Neutrophil count decreased: 41 (16) vs. 8 (3) · Nausea: 18 (7) vs. 1 (<1) · Fatigue: 15 (6) vs. 2 (<1) · Bodyweight decreased: 6 (2) vs. 2 (<1) · Vomiting: 4 (2) vs. 2 (<1) · ALT increased: 4 (2) vs. 12 (5) · Decreased appetite: 4 (2) vs. 1 (<1) · Diarrhea: 3 (1) vs. 2 (<1) · AST increased: 2 (<1) vs. 14 (5) · Grade ≥3 TEAEs · 145 (56) vs. 135 (52) · Drug related Grade ≥3 TEAEs: 121 (47) vs. 110 (42)
Im et al. 2022 [28] (Secondary)	Asia	<ul style="list-style-type: none"> · Asians, n: 309; prior taxane + trastuzumab · T-DM1, n: 160 · T-DXd, n: 149 	NR	NR	No grade 4/5 drug-related ILD/pneumonitis reported	NR

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
B. EMILIA Trial						
Verma <i>et al.</i> 2012 [32] (Primary)	Global EMILIA (NCT00829166) Randomized, open-label, multi-centre, phase 3	N=991; prior taxane + trastuzumab · T-DM1, n: 495 · Lapatinib plus capecitabine, n: 496 Median age, years ◦ T-DM1: 53 ◦ Lapatinib plus capecitabine: 53 ECOG 0, n (%) ◦ T-DM1: 299 (60) ◦ Lapatinib plus capecitabine: 312 (63) ECOG 1, n (%) ◦ T-DM1: 194 (39) ◦ Lapatinib plus capecitabine: 176 (35) ECOG NA, n (%) ◦ T-DM1: 2 (<1) ◦ Lapatinib plus capecitabine: 8 (2)	13	T-DM1: Left ventricular systolic dysfunction, n: 1	T-DM1: Gastrointestinal hemorrhage, n: 1	T-DM1 vs. Lapatinib plus capecitabine Hematologic toxicities · Neutropenia: 10 (2) vs 21 (4.3) · Hypokalemia: 11 (2.2) vs 20 (4.1) · Anemia: 13 (2.7) vs 8 (1.6) · Thrombocytopenia: 63 (12.9) vs 1 (0.2) Non-hematologic toxicities · Fatigue: 12 (2.4) vs 17 (3.5) · Nausea: 4 (0.8) vs 12 (2.5) · Diarrhea: 8 (1.6) vs 101 (20.7) · Palmar-plantar erythrodysesthesia: 0 vs 80 (16.4) · Vomiting: 4 (0.8) vs 22 (4.5) · Mucosal inflammation: 1 (0.2) vs 11 (2.3) · Elevated ALT: 14 (2.9) vs 7 (1.4) Elevated AST: 21 (4.3) vs 4 (0.8)

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Diéras <i>et al.</i> 2017 [29] (Secondary)			<ul style="list-style-type: none"> T-DM1: 47.8 (IQR 41.9–55.5) Lapatinib plus capecitabine: 41.9 (IQR 34.6–50.7) 	<ul style="list-style-type: none"> T-DM1 vs. Lapatinib plus capecitabine Hematologic toxicities Thrombocytopenia: 56 (11) vs. 0 Anemia: 18 (4) vs. 11 (2) Neutropenia: 9 (2) vs. 16 (3) Non-Hematologic toxicities Increased AST: 22 (4) vs. 7 (1) Increased ALT: 15 (3) vs. 9 (2) Diarrhoea: 9 (2) vs. 100 (21) Fatigue: 11 (2) vs. 16 (3) Peripheral neuropathy: 9 (2) vs. 1 (0.2) Hypokalemia: 11 (2) vs. 21 (4) Nausea: 4 (1) vs. 12 (3) Vomiting: 5 (1) vs. 23 (5) Asthenia: 4 (1) vs. 8 (2) Headache: 4 (1) vs. 4 (1) Back pain: 4 (1) vs. 2 (<1) Arthralgia: 3 (1) vs. 0 Insomnia: 3 (1) vs. 1 (<1) Dyspnea: 4 (1) vs. 1 (<1) UTI: 3 (1) vs. 0 Myalgia: 3 (1) vs. 0 Decreased appetite: 2 (<1) vs. 5 (1) Mucosal inflammation: 1 (<1) vs. 9 (2) Pain in extremity: 2 (<1) vs. 5 (1) Hyperbilirubinemia: 2 (0.4) vs. 6 (1.2) Palmar–plantar erythrodysesthesia syndrome: 0 vs. 86 (18) Rash: 0 vs. 7 (1) Paronychia: 0 vs. 6 (1) Dehydration: 0 vs. 7 (1.4) Hypertension: 7 (1.4) vs. 2 (0.4) Urticaria: 0 vs. 5 (1) 	<ul style="list-style-type: none"> T-DM1 vs. Lapatinib plus capecitabine Hematologic toxicities Thrombocytopenia: 14 (3) vs. 2 (<1) Neutropenia: 2 (<1) vs. 5 (1) Non-Hematologic toxicities Diarrhoea: 0 vs. 3 (1) Pulmonary embolism: 0 vs. 6 (1.2) 	<ul style="list-style-type: none"> Grade 3 or worse AE T-DM1 vs. Lapatinib plus capecitabine: 233 (48) vs. 291 (60) T-DM1 Hematologic toxicities Thrombocytopenia: 70 (14) Anaemia: 19 (4) Non-Hematologic toxicities Increased aspartate transaminase: 22 (5)

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Krop <i>et al.</i> 2015 [31] (Secondary)	CNS metastasis at baseline; prior taxane + trastuzumab stable <ul style="list-style-type: none"> · T-DM1, n: 45 (4.5) · Lapatinib plus capecitabine, n: 50 (5.0) Median age, years <ul style="list-style-type: none"> · T-DM1: 51 · Lapatinib plus capecitabine: 53 n (%) ECOG PS 0 <ul style="list-style-type: none"> · T-DM1: 22 (48.9) · Lapatinib plus capecitabine: 24 (49.0) ECOG PS 1 <ul style="list-style-type: none"> · T-DM1: 23 (51.1) Lapatinib plus capecitabine: 25 (51.0)	For ITT population <ul style="list-style-type: none"> · T-DM1: 19.1 Lapatinib plus capecitabine: 18.6	NR	NR	Patients with CNS metastases, n/N (%) <ul style="list-style-type: none"> · T-DM1: 21/43 (48.8%) Lapatinib plus capecitabine: 31/49 (63.3%)	
Im <i>et al.</i> 2021 [30] (Secondary)	Asia N=158; Asians with prior taxane + trastuzumab Enrolled <ul style="list-style-type: none"> · T-DM1, n: 82 · Lapatinib plus capecitabine, n: 76 Safety Evaluable <ul style="list-style-type: none"> · T-DM1, n: 80 · Lapatinib plus capecitabine, n: 75 	13	Hematologic toxicities (T-DM1 vs. Lapatinib plus capecitabine) Asia <ul style="list-style-type: none"> · Thrombocytopenia: 24 (30.5) vs. 0 (0) · Hemorrhage: 0 (0) vs. 2 (2.7) Global <ul style="list-style-type: none"> · Thrombocytopenia: 55 (11.2) vs. 0 (0) · Hemorrhage: 6 (1.2) vs. 4 (0.8) 	Hematologic toxicities (T-DM1 vs. Lapatinib plus capecitabine) Asia <ul style="list-style-type: none"> · Thrombocytopenia: 7 (8.8) vs. 0 (0) Global <ul style="list-style-type: none"> · Thrombocytopenia: 13 (2.7) vs. 1 (0.2) 	T-DM1 vs. Lapatinib plus capecitabine <ul style="list-style-type: none"> · Asia: 48 (60) vs. 41 (54.7) · Global: 200 (40.8) vs. 278 (57.0) 	

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
C. KAMILLA Trial Montemurro et al. 2020 [33] (Primary)	Global KAMILLA (NCT01702571) Single-arm, Ongoing, phase 3b	N=2,002; prior taxane, Trastuzumab, pertuzumab, Lapatinib, Endocrine therapy, Anthracyclines · BM at baseline: 398 · No BM at baseline: 1,604 Median age, years · Patients with BM at baseline: 52 · Patients without BM at baseline: 55 ECOG PS 0 · Patients with BM at baseline: 192 (48.2) · Patients without BM at baseline: 918 (57.2) ECOG PS 1 · Patients with BM at baseline: 174 (43.7) · Patients without BM at baseline: 601 (37.5) ECOG PS 2 · Patients with BM at baseline: 32 (8.0) · Patients without BM at baseline: 83 (5.2)	20.6	BM at baseline Hematologic toxicities · Anemia: 7 (1.8) · Platelet count decreased: 4 (1.0) Non-hematologic toxicities · Fatigue: 14 (3.5) · ALT increased: 10 (2.5) · Headache: 10 (2.5) · Asthenia: 9 (2.3) · Dyspnea: 8 (2.0) · Vomiting: 7 (1.8) · Hepatotoxicity: 7 (1.8) · GGT increased: 6 (1.5) · AST increased: 5 (1.3) · Confusional state: 5 (1.3) · Seizure: 5 (1.3) · Hypertension: 4 (1.0) · Diarrhea: 4 (1.0) · Dizziness: 4 (1.0) · Hyperglycemia: 4 (1.0) No BM at baseline · Hematologic toxicities · Anemia: 50 (3.1) · Thrombocytopenia: 30 (1.9) · Neutropenia: 16 (1.0) Non-hematologic toxicities · Fatigue: 36 (2.2) · GGT increase: 33 (2.1) · Asthenia: 26 (1.6) · AST increased: 24 (1.5) · Dyspnea: 22 (1.4) · Vomiting: 21 (1.3) · Hypertension: 20 (1.2)	None	None

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Wuerstlein <i>et al.</i> 2022 [34] (Secondary)	Global and Asia	N=2,183; prior anti-HER2 + CT <ul style="list-style-type: none"> • Cohort 1 (Global), n: 2,002 • Cohort 2 (Asia), n: 181 Median age, years <ul style="list-style-type: none"> ◦ Cohort 1: 55 ◦ Cohort 2: 51 ECOG PS 0, n (%) <ul style="list-style-type: none"> ◦ Cohort 1: 1110 (55.4) ◦ Cohort 2: 76 (42.0) ECOG PS 1, n (%) <ul style="list-style-type: none"> ◦ Cohort 1: 775 (38.7) ◦ Cohort 2: 101 (55.8) ECOG PS 2, n (%) <ul style="list-style-type: none"> ◦ Cohort 1: 115 (5.7) ◦ Cohort 2: 4 (2.2) ECOG PS missing, n (%) <ul style="list-style-type: none"> ◦ Cohort 1: 2 (0.1) ◦ Cohort 2: 0 (0.0) 	<ul style="list-style-type: none"> • Cohort 1: 20.6 • Cohort 2: 15.1 	Cohort 1 vs Cohort 2 <ul style="list-style-type: none"> • AEs related to T-DM1: 344 (17.2) vs 78 (43.1) Non-hematologic toxicities <ul style="list-style-type: none"> • Hepatic events: 132 (6.6) vs 22 (12.2) Hematologic toxicities <ul style="list-style-type: none"> • Thrombocytopenia: 62 (3.1) vs 58 (32.0) 	Cohort 1 vs Cohort 2 <ul style="list-style-type: none"> • AEs related to T-DM1: 31 (1.5) vs 27 (14.9) Hematologic toxicities <ul style="list-style-type: none"> • Thrombocytopenia: 12 (0.6) vs 23 (12.7) 	Cohort 1 vs Cohort 2 <ul style="list-style-type: none"> • Any TEAE: 816 (40.8) vs 123 (68.0) Hematologic toxicities <ul style="list-style-type: none"> • Thrombocytopenia: 55 (2.7) vs 37 (20.4) • Grade ≥3 AEs related to T-DM1: 368 (18.4) vs 88 (48.6) Non-hematologic toxicities <ul style="list-style-type: none"> • Grade ≥3 hepatic events: 139 (6.9) vs 22 (12.2) Hematologic toxicities <ul style="list-style-type: none"> • Grade ≥3 thrombocytopenia: 74 (3.7) vs 66 (36.5)
D. Other Trials						
Wang <i>et al.</i> 2023 [40] (Primary)	China ELAINA (NCT03084939) Randomized, open-label bridging, multi-centre, phase 3	N=200; prior taxane + trastuzumab <ul style="list-style-type: none"> • T-DM1, n: 151 • Lapatinib plus capecitabine, n: 49 Median age, years <ul style="list-style-type: none"> ◦ T-DM1: 51 ◦ Lapatinib plus capecitabine: 52 ECOG 0, n (%) <ul style="list-style-type: none"> ◦ T-DM1: 83 (55.0) ◦ Lapatinib plus capecitabine: 26 (53.1) ECOG 1, n (%) <ul style="list-style-type: none"> ◦ T-DM1: 68 (45.0) ◦ Lapatinib plus capecitabine: 23 (46.9) 	<ul style="list-style-type: none"> • T-DM1: 8.6 • Lapatinib plus capecitabine: 9.7 	NR NR	NR	T-DM1 vs. Lapatinib plus capecitabine <ul style="list-style-type: none"> • Overall: 82 (54.3) vs. 28 (57.1) • Any selected AE: 65 (43.0) vs. 4 (8.2) Hematologic toxicities <ul style="list-style-type: none"> • Thrombocytopenia: 61 (40.4) vs. 2 (4.1) Non-hematologic toxicities <ul style="list-style-type: none"> • Hepatotoxicity: 13 (8.6) vs. 1 (2.0) • Peripheral neuropathy: 0 vs. 1 (2.0)

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Wildiers <i>et al.</i> , 2022 [42] (Primary)	Europe EORTC 75111-10114 ETF/BCG Randomized, open-label, multi-centre, investigator-initiated, phase 2	N=40; prior trastuzumab + pertuzumab (TP) without or with metronomic oral cyclophosphamide (TPM) Median age, years ◦ TP: 76.2 ◦ TPM: 77.3 WHO PS 0, n (%) ◦ TP: 10 (25.6) ◦ TPM: 17 (41.5) WHO PS 1, n (%) ◦ TP: 17 (43.6) ◦ TPM: 17 (41.5) WHO PS 2, n (%) ◦ TP: 8 (20.5) ◦ TPM: 7 (17.1) WHO PS 3, n (%) ◦ TP: 4 (10.3) ◦ TPM: 0 (0.0)	33.7	NR	NR	Grade 3-5 (T-DM1) All AEs: 18 (45) Hematologic toxicities · Lymphopenia: 6 (15) · Neutropenia: 1 (2.5) · Thrombocytopenia: 1 (2.5) Non-hematologic toxicities Gastrointestinal · Diarrhea: 1 (2.5) General disorders · Fatigue: 3 (7.5) · Anorexia: 2 (5) · Hypertension: 2 (5) Respiratory · Dyspnea: 1 (2.5) · Epistaxis: 1 (2.5) Liver and kidney function · AST increase: 1 (2.5) · ALT increase: 1 (2.5) Special interest · Falls: 1 (2.5)

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Krop <i>et al.</i> 2017 [38] (Primary)	Global TH3RESA (NCT01419197) Randomized, open-label, multi-centre, phase 3	N=602; ≤2 prior HER2-directed therapy (trastuzumab, lapatinib and taxane) Safety population · T-DM1, n: 403 · Physician's choice, n: 184 Median age, years ◦ T-DM1: 53 ◦ Physician's choice: 54 ECOG PS 0, n (%) ◦ T-DM1: 180 (45) ◦ Physician's choice: 82 (41) ECOG PS 1, n (%) ◦ T-DM1: 200 (50) ◦ Physician's choice: 101 (51) ECOG PS 2, n (%) ◦ T-DM1: 22 (5) ◦ Physician's choice: 15 (8)	30.5	T-DM1 vs. Physician's choice Hematologic toxicities · Thrombocytopenia: 19 (5) vs. 4 (2) · Anemia: 12 (3) vs. 5 (3) · Neutropenia: 7 (2) vs. 20 (11) · Leukopenia: 2 (<1) vs. 4 (2) · Febrile neutropenia: 0 vs. 5 (3) Non-Hematologic toxicities · Fatigue: 9 (2) vs. 5 (3) · Dyspnea: 10 (2) vs. 7 (4) · AST increased: 10 (2) vs. 5 (3) · Alanine aminotransferase increased: 6 (2) vs. 4 (2) · Nausea: 4 (1) vs. 1 (1) · Diarrhoea: 3 (1) vs. 8 (4) · Asthenia: 4 (1) vs. 6 (3) · Abdominal pain: 5 (1) vs. 5 (3) · Vomiting: 4 (1) vs. 2 (1) · Pain in extremity: 3 (1) vs. 1 (1) · Myalgia: 2 (<1) vs. 1 (1) · Cellulitis: 2 (<1) vs. 4 (2)	T-DM1 vs. Physician's choice Hematologic toxicities · Neutropenia: 3 (1) vs. 9 (5) · Thrombocytopenia: 5 (1) vs. 1 (1) · Anemia: 2 (<1%) vs. 1 (1) · Febrile neutropenia: 1 (<1%) vs. 2 (1) · Leukopenia: 0 vs. 1 (1)	Grade 3 or worse AE Hematologic toxicities · T-DM1 vs Physician's choice: 161 (40) vs. 87 (47) ◦ Thrombocytopenia: 24 (6) vs. 5 (3) ◦ Neutropenia: 10 (3) vs. 29 (16)
Watanabe <i>et al.</i> 2017 [41] (Primary)	Japan JO29317 Single-arm, multi-centre, phase 2	N=232; prior CT and trastuzumab Median age, years: 57 n (%) · ECOG PS 0: 165 (71.1) · ECOG PS 1: 64 (27.6) · ECOG PS 2: 3 (1.3) · ECOG PS 3: 0 (0)	NR	Hematologic toxicities Thrombocytopenia: 60 (25.9) Non-Hematologic toxicities Hepatotoxicity: 25 (10.8)	Hematologic toxicities Thrombocytopenia: 9 (3.9)	Grade ≥3: 109 (47.0) Grade ≥3 AEs reported >2% of pts Hematologic toxicities · Thrombocytopenia: 69 (29.7) Non-Hematologic toxicities · AST increased: 12 (5.2) · Hepatic function abnormal: 12 (5.2)

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Yardley <i>et al.</i> , 2015 [43] (Primary)	USA T-PAS (TDM4884g/NCT01120561) Single-arm, multi-centre, expanded access	N=215; ≤2 prior HER2-directed therapy including trastuzumab and lapatinib + anthracycline and a taxane, and capecitabine or 5-fluorouracil <ul style="list-style-type: none"> Patients Having Received ≤18 Cycles of T-DM1, n: 175 Patients Having Received >18 Cycles of T-DM1, n: 40 Median age, years: 53 n (%) <ul style="list-style-type: none"> ECOG PS 0: 99 (46.3) ECOG PS 1: 91 (42.5) ECOG PS 2: 24 (11.2) 	5.9	Hematologic toxicities Thrombocytopenia: 11 (5.1) Non-Hematologic toxicities Peripheral neuropathy: 5 (2.3)	Hematologic toxicities Thrombocytopenia: 6 (2.8)	Overall, hemorrhagic event of grade 3 or greater: 4 (1.86) Overall, Common TEAEs Grade ≥3 AEs occurring in >2% of patients Hematologic toxicities <ul style="list-style-type: none"> Thrombocytopenia: 22 (10.2) Non-Hematologic toxicities <ul style="list-style-type: none"> Fatigue: 10 (4.7) Anemia: 8 (3.7) Increased AST: 8 (3.7) Pneumonia: 7 (3.3) Dyspnea: 5 (2.3) Patients Having Received ≤18 Cycles of T-DM1 vs. >18 Cycles of T-DM1 Grade ≥3 AE occurring in >1 patient Hematologic toxicities <ul style="list-style-type: none"> Thrombocytopenia: 17 (9.7) vs. 5 (12.5) Anemia: 4 (2.3) vs. 4 (10.0) Neutropenia: 1 (0.6) vs. 2 (5.0) Non-Hematologic toxicities <ul style="list-style-type: none"> Fatigue: 8 (4.6) vs. 2 (5.0) Dyspnea: 5 (2.9) vs. 0 (0) Increased AST: 5 (2.9) vs. 3 (7.5) Abdominal pain: 4 (2.3) vs. 0 Pneumonia: 4 (2.3) vs. 3 (7.5) Hypokalemia: 3 (1.7) vs. 1 (2.5)

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Gupta <i>et al.</i> 2013 [36] (Primary)	NR TDM4688g / NCT00943670 Single-arm, multi-centre, phase 2	N=51; prior CT (including anthracycline, taxane [paclitaxel/docetaxel] and capecitabine) + trastuzumab + lapatinib Median age, years: 53.5 n (%) ◦ ECOG PS 0: 28 (54.9) ◦ ECOG PS 1: 23 (45.1)	NR	Hematologic toxicities T-DM1 · Thrombocytopenia: 4 (7.8) Non-Hematologic toxicities T-DM1 · Increased serum AST: 5 (9.8) · Hyperglycemia: 2 (3.9) Pertuzumab plus T-DM1 · Increased serum AST: 1 (10.0)	T-DM1 vs. Pertuzumab plus T-DM1: 0 vs. 3 (15) T-DM1: 17 (33.3) vs. 12 (60.0)	<ul style="list-style-type: none"> · Fall: 2 (1.1) vs. 1 (2.5) · Musculoskeletal pain: 2 (1.1) vs. 1 (2.5) · Brain mass: 1 (0.6) vs. 1 (2.5) · Headache: 1 (0.6) vs. 1 (2.5) · Hypertension: 1 (0.6) vs. 2 (5.0) · Pain in extremity: 1 (0.6) vs. 2 (5.0) · Syncope: 1 (0.6) vs. 2 (5.0) · Decreased blood Phosphorus: 0 (0) vs. 2 (5.0) · Dyspareunia: 0 (0) vs. 2 (5.0) · Increased ALT: 0 (0) vs. 2 (5.0)

Study (Primary/Secondary Publication)	Study details (Country, Study name, design and duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Krop <i>et al.</i> 2012 [39] (Primary)	NR TDM437g Single-arm, phase 2	N=110; ≤2 prior HER2-directed therapy Median age, years: 52.5 n (%) ◦ ECOG PS 0: 54 (49.1) ◦ ECOG PS 1: 53 (48.2) ◦ ECOG PS 2: 3 (2.7)	17.4	<ul style="list-style-type: none"> At least one grade 3 AE: 52 (47.3) Hematologic toxicities Thrombocytopenia: 8 (7.3) Anemia: 2 (1.8) Non-Hematologic toxicities <ul style="list-style-type: none"> Fatigue: 5 (4.5) Increased AST: 3 (2.7) Back pain: 3 (2.7) Dyspnea: 3 (2.7) Increased ALT: 3 (2.7) Depression: 3 (2.7) Arthralgia: 2 (1.8) Pain in extremity: 2 (1.8) 	At least one grade 4 AE: 6 (5.45)	Hematologic toxicities <ul style="list-style-type: none"> Thrombocytopenia: 10 (9.1) Non-Hematologic toxicities <ul style="list-style-type: none"> Hepatic AE: 9 (8.2) Fatigue: 5 (4.5) Cellulitis: 4 (3.6)
Burris <i>et al.</i> 2011 [35] (Primary)	USA TDM4258g Single-arm, phase 2	N=112; ≥1 prior HER2-targeted therapy Median age, years: 54.5 n (%) ◦ ECOG PS 0: 60 (53.6) ◦ ECOG PS 1: 43 (38.4) ◦ ECOG PS 2: 8 (7.1) ◦ ECOG PS 3: 1 (0.9)	≥12	Hematologic toxicities <ul style="list-style-type: none"> Anemia: 3 (2.7) Non-Hematologic toxicities <ul style="list-style-type: none"> Hypokalemia: 10 (8.9) Fatigue: 5 (4.5) Epistaxis: 2 (1.8) Dyspnea: 3 (2.7) 	None	NR

Abbreviations: AEs: Adverse Events; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BM: Brain Metastasis; CT: Chemotherapy; HER2: Human Epidermal Growth Factor Receptor 2; ILD: Interstitial Lung Disease; IQR: Interquartile Range; LVEF: Left Ventricular Ejection Fraction; MedDRA: Medical Dictionary for Regulatory Activities; NR: Not Reported; Pts: Patients; SAEs: Serious Adverse Events; T-DM1: Trastuzumab Emtansine; T-DXd: Trastuzumab Deruxtecan; TEAEs: Treatment-Emergent Adverse Events; TKI: Tyrosine Kinase Inhibitor; TP: Trastuzumab plus Pertuzumab; TPM: Trastuzumab plus Pertuzumab and Metronomic Oral Cyclophosphamide; UTI: Urinary Tract Infection; WBC: White Blood Cell

Table 7. T-DM1 safety (grade ≥ 3) in pivotal HER2-positive advance/metastatic breast cancer in real-world studies.

Study details (Country, Study name, design, data source and study duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥ 3 AEs, n (%)
FIELD-PRACTICE study (two publications)					
Fabi <i>et al.</i> 2017 [45] Italy	N=303; Prior taxane / anthracycline based therapies Median age, years: 51	10	Hematologic toxicities · Thrombocytopenia: 7 (2) · Neutropenia: 2 (0.7) Non-hematologic toxicities · Alopecia: 5 (2) · Asthenia: 3 (1) · Transaminase: 2 (0.7)	Hematologic toxicities · Thrombocytopenia: 1 (0.3) · Neutropenia: 1 (0.3) Non-hematologic toxicities Transaminase: 1 (0.3)	NR
FIELD-PRACTICE – multi-centre study 2012–2016					
Fabi <i>et al.</i> 2017 [46]	N=107; 1L taxane + pertuzumab / trastuzumab pertuzumab / + trastuzumab, n: 34 trastuzumab, n: 73 Median age, years ◦ Trastuzumab/ Pertuzumab: 43 ◦ Trastuzumab: 51	NR	T-DM1 post Pertuzumab / +trastuzumab vs. Trastuzumab Hematologic toxicities Thrombocytopenia: 0 vs. 1 (1) Non-hematologic toxicities Pertuzumab / +trastuzumab vs. Trastuzumab Transaminases: 0 vs. 2 (3) Alopecia: 1 (3) vs. 1 (1) Asthenia: 0 vs. 2 (3)	T-DM1 post Pertuzumab / +trastuzumab vs. Trastuzumab Hematologic toxicities Thrombocytopenia: 0 vs. 1 (1)	NR
Real-world studies with single publication					
Baek <i>et al.</i> 2024 [49] Korea	HER2-positive MBC treated with T-DM1, N=824; Prior pertuzumab CNS, n (%): 145 (17.6) Median age, years: 58	16.8	NR	NR	Grade 3 or 4 Hematologic toxicities · Thrombocytopenia: 107 (13.2) · Neutropenia: 23 (2.8) · Anemia: 21 (2.6)
KCSG BR19-15, retrospective, non-interventional study 2017–2018	n (%) · ECOG PS 0-1: 695 (84) · ECOG PS 2: 74 (9) · Unknown: 54 (7)				Non-hematologic toxicities · AST/ALT elevation: 20 (2.5) · Fatigue: 17 (2.2) · Nausea: 5 (0.6) · Vomiting: 3 (0.4) · Diarrhea: 3 (0.4)

Study details (Country, Study name, design, data source and study duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
He et al. 2024 [61] China Multicentric, observational March 2023–June 2023	N=101; Prior trastuzumab and pertuzumab · Early vs. advanced stage: 31 vs. 70 Median age, years: 51 n (%) · ECOG PS 0-1: 101 (100)	7	NR	NR	Grade 3-4 Early vs. Advanced stage Hematologic toxicities · Thrombocytopenia: 9 (29.03) vs. 3 (4.29) · Leukopenia: 2 (6.45) vs. 1 (1.43) · Neutropenia: 2 (6.45) vs. 1 (1.43) · Anemia: 0 vs. 1 (1.43)
Bian et al. 2023 [52] China Retrospective study 2013–2022	N=213; Prior TKI therapy · T-DM1: 71 · ADC: 73 · Trastuzumab–pertuzumab (combined CT): 69 Median age, years: 47	NR	NR	NR	Grade 3 or 4 hemaatologic toxicities ADC group · Neutropenia: 15 (20.5) T-DM1 group · Thrombocytopenia: 20 (28.1) Non-hematologic toxicities ADC vs. T-DM1 · ILD: 4 (5.4) vs. 1 (1.4) · No grade 5 AEs occurred
Ji et al. 2023 [63] China Real-world retrospective study 2013–2022	N=144; TKI, Trastuzumab · Anti-HER2 ADC: 73 · T-DM1: 71 Median age, years · Anti-HER2 ADCs: 48 · T-DM1: 42	NR	NR	NR	Grade 3-4 T-DM1 vs. Novel anti-HER2 ADCs Hematologic toxicities · Thrombocytopenia: 20 (28.1) vs. 3 (4.1) · Neutropenia: 4 (5.6) vs. 15 (20.5) · Anemia: 4 (5.6) vs. 5 (6.8) · Leukopenia: 2 (2.8) vs. 6 (8.2) Non-hematologic toxicities · Elevated transaminase: 4 (5.6) vs. 2 (2.7) · Diarrhea: 0 vs. 6 (8.2) · Nausea: 0 vs. 9 (12.3) · Vomiting: 0 vs. 8 (11.0) · Fatigue: 2 (2.8) vs. 4 (5.4) · Peripheral neuropathy: 0 vs. 3 (4.1) · ILD: 0 vs. 1 (1.4)

Study details (Country, Study name, design, data source and study duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Martins <i>et al.</i> , 2023 [67] Portugal Retrospective study 2017–2023	N=32; 1L Pertuzumab / trastuzumab plus taxane Median age, years: 53	NR	NR	Non-hematologic toxicities Hepatic and cardiac toxicity: 3 (9.3)	No grade 5 AE
Gogia <i>et al.</i> , 2022 [59] India Retrospective study 2015–2021	N=80; Prior trastuzumab, pertuzumab Median age, years: 49 ECOG PS 0-1: 80%	18	NR	NR	Grade 3/4 (overall): 20 (25) Hematologic toxicities · Thrombocytopenia: 16 (20) · Anemia: 2 (2.5) Non-hematologic toxicities · Fatigue: 10 (12.5) · Transaminitis: 10 (12.5) · Peripheral Neuropathy: 2 (2.5)

Study details (Country, Study name, design, data source and study duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Bahceci <i>et al.</i> 2021 [50] Turkey Retrospective multi-centre study	N=414; Prior CT and Anti-HER2 Median age, years: 47	· Overall: 67.3 (42.6) · Post-T-DM1 follow-up: 13.7 (7.9)	NR	NR	<ul style="list-style-type: none"> · Grade 3-4 Hematologic toxicities · Thrombocytopenia: 11 (2.7) · Anemia: 5 (1.2) · Neutropenia: 5 (1.2) · Febrile neutropenia: 2 (0.5) · Leukopenia: 2 (0.4) Non-hematologic toxicities · GGT increased: 8 (2) · Liver failure: 6 (1.5) · Fatigue: 5 (1.3) · AST Increased: 5 (1.3) · Alanine aminotransferase Increased: 5 (1.3) · Alkaline phosphatase increased: 4 (1.1) · Total bilirubin increased: 4 (1.1) · Thromboembolic event: 3 (0.7) · Heart failure: 3 (0.7) · Hyperuricemia: 2 (0.6) · Hypercalcemia: 2 (0.6) · Pain: 2 (0.5) · Hyperglycemia: 2 (0.5) · Pneumonitis: 2 (0.5) · Paresthesia: 1 (0.3) · Hypokalemia: 1 (0.3) · Delirium: 1 (0.3) · Hyponatremia: 1 (0.3) · Portal hypertension: 1 (0.3) · Diarrhea: 1 (0.2) · Anaphylaxis: 1 (0.2)

Study details (Country, Study name, design, data source and study duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Li <i>et al.</i> 2021 [64] China Real-world study 2013–2019	N=105; Prior trastuzumab and lapatinib · Pyrotinib, n: 55 · T-DM1, n: 50 Median age, years · Pyrotinib, n: 47 · T-DM1, n: 46	NR	NR	NR	<ul style="list-style-type: none"> · Grade 3 or 4 · Pyrotinib vs. T-DM1 Hematologic toxicities <ul style="list-style-type: none"> · Thrombocytopenia: 0 (0) vs. 9 (18.0) · Anemia: 2 (3.6) vs. 0 (0) · Leukopenia: 2 (3.6) vs. 0 (0) · Neutropenia: 2 (3.6) vs. 2 (4) Non-Hematological toxicities <ul style="list-style-type: none"> · Diarrhoea: 12 (21.8) vs. 0 (0) · Nausea: 0 (0) vs. 3 (6.0) · Elevated transaminase: 1 (1.8) vs. 2 (4) · Fatigue: 0 (0) vs. 4 (8.0)
Tataroglu Ozyukseler <i>et al.</i> 2021 [77] Turkey Single-centre retrospective, observational study 2016–2019	N=78; 1L trastuzumab-based regimens · BM: 36 (46.2) · Non-BM: 42 (53.8) Median age, years: 52 % <ul style="list-style-type: none"> ◦ ECOG PS 0: 32 (41.0) ◦ ECOG PS 1: 38 (48.7) ◦ ECOG PS 2: 8 (10.3) 	12.9	Hematologic Toxicities <ul style="list-style-type: none"> · Thrombocytopenia: 6 (7.7) · Anemia: 2 (2.6) · Leukopenia: 1 (1.3) Non-hematologic toxicities <ul style="list-style-type: none"> · Increased AST and/or ALT: 3 (3.8) · Fatigue: 2 (2.6) · Nausea: 1 (1.3) · Diarrhoea: 1 (1.3) 	Hematologic Toxicities <ul style="list-style-type: none"> · Thrombocytopenia: 4 (5.1) · Non-hematologic toxicities · Increased AST and/or ALT: 2 (2.6) 	NR

Study details (Country, Study name, design, data source and study duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Battisti <i>et al.</i> 2020 [51]	<ul style="list-style-type: none"> T-DM1, N=128 ◦ 1L, n: 15 ◦ 2L+, n: 113 	NR	Hematologic Toxicities	Hematologic Toxicities	Grade ≥3 (overall): 46 (35.9)
UK Retrospective review	<ul style="list-style-type: none"> Median age, years: 55 n (%) 		<ul style="list-style-type: none"> Anemia: 8 (6.2) Thrombocytopenia: 5 (3.9) Neutropenia: 1 (0.8) 	Thrombocytopenia: 1 (0.8)	<ul style="list-style-type: none"> Liver toxicity: 25 (19.5) Anemia: 8 (6.2) Thrombocytopenia: 6 (4.7)
2014–2018	<ul style="list-style-type: none"> ◦ ECOG PS 0: 35 (27.3) ◦ ECOG PS 1: 80 (62.5) ◦ ECOG PS 2: 10 (7.8) ◦ ECOG PS 3: 3 (2.4) 		<ul style="list-style-type: none"> Non-hematologic toxicities Deranged liver function: 24 (18.7) Diarrhoea: 3 (2.3) Fatigue: 3 (2.3) Peripheral neuropathy: 3 (2.3) Nausea: 1 (0.8) Oral mucositis: 1 (0.8) 		
Italy Multi-centre retrospective study	<ul style="list-style-type: none"> ◦ Curative: 63 (49.2) ◦ Palliative: 113 (88.3) ◦ Total: 128 (100.0) ◦ Prior pertuzumab, n (%) ◦ Curative: 2 (1.6) ◦ Palliative: 37 (28.9) ◦ Total: 39 (30.5) 	10.3	Hematologic toxicities	None	NR
del Prete <i>et al.</i> 2020 [56]	<ul style="list-style-type: none"> N=135; 1L taxane + pertuzumab/trastuzumab Median age, years: 56 		Neutropenia: 1 (0.7)		
Spain TDM1RM study, retrospective observational study	<ul style="list-style-type: none"> N=52; 1L taxane + pertuzumab / trastuzumab Median age, years: 52 % ◦ ECOG PS 0: 15 ◦ ECOG PS 1: 61 ◦ ECOG PS 2: 23 	33	<ul style="list-style-type: none"> Hematologic toxicities Thrombopenia: 4 (8) Neutropenia: 2 (4) Anemia: 1 (2) Non-hematologic toxicities Asthenia: 2 (4) 	NR	NR
Martinez-Garcia <i>et al.</i> 2020 [66]					
2015–2020					

Study details (Country, Study name, design, data source and study duration)	Population; N; eligibility criteria	Median follow-up (months)	Grade 3 AEs, n (%)	Grade 4 AEs, n (%)	Grade ≥3 AEs, n (%)
Yeo <i>et al.</i> 2018 [79] Hong Kong Retrospective study 2013–2015	N=37; 2L+ prior anti-HER2 (trastuzumab / lapatinib / pertuzumab) / CT / endocrine therapy Median age, years: 52 N (%) • ECOG PS 0: 4 (10.8) • ECOG PS 1: 29 (78.4) • ECOG PS 2: 4 (10.8)	15.6	Hematologic toxicities • Thrombocytopenia: 3 (8.1) • Anemia: 2 (5.4) Non-hematologic toxicities • Raised alanine transaminase: 3 (8.1) • Hypokalemia: 1 (2.7)	Hematologic toxicities Thrombocytopenia: 2 (5.4)	None
Vici <i>et al.</i> 2017 [78] Italy Retrospective observational study 2013–2016	N=250; 1L pertuzumab Median age, years: 56 % • ECOG PS 0: 140 (56) • ECOG PS 1: 91 (36.4) • ECOG PS 2: 19 (7.6)	15	Hematologic toxicities • Thrombocytopenia: 3 (1.2) Non-hematologic toxicities • Fatigue: 5 (2) • Nausea: 2 (0.8) • Hyper-transaminasemia: 1 (0.4)	NR	NR
Michel <i>et al.</i> 2015 [68] Germany Retrospective chart review 2010–2014	N=23, prior HER2-directed therapy (trastuzumab, lapatinib, pertuzumab), (neo-) adjuvant cytotoxic therapy Median age, years: 54.6 % • ECOG PS 0: 37 (55.2) • ECOG PS 1: 25 (37.3) • ECOG PS 2: 3 (4.5) • ECOG PS 3: 2 (3.0)	9.3	SAEs Hematologic toxicities • Thrombopenia: 1 (4.3) • Elevated liver enzyme: 1 (4.3) Non-hematologic toxicities • Fatigue: 5 (21.7) • Infection: 1 (4.3)	SAEs Hematologic toxicities Elevated liver enzyme: 1 (4.3)	No grade 5 toxicity

Abbreviations: 1L: First-line; 2L: Second-line; 3L: Third-line; 4L: Fourth line; ADC: Antibody-Drug Conjugate; AEs: Adverse Events; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BM: Brain Metastasis; CNS: Central Nervous System; CT: Chemotherapy; GGT: Gamma-Glutamyl Transferase; HER2: Human Epidermal Growth Factor Receptor 2; ILD: Interstitial Lung Disease; LVEF: Left Ventricular Ejection Fraction; mBC: Metastatic Breast Cancer; NR: Not Reported; Pts: Patients; SAEs: Serious Adverse Events; SS: Sum of Squares; T-DM1: Trastuzumab Emtansine; TEAEs: Treatment-Emergent Adverse Events; TKI: Tyrosine Kinase Inhibitor; UK: United Kingdom; US: United States; UTI: Urinary Tract Infection; vs: Versus

Safety concordance was strong, with grade ≥ 3 thrombocytopenia and hepatic laboratory abnormalities as leading toxicities in trials [32,34,80] as well as RWE [49,52,59,63].

Quality assessment

A total of 42 references were assessed for RoB using Cochrane tools. Of these, seven randomized trials were assessed using RoB2.0 and 35 non-randomized trials were assessed using ROBINS-I.

Cochrane risk of bias (RoB 2.0) assessment for randomized studies

A total of seven publications [26,27,29,31,32,38,40] were assessed using the RoB 2.0 tool. Of these, five publications [26,27,29,38,40] were classified as high RoB, primarily due to shortcomings in the randomization process (domain 1) and outcome measurement (domain 4). Krop *et al.* (2015) [31] was judged to have some concerns due to uncertainties in randomization procedures, while Verma *et al.* (2012) [32] was the sole study with low RoB across all domains (**Figure S1**). The detailed assessments of each RCTs along with the checklist are provided as supplemental information – **Appendix A**.

Cochrane risk of bias in non-randomized studies of interventions (ROBINS-I)

A total of 35 publications (8 single-arm clinical and 27 real-world studies) were assessed using the ROBINS-I tool. Of these, the majority (85.7%, 30/35) was judged to have a serious RoB, primarily due to critical limitations such as uncontrolled confounding variables, incomplete adjustment for baseline differences, or substantial missing outcome data [34–37,43–46,48–51,54–56,58,60,61,63–65,68–72,74,77–79]. Four studies (11.4%) exhibited a moderate risk [33,39,41,75], and a single study with an overall low-risk showed minimal bias across all domains [47]. Among the four moderate-risk studies [33,39,41,75], limitations were primarily due to the confounding factors (Domain 1), deviations from interventions (domain 4), or missing data (domain 5) (**Figure S2**). The detailed assessments of each real-world studies along with the checklist are provided as supplemental information – **Appendix B**.

Discussion

The present SLR suggests that the real-world efficacy and safety outcomes of T-DM1 corroborate with those observed in clinical trials. Clinical trials have demonstrated response with T-DM1 therapy in patients previously treated with trastuzumab-based combination therapy and better efficacy than lapatinib plus capecitabine. Real-world studies have shown better response and survival outcomes with T-DM1 in pertuzumab-naïve patients and with early treatment compared to heavily treated patients. The safety outcomes highlighted thrombocytopenia and hepatic dysfunction as the most frequently reported grade ≥ 3 AEs. Although patients with CNS involvement often experience shorter PFS and OS, T-DM1 remains beneficial in this subgroup.

T-DM1 was initially approved for the treatment of HER2-positive mBC after prior treatment with trastuzumab and taxanes (considered a preferred 1L regimen option) [3]. Since the approval of pertuzumab as 1L therapy for HER2-positive mBC, guidelines have recommended its use in combination with trastuzumab as 1L therapy for HER2-positive mBC. Prospectively designed trials evaluating T-DM1 efficacy in patients previously exposed to pertuzumab are

scarce. However, real-world studies identified in this SLR reported outcomes for T-DM-1 in population pre-treated with pertuzumab.

Across randomized trials and diverse real-world cohorts, T-DM1 showed consistent antitumor activity and a predictable safety profile, indicating that pivotal results translate to clinical practice [26,29,32,34,40,45,49,51,63,78,80]. Patterns of response, disease control, and survival in trials overlapped in observational datasets despite broader eligibility, variable imaging schedules, and heterogeneous pre-treatment histories [45,51,74,78,79]. Concordant subgroup findings, especially maintained activity despite poorer prognosis of patients with CNS disease further support generalizability [27,31,33,44,71,75,77]. Where reported, discontinuations were predominantly driven by progression, with toxicity-related stops being uncommon [45,51]. The gaps observed were best explained by contemporary sequencing and later-line, more refractory use rather than loss of intrinsic efficacy [46,72,74,78].

Published clinical trial data provide evidence for the efficacy and safety of T-DM1 for the treatment of HER2-positive mBC based on data from approximately 3,500 heavily pre-treated patients (median prior LoT of ≥ 3). The included trials generally required patients to have progressed on ≥ 1 or ≥ 2 HER2-directed regimens, largely including trastuzumab and TKIs. Real-world studies provide complimentary data highlighting earlier use of T-DM1, i.e., as 2L or 3L therapy following progression on both trastuzumab and pertuzumab. The real-world studies therefore include broader patient populations than the clinical trials and provide a consolidated evidence base to appraise T-DM1 treatment as part of currently utilized therapeutic regimens for HER2-positive mBC, in particular as 2L treatment after 1L pertuzumab.

Considering T-DM1 efficacy, the observed mPFS from clinical trials (4.3–9.6 months) [26,32,34–37,39,40,43] and real world studies (2.8–10.5 months) [46,48,54,56,66,70–74,78] were largely consistent. However, the observed mOS from real-world studies (12.0–45.0 months) was more variable compared to observations from the clinical trials (22.7–34.3 months), potentially due to the former encompassing a heterogeneous patient population with possibly greater variability in lines of treatment [30,38,74,78]. Similarly, ORR was more variable in the real-world studies (21.9–80.0%) than clinical trials (25.0–50.4%) [40,42,45,46,48,50,59,64,67,68]. Notwithstanding the variability of clinical outcomes, the observations suggest that T-DM1 is an effective treatment in a broad patient population within the licensed indication. Furthermore, although the benefit of T-DM1 is more marked in patients who have not received pertuzumab (including trastuzumab pre-treated patients) based on real-world observations, patients may still benefit from T-DM1 at 2L [46,74] or later LoT [49,60,63,79]. Real-world studies also indicate better outcomes when T-DM1 is used in earlier LoT [45,50,69], suggesting T-DM1 should be initiated following relapse on 1L or 2L HER2-directed therapy rather than later in the treatment sequence. Further evidence from both trials and real-world studies support the use of T-DM1 in patients with BM/CNS metastasis [31,33,43–45]; The observed mPFS in real-world studies (6.0–7.0 months) [44,45,60] and clinical trials (5.5–6.9 months) [31,33,43] were consistent. However, both trial and real-world data indicate that survival outcomes were better for patients without BM [33,44,45,60]. Of note, results of the phase 3 trial of T-DXd suggest that, where available, T-DXd may be a better option in patients with BM [27].

With regards to safety of T-DM1 regimen, safety data from real-world studies [45–47,49–52,56,59,61,63,64,66–68,77–79] and clinical trials [26,28–30,32–36,38–43] were consistent in terms of types of grade 3 or worse AEs, with the most frequently reported being hematological AEs (thrombocytopenia, neutropenia, anemia) and liver toxicity/dysfunction. Other non-hematological AEs such as fatigue and nausea occurred less frequently. Thrombocytopenia emerged as a source of concern that needs attention with the incidence ranging from 2.5% to 40.4% and 1.2% to 29.0% were reported from the clinical trials [26,29,30,33,34,36,38–43] and RWE studies [45,46,49–52,59,61,63,64,66,68,77–79] respectively. A geographical variation in thrombocytopenia incidence was also noted, with considerably lower rates (2% to 8%) reported in studies conducted in the US and Europe [35,45,46,51,66,68] compared to those from Asia (12.8% to 29.0%) [49,52,59,61,63,64,77,79]. The observation may reflect regional differences in patient management, such as more proactive approaches to thrombocytopenia prevention and treatment in the US and Europe.

Overall, the analyzed evidence base demonstrated the efficacy and safety of T-DM1 within its licensed indication in the real-world setting. Despite the superior efficacy demonstrated with T-DXd and other emerging therapies [81,82], the clinical role of T-DM1 remains relevant due to its continued widespread global use, driven by factors such as accessibility, affordability in low- and middle-income settings, safety profile, and patient-specific therapeutic considerations. T-DM1 retains clinical relevance in settings where newer ADCs are unavailable, inaccessible, or contraindicated.

A comparison with previously published SLRs emphasizes the novelty and relevance of this review. Martin Huertas *et al.* (2021) [18] exclusively reviewed observational studies on T-DM1 monotherapy, excluding clinical trials and combination therapies, limiting the breadth of patient populations and treatment contexts assessed. Similarly, Zhang *et al.* (2021) and Yeh *et al.* (2022) focused exclusively on RCTs, thus excluding valuable real-world insights and broader applicability to diverse patient scenarios [15,17]. Omarini *et al.* (2021) [19] combinedly analyzed both clinical trials and real-world studies and confined their analysis to patients pre-treated with trastuzumab and pertuzumab, thus narrowing their population scope relative to our comprehensive assessment of both pertuzumab-naïve and pre-treated populations. Lastly, Liu *et al.* (2024) [16] incorporated RCTs and non-randomized trials but broadened their focus to include early-stage and locally advanced breast cancer, reducing specificity to metastatic disease and limiting their applicability to advanced stage settings.

In contrast, our review's strength lies in its comprehensive synthesis across a broader range of study designs (both clinical trials and observational studies). Additionally, our inclusion criteria encompass a wider spectrum of patients; those with varying degrees of prior HER2-targeted therapies, brain metastasis status, and distinct regional contexts, thereby enhancing the external validity and applicability of the findings. Furthermore, unlike the earlier reviews, our SLR explicitly analyzes subgroup variations by geographic regions, providing insights into population-specific efficacy and safety outcomes, particularly regarding thrombocytopenia incidence, which revealed important regional differences.

This review has however several limitations reflecting potential shortcomings in the identified literature. The trials were largely conducted in heavily pre-treated patients, and prior treatments might

not reflect current treatment landscape which limits application to current clinical practice. Additionally, there are limitations inherent to real-world studies including heterogeneity in the patient population and the fact that these studies are not powered to demonstrate differences between treatment groups. Furthermore, we kept the comparison between studies as simple due to the diverse regimens and variable LoTs used in different studies. The limited follow-up, particularly in real-world studies also meant that OS data were not reported and/or may not be mature. Absence of OS and safety data in some studies also indicate the existence of some evidence gap. Only EMILIA trial, with a median follow-up of 47.8 months, reported long-term outcomes. Furthermore, the present analysis focused mainly on efficacy and safety data, without incorporating quality-of-life outcomes, which limits a comprehensive understanding of the long-term benefits of T-DM1. Given the methodological limitations and heterogeneity across studies – including differences in design, baseline patient characteristics (e.g., presence of brain metastases), lines of therapy, and comparators – a formal meta-analysis was not conducted, which restricts the ability to draw robust conclusions. Instead, the data were summarized descriptively. A large proportion of the included studies (83.3%, 35/42) demonstrated a high to serious risk of bias, primarily due to limitations in study design and potential confounding factors. These methodological limitations may have influenced the robustness and reliability of the reported findings.

Conclusion

The findings from this review collectively demonstrate that T-DM1 can be an effective therapeutic option for the treatment of HER2-positive mBC in the 2L or later setting and has an acceptable safety profile. T-DM1 may be preferable to regimens that do not include HER2-directed therapy and should be considered as early as possible in the treatment sequence, including in patients with BM, particularly when T-DXd is not a treatment option due to cost or availability. However, further research is warranted.

Conflict of Interest

All authors declare that they have no conflicts of interest.

Acknowledgement

The authors would like to express their sincere gratitude to all colleagues who contributed to this study.

Author Contributions

All authors contributed significantly to the work. Their specific roles are outlined as follows – Conceptualization: Kunal Jain, Rajinder Chawla and Amit Kishore; Data Curation: Bivek Shah, Amit Kishore; Formal Analysis: Bivek Shah, Amit Kishore; Investigation: Bivek Shah; Methodology: Bivek Shah, Amit Kishore; Project Administration: Rajinder Chawla, Amit Kishore; Software: Bivek Shah, Amit Kishore; Supervision: Rajinder Chawla, Amit Kishore; Validation: Amit Kishore, Kunal Jain; Visualization: Bivek Shah, Amit Kishore; Writing – Original Draft: Bivek Shah, Sola Lawal, Kunal Jain, Amit Kishore; Writing – Review and Editing: Kunal Jain, Rajinder Chawla, Sola Lawal, Amit Kishore.

Supplementary Information

Supplementary Table S1. Search strategies for (A) PubMed, (B) Embase and (C) Cochrane database.

Supplementary Table S2. Eligibility criteria for identification of relevant literature.

Supplementary Table S3. Other grade AEs with T-DM1 in pivotal HER2-positive advanced/metastatic breast cancer clinical trials.

Supplementary Table S4. Other grade AEs with T-DM1 in pivotal HER2-positive advanced/metastatic breast cancer in real-world studies.

Supplementary Figure S1. ROB 2.0 based risk of bias assessed in Randomized studies as (A) traffic plot and (B) unweighted summary bar plot.

Supplementary Figure S2. ROBINS-I based risk of bias assessed in non-Randomized studies as (A–C) traffic plots and (D) unweighted summary bar plot.

Appendix A. Quality assessment using Cochrane ROB 2.0

Appendix B. Quality assessment using Cochrane ROBINS-I.

References

- Schlam I, Tarantino P, Waks A, Tolaney SM. Tailoring the Treatment of Early-stage HER2-positive Breast Cancer: One Size Does Not Fit All. *Breast Cancer.* 2023;19(1):11–16.
- Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Guidelines Committee. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol.* 2021 Dec;32(12):1475–95.
- NCCN. NCCN Clinical Practice Guidelines in Oncology, Breast Cancer. v4 2023, March 2023, Available at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf Accessed Sept 2023.
- Roche GmbH. Herceptin (trastuzumab) SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/herceptin-epar-product-information_en.pdf. Accessed December 2023.
- Roche GmbH. Perjeta (pertuzumab) SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/perjeta-epar-product-information_en.pdf. Accessed December 2023.
- Li N, Yang L, Zhao Z, Du T, Liang G, Li N, et al. Antibody-drug conjugates in breast cancer: current evidence and future directions. *Exp Hematol Oncol.* 2025 Mar 20;14(1):41.
- Roche GmbH. Kadcyla (ado-trastuzumab emtansine) SmPC Setp 2018 Available at: https://www.ema.europa.eu/en/documents/product-information/kadcyla-epar-product-information_en.pdf Accessed Sept 2023.
- Daiichi Sankyo Europe GmbH. ENHERTU® (fam-trastuzumab deruxtecan-nxki). Prescribing information. July 2023. available at: https://www.ema.europa.eu/en/documents/product-information/enherthu-epar-product-information_en.pdf Accessed Sept 2023.
- Novartis. Tyverb (Lapatinib) SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/tyverb-epar-product-information_en.pdf. Accessed December 2023.
- Schettini F, Conte B, Buono G, De Placido P, Parola S, Griguolo G, et al. T-DM1 versus pertuzumab, trastuzumab and a taxane as first-line therapy of early-relapsed HER2-positive metastatic breast cancer: an Italian multicenter observational study. *ESMO Open.* 2021 Apr;6(2):100099.
- Im SA, Gennari A, Park YH, Kim JH, Jiang ZF, Gupta S, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with metastatic breast cancer. *ESMO Open.* 2023 Jun;8(3):101541.
- FDA approves new treatment option for patients with HER2-positive breast cancer who have progressed on available therapies [press release]. 2019.
- Jelovac D, Emens LA. HER2-directed therapy for metastatic breast cancer. *Oncology (Williston Park).* 2013 Mar;27(3):166–75.
- Stanowicka-Grada M, Senkus E. Anti-HER2 Drugs for the Treatment of Advanced HER2 Positive Breast Cancer. *Curr Treat Options Oncol.* 2023 Nov;24(11):1633–50.
- Zhang X, Leng J, Zhou Y, Mao F, Lin Y, Shen S, et al. Efficacy and Safety of Anti-HER2 Agents in Combination With Chemotherapy for Metastatic HER2-Positive Breast Cancer Patient: A Network Meta-Analysis. *Front Oncol.* 2021 Aug 19;11:731210.
- Liu F, Li Y, Yang D, Tang L, Yang Q, Jiang M, et al. Meta-analysis of the clinical efficacy and safety of T-DM1 in the treatment of HER2-positive breast cancer. *Indian J Cancer.* 2024 Jan 1;61(1):146–55.
- Yeh Y, Chen C, Ko Y. Effectiveness and cost-effectiveness of trastuzumab emtansine in women with HER2-positive locally advanced or metastatic breast cancer: A systematic review and meta-analysis. *J Cancer Res Ther.* 2022 Jul-Sep;18(4):1061–72.
- Martin Huertas R, Fernández Abad M, Corral de la Fuente E, Serrano Domingo JJ, Martínez Jáñez N. Prolonged Responses With Trastuzumab Emtasine Treatment of Human Epidermal Growth Factor Receptor 2-positive Metastatic Breast Cancer Refractory to Trastuzumab and Pertuzumab: Systematic Review of Evidence. *Clin Breast Cancer.* 2021 Oct;21(5):391–8.
- Omarini C, Piacentini F, Sperduti I, Cerma K, Barbolini M, Canino F, et al. T-DM1 efficacy in trastuzumab-pertuzumab pre-treated HER2 positive metastatic breast cancer patients: a meta-analysis. *BMC Cancer.* 2022 Jun 7;22(1):623.
- Shamseer L, Moher D, Clarke M, Ghera D, Liberati A, Petticrew M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015 Jan 2;350:g7647.
- AccuScreener. Accessed at: <https://accuscript.ai/>, accessed on 23rd May 2024. Accessed May 26, 2024.
- SymproAI. An artificial intelligence based systematic literature management and processing software. Available at: <https://sympro.ai/>
- Higgins JP, Savović J, Page MJ, Sterne JA. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). *Cochrane Handbook for Systematic Reviews of Interventions.* Published August 22, 2019.
- Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *bmj.* 2016;355.
- Cortés J, Im SA, Iwata H, Hamilton EP, Hurvitz SA, Egorov A, et al. “236P Subgroup analysis by disease history and prior treatments of patients (pts) with HER2-positive (HER2+) metastatic breast cancer (MBC) from DESTINY-Breast03, a randomized phase III study of trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1).” *Annals of Oncology* 33 (2022): S645–46.
- Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet.* 2023 Jan 14;401(10371):105–17.

27. Hurvitz SA, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer patients with brain metastases from the randomized DESTINY-Breast03 trial. *ESMO Open.* 2024 May;9(5):102924.
28. Im S-A, Xu B, Kim S-B, Chung W-P, Park YH, Kim M-H, et al. PS2-1 Trastuzumab deruxtecan vs T-DM1 in HER2+ mBC in Asian subgroup: Results of the randomized phase 3 study DESTINY-Breast03." *Annals of Oncology* 33 (2022): S464–65.
29. Diéras V, Miles D, Verma S, Pegram M, Welslau M, Baselga J, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2017 Jun;18(6):732-42. doi: 10.1016/S1470-2045(17)30312-1. Epub 2017 May 16. Erratum in: *Lancet Oncol.* 2017 Aug;18(8):e433.
30. Im SA, Park I, Sohn JH, Im YH, Lee SC, Chang HK, et al. "284P Trastuzumab emtansine (T-DM1) in Asian patients with previously treated HER2-positive locally advanced (LA) or metastatic breast cancer (MBC): data from the phase III EMILIA study." *Annals of Oncology* 32 (2021): S488–89.
31. Krop IE, Lin NU, Blackwell K, Guardino E, Huober J, Lu M, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol.* 2015 Jan;26(1):113–19.
32. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012 Nov 8;367(19):1783–91.
33. Montemurro F, Delaloge S, Barrios CH, Wuerstlein R, Anton A, Brain E, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial. *Ann Oncol.* 2020 Oct;31(10):1350–58.
34. Wuerstlein R, Ellis P, Montemurro F, Antón Torres A, Delaloge S, Zhang Q, et al. Final results of the global and Asia cohorts of KAMILLA, a phase IIIb safety trial of trastuzumab emtansine in patients with HER2-positive advanced breast cancer. *ESMO Open.* 2022 Oct;7(5):100561.
35. Burris HA 3rd, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol.* 2011 Feb 1;29(4):398–405.
36. Gupta M, Wang B, Carrothers TJ, LoRusso PM, Chu YW, Shih T, et al. Effects of Trastuzumab Emtansine (T-DM1) on QT Interval and Safety of Pertuzumab Plus T-DM1 in Patients With Previously Treated Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. *Clin Pharmacol Drug Dev.* 2013 Jan;2(1):11–24.
37. Kashiwaba M, Ito Y, Takao S, Doihara H, Rai Y, Kanatani K, et al. A multicenter Phase II study evaluating the efficacy, safety and pharmacokinetics of trastuzumab emtansine in Japanese patients with heavily pretreated HER2-positive locally recurrent or metastatic breast cancer. *Jpn J Clin Oncol.* 2016 May;46(5):407–14.
38. Krop IE, Kim SB, Martin AG, LoRusso PM, Ferrero JM, Badovinac-Crnjevic T, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol.* 2017 Jun;18(6):743–54.
39. Krop IE, LoRusso P, Miller KD, Modi S, Yardley D, Rodriguez G, et al. A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. *J Clin Oncol.* 2012 Sep 10;30(26):3234–41.
40. Wang X, Li W, Yin Y, Tong Z, Zhang Q, Zheng H, et al. Primary results of ELAINA: a randomized, multicenter, open-label, phase III study of the efficacy and safety of trastuzumab emtansine vs. lapatinib plus capecitabine in Chinese patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy. *Transl Breast Cancer Res.* 2023 Jan 31;4:3.
41. Watanabe J, Ito Y, Saeki T, Masuda N, Takano T, Takao S, et al. Safety Evaluation of Trastuzumab Emtansine in Japanese Patients with HER2-Positive Advanced Breast Cancer. *In Vivo.* 2017 May-Jun;31(3):493–500.
42. Wildiers H, Meyskens T, Marréaud S, Lago LD, Vuylsteke P, Curigliano G, et al. Long term outcome data from the EORTC 75111–10114 ETF/BCG randomized phase II study: Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer, followed by T-DM1 after progression. *Breast.* 2022 Aug;64:100–111.
43. Yardley DA, Krop IE, LoRusso PM, Mayer M, Barnett B, Yoo B, et al. Trastuzumab Emtansine (T-DM1) in Patients With HER2-Positive Metastatic Breast Cancer Previously Treated With Chemotherapy and 2 or More HER2-Targeted Agents: Results From the T-PAS Expanded Access Study. *Cancer J.* 2015 Sep-Oct;21(5):357–64.
44. Fabi A, Alesini D, Valle E, Moscetti L, Caputo R, Caruso M, et al. T-DM1 and brain metastases: Clinical outcome in HER2-positive metastatic breast cancer. *Breast.* 2018 Oct;41:137–43.
45. Fabi A, De Laurentiis M, Caruso M, Valle E, Moscetti L, Santini D, et al. Efficacy and safety of T-DM1 in the 'common-practice' of HER2+ advanced breast cancer setting: a multicenter study. *Oncotarget.* 2017 Mar 18;8(38):64481–89.
46. Fabi A, Giannarelli D, Moscetti L, Santini D, Zambelli A, Laurentiis M, et al. Ado-trastuzumab emtansine (T-DM1) in HER2+ advanced breast cancer patients: does pretreatment with pertuzumab matter? *Future Oncol.* 2017 Dec;13(30):2791–97.
47. Acibuca A, Sezer A, Yilmaz M, Sumbul AT, Demircan S, Muderrisoglu IH, et al. Cardiotoxicity of trastuzumab emtansine (T-DM1): a single-center experience. *J Int Med Res.* 2021 Dec;49(12):3000605211053755.
48. Al Rabadi LS, Cook MM, Kaempf AJ, Saraceni MM, Savin MA, Mitri ZI. Ado-trastuzumab for the treatment of metastatic HER2-positive breast cancer in patients previously treated with Pertuzumab. *BMC Cancer.* 2021 Oct 27;21(1):1150.
49. Baek SK, Jeong JH, Jung K, Ahn HK, Kim MH, Sohn J, et al; Korean Cancer Study Group (KCSG). A nationwide real-world study for evaluation of effectiveness and safety of T-DM1 in patients with HER2-positive metastatic breast cancer in Korea (KCSG BR19-15). *Ther Adv Med Oncol.* 2024 Jan 28;16:17588359231225029.
50. Bahçeci A, Paydaş S, Ak N, Ferhatoğlu F, Saip PM, Seydaoğlu G, et al. Efficacy and Safety of Trastuzumab Emtansine in Her2 Positive Metastatic Breast Cancer: Real-World Experience. *Cancer Invest.* 2021 Jul-Aug;39(6-7):473–81.
51. Battisti NML, Rogerson F, Lee K, Shepherd S, Mohammed K, Turner N, et al. Safety and efficacy of T-DM1 in patients with advanced HER2-positive breast cancer The Royal Marsden experience. *Cancer Treat Res Commun.* 2020;24:100188.

52. Bian L, Li F, Ji C, Li J, Yuan Y, Zhang H, et al. ADC vs HP dual-antibody for HER2-positive advanced breast cancer after failed to TKI. *J Clin Oncol.* 2023;41:e13036.
53. Audi Blotta D, Gomes JR, Moreira SB, Colosimo DF, Araujo J, Cavalcanti Gonçalves Ferreira C, et al. Real-world outcomes of long-term efficacy of T-DM1 after discontinuation due to limiting toxicity in patients with HER2-positive metastatic breast cancer. *J Clin Oncol.* 2023;41:e13034.
54. Conte B, Fabi A, Poggio F, Blondeaux E, Dellepiane C, D'Alonzo A, et al; Gruppo Italiano Mammella (GIM) study group. T-DM1 Efficacy in Patients With HER2-positive Metastatic Breast Cancer Progressing After a Taxane Plus Pertuzumab and Trastuzumab: An Italian Multicenter Observational Study. *Clin Breast Cancer.* 2020 Apr;20(2):e181–7.
55. Daniels B, Kiely BE, Tang M, Houssami N, Lord SJ, Pearson SA. Trastuzumab emtansine for HER2-positive metastatic breast cancer: Outcomes from a whole-of-population Australian cohort. *Breast.* 2021 Aug;58:106–12.
56. Prete SD, Montella L, Arpino G, Buono G, Buonerba C, Dolce P, et al. Second line trastuzumab emtansine following horizontal dual blockade in a real-life setting. *Oncotarget.* 2020 Jun 2;11(22):2083–91.
57. Joshua Z Drago, Patricia R Pereira, Anton Safonov, Antonio Marra, Yi Rao, Bo Liu, et al; Abstract P2-13-19: Statin modulation of antibody drug conjugate activity in breast cancer models and patients. *Cancer Res* 15 February 2022; 82 (4_Supplement): P2–13–19.
58. Dzimitrowicz H, Berger M, Vargo C, Hood A, Abdelghany O, Raghavendra AS, et al. T-DM1 Activity in Metastatic Human Epidermal Growth Factor Receptor 2-Positive Breast Cancers That Received Prior Therapy With Trastuzumab and Pertuzumab. *J Clin Oncol.* 2016 Oct 10;34(29):3511–17.
59. Gogia A, Gupta A, Deo SV, Sharma D, Mathur S. Safety, efficacy and survival outcome of Ado-trastuzumab emtansine (T-DM1) in patients with metastatic HER2-positive breast cancer: An Indian experience. *J Clin Oncol.* 2022;40:e13008.
60. Hardy-Werbin M, Quiroga V, Cirauqui B, Romeo M, Felip E, Teruel I, et al. Real-world data on T-DM1 efficacy - results of a single-center retrospective study of HER2-positive breast cancer patients. *Sci Rep.* 2019 Sep 4;9(1):12760.
61. He M, Zhao W, Wang P, Li W, Chen H, Yuan Z, et al. Efficacy and safety of Trastuzumab Emtansine in treating human epidermal growth factor receptor 2-positive metastatic breast cancer in Chinese population: a real-world multicenter study. *Front Med (Lausanne).* 2024 Apr 29;11:1383279.
62. Hsieh W, Chang CL. Retrospective observational study of outcomes in HER2-positive metastatic breast cancer patients treated with trastuzumab emtansine in single center. *JCO Glob Oncol.* 2023;9:15.
63. Ji C, Li F, Yuan Y, Zhang H, Bian L, Zhang S, et al. Novel Anti-HER2 Antibody-Drug Conjugates Versus T-DM1 for HER2-Positive Metastatic Breast Cancer After Tyrosine Kinase Inhibitors Treatment. *Oncologist.* 2023 Oct 3;28(10):e859–66.
64. Li F, Xu F, Li J, Wang T, Bian L, Zhang S, et al. Pyrotinib versus trastuzumab emtansine for HER2-positive metastatic breast cancer after previous trastuzumab and lapatinib treatment: a real-world study. *Ann Transl Med.* 2021 Jan;9(2):103.
65. Lupichuk S, Cheung WY, Stewart D. Pertuzumab and Trastuzumab Emtansine for Human Epidermal Growth Factor Receptor-2-Positive Metastatic Breast Cancer: Contemporary Population-Based Outcomes. *Breast Cancer (Auckl).* 2019 Oct 9;13:1178223419879429.
66. Martinez-Garcia J, Boix AP, Henarejos PS, Lucas MJ, Saura AS, Luengo M, et al. 291P Trastuzumab emtansine in HER2-positive metastatic breast cancer after pertuzumab and trastuzumab: TDM1RM Study. *Annals of Oncology.* 2020 Sep 1;31:S358.
67. Martins CH, Pereira MV, Rocha JM, Oliveira C, Peixoto M, Rodrigues JR, et al. PR128 TRANSTUZUMAB EMTANSINE IN HER-2 POSITIVE METASTATIC BREAST CANCER: A RETROSPECTIVE STUDY IN A PORTUGUESE CENTRAL HOSPITAL. *The Breast.* 2023 Oct 1;71:S59–60.
68. Michel LL, Bermejo JL, Gondos A, Marmé F, Schneeweiss A. T-DM1 as a New Treatment Option for Patients with Metastatic HER2-positive Breast Cancer in Clinical Practice. *Anticancer Res.* 2015 Sep;35(9):5085–90.
69. Michel LL, Hartkopf AD, Fasching PA, Kolberg HC, Hadji P, Tesch H, et al. Progression-Free Survival and Overall Survival in Patients with Advanced HER2-Positive Breast Cancer Treated with Trastuzumab Emtansine (T-DM1) after Previous Treatment with Pertuzumab. *Cancers (Basel).* 2020 Oct 17;12(10):3021.
70. Migeotte A, Dufour V, van Maanen A, Berliere M, Canon JL, Taylor D, et al. Impact of the line of treatment on progression-free survival in patients treated with T-DM1 for metastatic breast cancer. *BMC Cancer.* 2021 Nov 11;21(1):1204.
71. Moinard-Butot F, Saint-Martin C, Pflumio C, Carton M, Jacot W, Cottu PH, et al. Efficacy of trastuzumab emtansine (T-DM1) and lapatinib after dual HER2 inhibition with trastuzumab and pertuzumab in patient with metastatic breast cancer: Retrospective data from a French multicenter real-life cohort. *Breast.* 2022 Jun;63:54–60.
72. Noda-Narita S, Shimomura A, Kawachi A, Sumiyoshi-Okuma H, Sudo K, Shimoi T, et al. Comparison of the efficacy of trastuzumab emtansine between patients with metastatic human epidermal growth factor receptor 2-positive breast cancers previously treated with combination trastuzumab and pertuzumab and with trastuzumab only in Japanese population. *Breast Cancer.* 2019 Jul;26(4):492–8.
73. Peters S, Tang HC, Shafiq T, Karim S, Khan S, Trivedi S, et al. A UK Real-world Evaluation of Efficacy and Toxicity of Second-line Trastuzumab Emtansine and Third-line Trastuzumab Deruxtecan in HER2-positive Advanced Breast Cancer. *Clinical Oncology.* 2023 Jun 1;35(6):e419.
74. Pizzuti L, Krasniqi E, Sperduti I, Barba M, Gamucci T, Mauri M, et al. PANHER study: a 20-year treatment outcome analysis from a multicentre observational study of HER2-positive advanced breast cancer patients from the real-world setting. *Ther Adv Med Oncol.* 2021 Nov 29;13:17588359211059873.
75. Sanglier T, Shim J, Lamarre N, Peña-Murillo C, Antao V, Montemurro F. Trastuzumab emtansine vs lapatinib and capecitabine in HER2-positive metastatic breast cancer brain metastases: A real-world study. *Breast.* 2023 Jun;69:441–50.
76. Silva D, Duarte H, Leite-Silva P, Ferro JF, Prospero I, Barbosa D, et al. Is T-DM1 cardiotoxicity close monitoring relevant in palliative breast cancer patients? A single center experience using equilibrium radionuclide ventriculography (ERNV). *European Journal of Nuclear Medicine and Molecular Imaging.* 2023 Sep 1;50(Suppl 1):S617.
77. Tataroglu Ozyukseler D, Basak M, Ay S, Koseoglu A, Arici S, Oyman A, et al. Prognostic factors of ado-trastuzumab emtansine treatment in patients with metastatic HER-2 positive breast cancer. *J Oncol Pharm Pract.* 2021 Apr;27(3):547–54.
78. Vici P, Pizzuti L, Michelotti A, Sperduti I, Natoli C, Mentuccia L, et

- al. A retrospective multicentric observational study of trastuzumab emtansine in HER2 positive metastatic breast cancer: a real-world experience. *Oncotarget.* 2017 May 25;8(34):56921–31.
79. Yeo W, Luk MY, Soong IS, Yuen TY, Ng TY, Mo FK, Chan K, Wong SY, Tsang J, Leung C, Suen JJ, Ngan RK. Efficacy and tolerability of trastuzumab emtansine in advanced human epidermal growth factor receptor 2-positive breast cancer. *Hong Kong Med J.* 2018 Feb;24(1):56–62.
80. Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al; DESTINY-Breast03 Trial Investigators. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med.* 2022 Mar 24;386(12):1143–54.
81. Modi S, Jacot W, Iwata H, Park YH, Vidal Losada M, Li W, et al. Trastuzumab deruxtecan in HER2-low metastatic breast cancer: long-term survival analysis of the randomized, phase 3 DESTINY-Breast04 trial. *Nat Med.* 2025 Dec;31(12):4205–13.
82. Schettini F, Nucera S, Pascual T, Martínez-Sáez O, Sánchez-Bayona R, Conte B, et al. Efficacy and safety of antibody-drug conjugates in pretreated HER2-low metastatic breast cancer: A systematic review and network meta-analysis. *Cancer Treat Rev.* 2025 Jan;132:102865.