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Galaxy Publication

Real-World Evidence on Trastuzumab–Deruxtecan in Metastatic HER2-Positive and HER2-Low Breast Cancer

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ABSTRACT

Trastuzumab–deruxtecan (T-DXd), an innovative antibody-drug conjugate, has markedly boosted survival rates and clinical outcomes for individuals with advanced HER2-positive/HER2-low breast cancer, as evidenced by randomized controlled trials, alongside a tolerable toxicity profile. Findings from these trials provide essential insights for routine patient care, including populations often ineligible for trial participation due to strict entry criteria. Through this narrative review, we summarize and critically appraise published real-world investigations on T-DXd therapy in metastatic breast cancer (MBC) patients expressing HER2-positive or HER2-low status, focusing on clinically relevant scenarios. A PubMed query revealed nine published real-world analyses of T-DXd. These retrospective cohorts involved a combined total of 7146 patients. Furthermore, 5/9 investigations encompassed HER2-low MBC cases. Patients typically exhibited extensive tumor involvement, commonly affecting lungs and liver. Key topics explored include individuals with multiple prior treatments, reduced performance status, comparisons between HER2-positive and HER2-low subtypes, central nervous system metastases, geriatric populations, interstitial lung disease risks, general tolerability, and treatment dose adaptations. This evaluation validates the therapeutic effectiveness of T-DXd reported in everyday practice settings and highlights an advantageous tolerability profile with adverse events that can be effectively managed.

Keywords: Trastuzumab–deruxtecan, Metastatic breast cancer, HER2-positive, HER2-low.

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Introduction

Breast cancer (BC) stands as the second leading malignancy and the fourth primary contributor to cancer deaths across the globe [1]. Amplification or overexpression of human epidermal growth factor receptor 2 (HER2) affects as many as 20% of breast cancer instances, linking to greater tumor aggressiveness and inferior outcomes [2]. Metastatic breast cancer (MBC), though responsive to therapy, is generally not curable, showing a 5-year overall survival (OS) rate of just 31% [3]. Recent years have seen the emergence of advanced anti-HER2 treatments that have considerably enhanced prognosis for patients with either HER2-positive or HER2-low MBC [4] **(Figure 1).**

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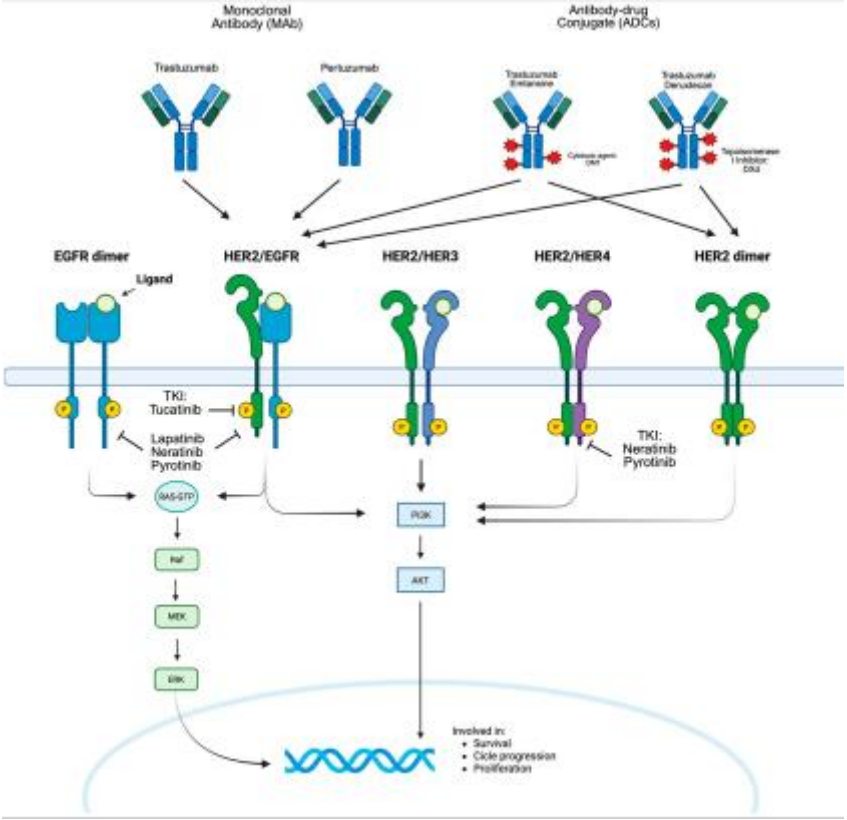

Figure 1. The illustration depicts the manner in which external growth stimuli and internal signaling cascades drive cellular division. It specifically outlines members of the epidermal growth factor receptor family, alongside licensed medications targeting HER2-positive breast cancers and their specific action mechanisms. Figure modified from BioRender, with authorization (Created in BioRender. Luelli, F. (2025) https://BioRender.com/w47f0s6 (accessed on 15 June 2025)).

Dual HER2-directed monoclonal antibodies—trastuzumab and pertuzumab—paired with taxane chemotherapy form the cornerstone first-line regimen, delivering a median progression-free survival (mPFS) of 18.7 months in untreated HER2-positive MBC cases and a median OS (mOS) of 56.5 months [5]. After progression on initial therapy, antibody-drug conjugates (ADCs) become the favored strategy. Approval for Trastuzumab–deruxtecan (T-DXd) in this line stemmed from the striking findings of the DESTINY-Breast03 study [6]. This advanced ADC outperformed the prior-generation trastuzumab emtansine (T-DM1), registering a mPFS of 28.8 months (95% CI: 22.4–37.9) against 6.8 months (range: 5.6–8.2), while median OS remained unreached in both groups (95% CI: 40.5 months–not estimable versus 34.0 months–not estimable). Other trials have additionally confirmed the notable potency of T-DXd in multiple settings **(Table 1)** [6-10].

Table 1. Randomized phase III clinical trials of T-DXd published in metastatic breast cancer.

Characteristic	DESTINY-Breast 01 [7]	DESTINY-Breast 02 [8]	DESTINY-Breast 03 [6]	DESTINY-Breast 04 [9]	DESTINY-Breast 12 [10]
Study phase & design	Phase II, open-label, single-arm	Phase III, open-label, randomized (2:1)	Phase III, open-label, randomized (1:1)	Phase III, open-label, randomized (2:1)	Phase IIIb/IV, open-label, single-arm with two cohorts
Line of therapy	≥3	≥3	Second-line	≥2 (1–2 prior lines)	≥2
Treatment arms	T-DXd (post–T-DM1)	T-DXd vs physician's choice (TPC)	T-DXd vs T-DM1	T-DXd vs TPC	T-DXd
Primary endpoint(s)	Objective response rate (ORR)	Progression-free survival (PFS)	PFS	PFS	PFS, ORR

Secondary endpoints	PFS, overall survival (OS), response rate, duration of response	OS, ORR, duration of response (DoR), safety	OS, ORR, safety	OS (HR+ subgroup and overall population), ORR, safety	(CNS) PFS, ORR, time to second progression, (CNS) ORR, new symptomatic brain metastases, time to progression (TTP), DoR, OS, safety
Visceral metastases	91.8%	78%	70%	—	—
Bone-only disease	—	—	—	—	With BM: 36.9%; without BM: 35.3%
Liver metastases	54.9%	—	—	70%	With BM: 22.1%; without BM: 27.4%
Brain metastases	13%	18%	15.6%	6.4%	52.2%
Age <65 years	—	79.8%	79.8%	76.5%	—
Age ≥65 years	23.9%	20.2%	20.2%	23.5%	—
Median age	—	54.8 years	54.4 years	57 years	With BM: 52 years; without BM: 54 years
HER2 IHC 3+	83.7%	80%	88.9%	—	With BM: 71.1%; without BM: 58.5%
HER2 IHC 2+	15.2%	19%	10.4%	—	With BM: 0.8%; without BM: 2.1%
HER2-low (IHC 2+)	—	—	—	42%	—
HER2-low (IHC 1+)	—	—	—	58%	—
HER2 1+/2+, ISH-positive	15.2%	—	—	—	—
HER2 status unknown	1.1%	—	<1%	—	—
Median prior treatment lines	6	2	2	3	With BM: >1 metastatic line
Hormone receptor–positive (HR+)	52.7%	59%	50%	88.7%	With BM: 62.7%; without BM: 62.2%
Hormone receptor–negative (HR−)	45.1%	41%	50%	11.3%	—
HR status unknown	2.2%	—	—	—	—

Abbreviations: BM, brain metastasis; CNS, central nervous system; DoR, duration of response; HR, hormone receptor; ISH, in situ hybridization; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RR, response rate; T-DXd, trastuzumab–deruxtecan; T-DM1, trastuzumab emtansine; TPC, physician choice of treatment; TTP, time to progression; \\, no data available.

Direct comparative trials have established that T-DXd outperforms treatment with trastuzumab or lapatinib plus capecitabine, recording a median progression-free survival of 17.8 months against 6.9 months and median overall survival of 39.2 months against 26.5 months [8]. A viable alternative in second- or third-line settings, notably for individuals with brain metastases, involves tucatinib—a tyrosine kinase inhibitor—administered alongside trastuzumab and capecitabine, as validated by the HER2CLIMB study [11, 12]. This triplet therapy yielded notable improvements in progression-free and overall survival over trastuzumab-capecitabine alone, both overall (median PFS 7.6 versus 4.9 months; median OS 24.7 versus 19.2 months) and among those with brain involvement (median OS 18.1 months). Further evidence from the DESTINY-Breast12 study examined T-DXd in patients with HER2-positive metastatic breast cancer who had brain metastases [10, 13]. In this group, progression-free survival at 12 months was 61.6% (95% CI: 54.9–67.6), and central nervous system progression-free survival at 12 months reached 58.9% (95% CI: 51.9–65.3), confirming meaningful, lasting control both systemically and intracranially, thus justifying T-DXd employment in pretreated HER2-positive cases irrespective of brain metastasis.

Additionally, favorable data have surfaced for HER2-low disease, classified as immunohistochemistry score 1+ or 2+ without amplification on in situ hybridization [9]. Results from DESTINY-Breast04 indicated that, in hormone receptor-positive cases, T-DXd extended median PFS to 10.1 months versus 5.4 months for treatment of physician's choice (hazard ratio [HR] = 0.51; $p < 0.001$) and median OS to 23.9 versus 17.5 months (HR = 0.64; $p = 0.003$). For the full cohort, median PFS was 9.9 versus 5.1 months (HR = 0.50; $p < 0.001$), while overall survival reached 23.4 versus 16.8 months (HR = 0.64; $p = 0.001$). While substantial progression-free survival benefits have proven reliable throughout the DESTINY-Breast program in every analyzed subgroup—unaffected by stratification or baseline traits—there persists a critical demand to investigate populations displaying more varied clinical conditions and concomitant illnesses typical of standard oncology care.

The objective of this review is to gather current real-world evidence on T-DXd utilization across metastatic breast cancer encompassing HER2-positive and HER2-low expressions, informed by outcomes from published randomized studies.

Materials and Methods

Within this narrative review, we present and appraise available real-world reports addressing T-DXd application in metastatic breast cancer with HER2-positive or HER2-low status, delivering focused critical commentary on scenarios holding particular clinical significance. Attention is also directed toward the agent's toxicity pattern among broader, non-selected cohorts. Literature retrieval relied mainly on PubMed owing to its broad scope in biomedical publications. Relevant papers through July 2025 were located via combinations of keywords and MeSH headings linked to "trastuzumab deruxtecan," "metastatic breast cancer," and "real-world studies." Employed search elements included: "trastuzumab deruxtecan", "metastatic breast cancer" or "advanced breast cancer"; "real-world evidence" or "observational study" or "registry" or "real-world study" or "real-life studies". Initial searches imposed no language barriers, though solely English publications were ultimately selected. To maximize coverage and limit bias from publication practices, bibliographies of chosen works and pertinent overviews were manually reviewed for supplementary references. Studies qualified for inclusion if they documented efficacy endpoints, tolerability data, or administration trends for T-DXd among adult metastatic breast cancer patients in routine practice; involved participants aged ≥18 years; appeared in English; and were released in the preceding 10 years. Works were excluded if they constituted preclinical experiments, controlled interventional trials, case series of under 10 individuals, conference abstracts, reviews devoid of new data, or non-English texts.

Results and Discussion

Real-world studies

A total of nine real-world investigations examining T-DXd for metastatic breast cancer have been published **(Table 2)** [14-22]. Eight of these were multicenter retrospective analyses, with one conducted at a single institution. The patient groups and treatment positions varied widely across reports. Altogether, 7146 individuals participated in these analyses. Participants had an average age of 57 years and had all completed at least three systemic regimens before receiving T-DXd. Five of the nine reports also enrolled cases with HER2-low disease. The majority of cases involved extensive tumor spread, commonly to pulmonary and hepatic regions. Just one report concentrated solely on individuals with central nervous system involvement [21]. The chief endpoint in nearly all investigations was therapeutic efficacy, determined through overall response rate or response classifications (complete response, partial response, stable disease, progressive disease), apart from the work by Joudain *et al*. (primary focus on overall survival) and that by Nakajima *et al*. (which measured efficacy via overall survival, progression-free survival, and 24-month overall survival) [17, 18]. Tolerability assessment was a secondary focus throughout.

Table 2. Real-world analyses of T-DXd application in metastatic breast cancer.

Author (Ref.) Study design Patients (N) / Mean age	Prior systemic therapies	Treatment line	HER2-low population	Metastatic involvement	Efficacy outcomes	Any-grade toxicity	Grade 3–4 toxicity
Petit *et al.*, 2023 [14] Retrospective, multicenter 459 / 58 years	2 lines: 21.1%3 lines: 19.6%4 lines: 14.2%5 lines: 14.6%≥6 lines: 30.5%Median (range): 4	NA	IHC 2+/ISH−: 1 (0.2%)IHC 2+/ISH NA: 3 (0.7%)IHC 1+/ISH NA: 1 (0.2%)Total: 1.1%	Bone: 57.3%Lymph nodes: 51.6%Lung: 36.2%Liver: 33.1%Brain: 28.1%Other: 15.3%Cutaneous/subcutaneous: 13.9%	iORR: 35.7%iPD: 5.4%ORR: 56.7%PD: 12.1%	Nausea: 20.2%Fatigue: 12.1%Vomiting: 6.5%Neutropenia: 4.5%Anemia: 4%Diarrhea: 3.5%Alopecia: 2.5%Constipation: 0.5%	ILD: 4.5%Infections/infestations: 4.5%Nausea: 2.5%
Botticelli *et al.*, 2024 [15] Retrospective, multicenter 143 / 66 years	0 lines: 4 (3%)1 line: 16 (11%)2 lines: 42 (29%)≥3 lines: 81 (57%)	NA	NA	Visceral: 59%Brain: 2.5%	CR: 6%DCR: 93%ORR: 68%PD: 7%PR: 62%SD: 25%	Nausea: 32%Fatigue: 20%Neutropenia: 20%Platelet reduction: 8%Anemia: 6%Alopecia: 6%Elevated liver enzymes: 5%ILD: 2%Diarrhea: 1%	Neutropenia: 10%ILD: 2%Anemia: 0.6%Nausea: 1.3%Diarrhea: 0.5%Fatigue: 0%Platelet reduction: 0%Alopecia: 0%Liver enzymes increase: 0%
Fountzilas *et al.*, 2024 [16] Retrospective, multicenter 312 / 51 years	1 line: 14 (4.5%)2 lines: 70 (22.5%)≥3 lines: 227 (73%)	≥3: 227 (73%)	49.2%	Liver: 47.2%Lung: 36.1%Bone: 36.1%Nodes: 27.8%Brain: 23.5%	CBR: 55.6%ORR: 29.2%PFS: 5.7 months	Fatigue: 28.2%Nausea: 25.8%Vomiting: 13.9%Leukopenia: 9.9%Anemia: 8.7%Diarrhea: 8.3%ILD: 6.7%Neutropenia: 5.9%Infection: 1.6%Dizziness: 1.6%Stomatitis: 1.2%	Fatigue: 1.6%Leukopenia: 1.6%Nausea: 1.6%Neutropenia: 1.6%Vomiting: 1.6%ILD: 1.2%Anemia: 0.8%Diarrhea: 0.8%
Jourdain *et al.*, 2024 [17] Retrospective, multicenter 5890 / 59 years	0 lines: 95 (1.6%)1 line: 1109 (18.8%)2 lines: 1796 (30.5%)3 lines: 1356 (23%)≥4 lines: 1534 (26%)	NA	44.5%	Digestive: 43.2%Brain: 25.4%	HER2-positive: mOS 30.2 monthsHER2-low: mOS 16.8 months	HER2-positive: hematologic 7.2%; headache/pain/fatigue 6.9%; neurologic 3.1%; ascites 1.7%; nausea/vomiting 1.4%HER2-low: hematologic 8.1%; headache/pain/fatigue 7.1%; ascites 3.3%; neurologic 1.4%; nausea/vomiting 1.2%	NA

Nakayama *et al.*, 2024 [18] Retrospective, multicenter 104 / NA	0–2 lines: 24%≥3 lines: 76%	NA	NA	Brain: 100%Visceral: 76%	OS: all NRActive BM: 27 monthsOverall: 14.6 monthsActive BM: 13.2 months24-month OS: 56%TTF: 9.3 months	NA	ILD: 23.1%
Fabi *et al.*, 2025 [19] Retrospective, multicenter 39 / 55 years (35–72)	0 lines: 5.1%1 line: 38.5%2 lines: 25.6%3 lines: 20.5%>4 lines: 10.3%	0: 5.1%1: 30.8%2: 20.5%3: 20.5%>4: 23.2%	0	Brain: 100%	iCRr: 69.2% (6 mo)iCRr: 59% (12 mo)iDCR: 94.9%iDoR: 11.9 monthsiORR: 59%iPFS: 15.6 monthsOS: NRmPFS: 11.8 months	Alopecia: 59%Fatigue: 53.8%Nausea: 46.1%Neutropenia: 35.9%Constipation: 30.7%Diarrhea: 28.2%Anemia: 23.1%Vomiting: 10.2%LVEF decrease: 2.5%	Fatigue: 18%Neutropenia: 15.3%Diarrhea: 10.2%Nausea: 7.7%Anemia: 5.1%Mucositis: 5.1%Thrombocytopenia: 2.5%Transaminase increase: 2.5%Pneumonitis: 2.5%Vomiting: 2.5%
Bizarro *et al.*, 2025 [20] Retrospective, multicenter 100 / 53.9 years	1: 10%2: 52%3: 15%4: 6%5: 6%6: 6%7: 5%	≥3	NA	Visceral: 72%Nodes: 69%Bone: 61%Liver: 56%Lung: 54%Brain: 21%Skin: 21%	CBR: 80%CR: 8%ORR: 44%mPFS: 13 monthsPD: 20%PR: 36%SD: 36%	Nausea: 49%Neutropenia: 37%Alopecia: 34%	Not specified: 16%
Lazarotos *et al.*, 2025 [21] Retrospective, single-center 38 / 57 years	<4 lines: 42.1%≥4 lines: 57.9%	NA	60.5%	Bone: 68.4%Lung: 50%Liver: 47.4%Brain: 39.5%	CR: 9%OS: 14 monthsPFS: 10 monthsPD: 18.4%PR: 63%SD: 13.2%HER2-positive: CR 20%, PD 13.3%, PR 33.3%, SD 20%HER2-low: CR 0%, PD 21.7%, PR 56.5%, SD 8.7%	Nausea/vomiting: 63%Fatigue: 55.6%Diarrhea: 25.9%Alopecia: 18.5%Neuropathy: 18.5%Neutropenia: 14.8%Pneumonitis: 14.8%Anemia: 7.4%Thrombocytopenia: 7.4%	Unspecified grade 3: 15.8%Grade 4: 0%
Sang *et al.*, 2025 [22] Retrospective, multicenter 61 / 55 years	0–1 lines: 22.95%2–3 lines: 45.9%≥4 lines: 31.15%	NA	47.5%	Visceral: 85.25%Liver: 55.74%Lung: 49.18%Brain: 27.87%	HER2-low: ORR 37.93%, DCR 79.31%, PFS 10.51 mo, PD 20.69%, PR 37.93%, SD 41.38%, TTR 1.28 moHER2-positive: ORR 62.50%, DCR 87.5%, PFS 10.18 mo, PD 12.5%, PR 56.25%, SD 25%, TTR 1.31 mo	Nausea: 78.69%Anorexia: 73.77%Leukopenia: 34.43%Anemia: 29.51%Alopecia: 22.95%Vomiting: 19.67%Diarrhea: 14.75%Thrombocytopenia: 14.75%Constipation: 9.84%Pneumonia: 1.64%	Leukopenia: 8.20%Anemia: 6.56%Thrombocytopenia: 1.64%

Abbreviations: AI aromatase inhibitor; CBR clinical benefit rate; CR, complete response; DCR, disease control rate; ICBr, clinical benefit rate at 6 and 12 months; iDCR, intracranial disease control rate; iDoR, intracranial duration of response; ILD, interstitial lung disease; iORR, intracranial overall response rate; iPD, intracranial progression disease; iPFS, intracranial progression free survival; mo: months; mOS, median

overall survival; mPFS, median progression free survival; NA, not available; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTF, time-to-treatment failure.

Heavily pretreated patients

Six reports specifically explored T-DXd effectiveness among patients with multiple previous therapies. The earliest analysis, by Fountzilas *et al*., included 312 cases: 72.4% received T-DXd, 19.2% sacituzumab govitecan, and 8.3% both drugs [16]. In HER2-positive cases, 12-month progression-free survival stood at 69.6% (95% CI, 61.4% to 79%), with comparable median progression-free survival whether given in first/second line or third line and beyond (17.31 months, 95% CI, 11.21 months to non-estimable versus 15.27 months, 95% CI, 11.79 to 22.04 months; HR 1.07 [95% CI, 0.71 to 1.61]; p = 0.752). For HER2-low cases in this cohort, 12-month progression-free survival was 36.5% (95% CI, 28.6% to 46.5%), and median progression-free survival proved longer with earlier positioning (11.56 months, 95% CI, 9.72–17.71 versus 6.34 months, 95% CI, 4.37–17.31; HR 0.47 [95% CI, 0.29–0.81]; p = 0.006). The respective 12-month rates for early versus later use were 51.3% (95% CI, 39.5% to 66.8%) and 35.7% (95% CI, 18.5% to 69.1%).

Botticelli *et al*. analyzed 143 cases, administering T-DXd in first, second, third, or later lines for 3%, 11%, 29%, and 57% of participants, respectively [15]. The median number of prior metastatic regimens was 4 (range 1 to 11). Earlier administration showed a promising progression-free survival advantage (17 versus 15 months; p = 0.098), though overall response rates remained similar (72% versus 67%; p = 0.88). These patterns mirror observations from DESTINY-Breast01 and DESTINY-Breast02, despite differing pretreatment levels. In the DE-REAL analysis, early-line use was uncommon, yet results approached DESTINY-Breast03 standards: 12-month progression-free survival 75.2%, 12-month overall survival 94.1%, and overall response rate 79%.

Sang *et al*. described 61 participants [22], with T-DXd mostly positioned late (third/fourth line: 28 patients [45.9%]; beyond fourth: 19 patients [31.15%]). Cases with ≤1 prior chemotherapy achieved unreached median progression-free survival (95% CI, 1.58–not estimable), versus 10.51 months (95% CI, 1.64–not estimable) for >1 prior chemotherapy.

Bizarro *et al*. evaluated 100 women with metastatic disease, each having ≥2 prior advanced therapies [20]. T-DXd positioning was third line in 52%, fourth in 15%, and fifth or later in 23%. Later use correlated with diminished overall response rate (44%) relative to pivotal studies like DESTINY-Breast02 (70%), although clinical benefit rate reached 80%. Median progression-free survival was 13 months (95% CI: 10–16 months), with 12-month progression-free survival at 54%.

Petit *et al*. conducted a real-world analysis involving 459 patients with metastatic breast cancer who received T-DXd through a temporary authorization program in France [14]. These individuals had undergone a median of 4 previous treatment regimens in the metastatic setting (range 2–22). Prior to study entry, 81.7% had undergone radiotherapy, and 76.5% had surgery. Among 160 participants with assessable lesions, the overall response rate reached 56.7%, while 12.1% showed disease progression.

The most recent report by Lazarotos *et al*. described 38 extensively pretreated cases [21]. Participants had completed a median of four therapeutic lines (range 1–12) before T-DXd initiation. Of 33 assessable individuals, 21 (63.6%) achieved a response, comprising 3 complete responses (9.1%) and 18 partial responses (54.5%). Five patients (15.2%) maintained stable disease, whereas seven (21.2%) progressed.

Overall, these investigations uniformly highlight the strong anticancer effects of T-DXd in patients with multiple prior therapies, including those with notable comorbidities and extensive tumor involvement—groups frequently underrepresented in controlled randomized studies. This supports T-DXd as a valuable choice even in challenging everyday clinical situations involving numerous previous treatments. Notably, the extent of prior anti-HER2 exposure does not appear to substantially reduce responsiveness in HER2-positive metastatic breast cancer. This implies that resistance developed from earlier regimens may not completely abolish the drug's effectiveness. Rather, response seems more dependent on inherent tumor characteristics, especially HER2 expression levels on cell surfaces and the cells' baseline sensitivity to the payload DXd.

Poor ECOG PS patients

The ECOG Performance Status (PS) scale is a widely adopted tool in oncology to measure a patient's level of functioning and capacity for routine tasks. It spans from 0 (completely asymptomatic and active) to 5 (deceased). This metric plays a key role in treatment planning and prognostic evaluation [23].

Among the nine real-world reports reviewed here, only five provided details on patients' ECOG PS, which was generally good (0–2) for most participants.

Nakayama and colleagues presented updated findings from the ROSET-BM study, encompassing 104 HER2-positive metastatic breast cancer cases with brain metastases and/or leptomeningeal involvement. This cohort also featured individuals with worse functional status: 26% ECOG PS 0, 51.9% ECOG PS 1, 11.5% ECOG PS 2, and 3.8% ECOG PS 3–4 [18]. Analysis revealed that various baseline variables—such as leptomeningeal disease, elements of the Graded Prognostic Assessment (GPA) including age, brain metastasis count, extracranial disease, ECOG PS, plus additional aspects (HER2 status, IHC, estrogen receptor, concurrent steroids, prior surgery, and treatment sequence)—did not emerge as predictors of overall survival.

Petit *et al*. enrolled cases up to ECOG PS 3 (36.4% ECOG PS 0, 54% ECOG PS 1, 9.2% ECOG PS 2, and 0.4% ECOG PS 3) [14]. The two patients with ECOG PS 3 received a lower starting dose of T-DXd (4.4 mg/kg) rather than the standard 5.4 mg/kg. No adverse events linked to performance status were noted, and efficacy data for this group were not detailed.

Sang *et al*. incorporated both HER2-positive and HER2-low cases [22]. Participants were categorized by baseline ECOG PS (68.85% scored 0–1; 31.15% scored 2–4), with 40% of HER2-positive individuals having ECOG PS 2 and less favorable features overall. Those with higher PS received reduced starting doses, though subgroup-specific efficacy results were not provided.

Fabi *et al*. restricted inclusion to ECOG PS 0–2 (30.8% ECOG PS 0, 51.3% ECOG PS 1, 17.9% ECOG PS 2) [19]. However, no breakdown of T-DXd effectiveness by performance status was presented. Bizzaro *et al*. reported a median ECOG PS of 1 (range 0–2), again without correlations to treatment outcomes [20].

Collectively, although limited, the evidence regarding T-DXd in patients with compromised ECOG PS is promising. Crucially, no unforeseen toxicities or deterioration of preexisting conditions occurred in this fragile population. These observations indicate that T-DXd could remain a feasible approach for individuals with reduced functional capacity—a cohort commonly barred from registrational studies and minimally represented in the core DESTINY-Breast trials. A striking feature of routine practice is the frequent use of lower initial doses for poorer PS patients, diverging from approved labeling and untested in pivotal trials. This clinician-driven adaptation likely seeks to optimize the risk-benefit ratio in higher-risk scenarios involving frailty, concurrent illnesses, or heavy tumor load. Nevertheless, prospective evidence on dose adjustments for ECOG PS ≥ 2 remains absent, and no definitive recommendations exist on whether reduced starting doses affect efficacy or enhance tolerability.

HER2-Low versus HER2-positive

Four reports from the examined set featured individuals diagnosed with HER2-low metastatic breast cancer. In the earliest contribution from Sang and associates, a direct evaluation of T-DXd's performance and tolerability was performed in a group of Chinese females affected by either HER2-low or HER2-positive conditions [22]. The duration without progression averaged 10.51 months (95% CI, 3.02–not estimable) for HER2-low participants and 10.18 months (95% CI, 3.88–not estimable) for HER2-positive ones. Response frequencies reached 37.93% versus 62.50%, control of illness in 79.31% versus 87.50%, and average interval to observable improvement in 1.28 versus 1.31 months. Full tumor disappearance occurred exclusively in the HER2-positive subset, affecting two cases (6.25%), whereas incomplete shrinkage involved 11 (37.93%) HER2-low and 18 (56.25%) HER2-positive instances; unchanged status in 12 (41.38%) and 8 (25.00%); and advancement in six (20.69%) HER2-low and four (12.50%) HER2-positive cases.

An additional investigation dedicated to cases combining HER2-positive and HER2-low metastatic disease detected no meaningful variation in response frequency across categories, despite a suggestion of prolonged duration without progression favoring HER2-positive individuals that lacked statistical confirmation [21].

The broadest everyday-practice analysis, authored by Jourdain and team, covered 5890 cases: 2010 (34.1%) HER2-positive managed in third sequence, 1260 (21.4%) in second sequence, and 2620 (44.5%) HER2-low [17]. Third-sequence HER2-positive treatment yielded average lifespan of 30.2 months (95% CI, 28.1–33.5) alongside yearly endurance probability of 80.5% (95% CI, 78.7–82.3%). Second-sequence HER2-positive cases lacked a defined average lifespan, registering yearly endurance at 85.6% (95% CI, 83.4–87.9%). HER2-low individuals recorded average lifespan of 16.8 months (95% CI, 14.5–not reached) with yearly endurance of 62.3% (95% CI, 59.7–65.0%). Average duration until regimen cessation spanned 10.8 months (95% CI, 10.4–11.5) for third-sequence HER2-positive, 11.7 months (95% CI, 11.0–12.9) for second-sequence HER2-positive, and 5.6 months (95% CI, 5.5–5.9) for HER2-low. Post-cessation, 58.8% adopted single-agent trastuzumab (594/1011) while 18.9% chose pill-based cytotoxics (191/1011). Second-sequence HER2-positive displayed extended average interval to next regimen at 14.6 months (95% CI, 13.8–16.4), chiefly single trastuzumab (45.4%, 189/416). HER2-

low averaged 8.4 months to next regimen (95% CI, 8.1–8.7), favoring pill cytotoxics (48.7%, 399/819) and sacituzumab govitecan (38.7%, 317/819). Multi-factor regression pinpointed advanced years, multiple previous regimens, visceral or central nervous system spread, prompt cancer detection, and concurrent illnesses as mortality enhancers. Both categories noted heightened inpatient stays for breathing, gut, and blood-related issues after T-DXd commencement, possibly stemming from advanced illness, accompanying conditions, and general cancer vulnerability rather than solely the medication.

Fountzilas and collaborators assessed 122 HER2-low alongside 128 HER2-positive metastatic cases [16]. T-DXd delivered noteworthy benefit in HER2-low malignancy, albeit inferior to HER2-positive counterparts. Yearly duration without progression hit 36.5% (interquartile range [IQR], 28.6–46.5) in HER2-low versus 69.6% (IQR, 61.4–79.0) in HER2-positive. As anticipated, prompt T-DXd deployment in HER2-low extended duration without progression over delayed (11.56 months, 95% CI 9.72–17.71 versus 6.34 months, 95% CI 4.37–17.31; HR 0.47 [95% CI 0.29–0.81]; p = 0.006). Yearly rates for prompt versus delayed stood at 51.3% (95% CI 39.5–66.8%) and 35.7% (95% CI 18.5–69.1%). HER2-positive sustained 69.6% yearly duration without progression (95% CI 61.4–79.0%), showing minimal average variation by sequence (17.31 months, 95% CI 11.21–not estimable versus 15.27 months, 95% CI 11.79–22.04; HR 1.07 [95% CI 0.71–1.61]; p = 0.752).

In summary, available observations reveal T-DXd's capacity to stabilize illness in HER2-low cases, though with lesser response intensity, briefer gains, and swifter shifts to options like sacituzumab govitecan or pill cytotoxics. These variances reflect fundamental biological distinctions, likely driven by variable HER2 quantities affecting binding and conjugate potency. Consistently, prompt incorporation (first or second sequence) linked to superior HER2-low results. This informs sequencing choices: T-DXd viability spans lines, but peak HER2-low advantage may hinge on early adoption. By comparison, antecedent anti-HER2 interventions scarcely blunt T-DXd potency in HER2-positive illness, upholding reliability in advanced sequences.

Brain metastasis

Published estimates indicate 30–50% of HER2-positive breast cancer cases ultimately manifest central nervous system spread, owing to extended lifespan via modern anti-HER2 approaches plus superior detection through contemporary scans. Central nervous system territory remains formidable, given blood-brain barrier hindrance to numerous therapeutics, including cytotoxics and directed agents, yielding diminished outlook for involved patients. Conventional handling emphasized regional modalities—full-brain irradiation (WBRT), focused beam (SRT), precise surgery (SRS), and operative removal—although rising publications validate antibody-drug conjugate utility and acceptability in metastatic breast cancer featuring central nervous system lesions. Initial insights from single-arm DEBBRAH highlighted favorable internal and external control by T-DXd in varied pretreated subsets: post-local stabilized lesions, silent untreated ones, and advancing post-local disease [24]. Single-arm phase 2 TUXEDO reported 73.3% internal response in HER2-positive metastatic cases [25]. DESTINY-Breast12 outcomes affirmed marked, enduring whole-body and central nervous system gains with T-DXd in HER2-positive breast cancer harboring central nervous system lesions, independent of baseline stabilized or progressing state [10] **(Table 1).**

oncerning real-world evidence, every study incorporated patients presenting with brain metastases. The investigation conducted by Fabi *et al*. was dedicated exclusively to individuals with brain metastases [19]. In this particular study, the main outcome measure was the intracranial objective response rate (iORR). Additional outcome measures encompassed intracranial and overall progression-free survival (iPFS—gPFS), along with intracranial disease control rate (iDCR), duration of intracranial response (iDoR), clinical benefit rate at 6 and 12 months (iCBr), overall survival (OS), and tolerability. The analysis involved 39 patients, yielding an iORR of 59%, iPFS of 15.6 months, gPFS of 11.8 months, iDCR of 94.9%, iDoR of 11.9 months, and iCBr of 69.2% at 6 months and 59% at 12 months. Overall survival had not been reached, with 77.9% of patients remaining alive at 12 months. Efficacy results showed no dependence on prior treatment lines, and the regimen demonstrated an acceptable safety profile. Median PFS did not differ between patients who underwent local therapy for brain metastases and those who did not (15.8 versus 15.6 months, p = 0.45).

A separate investigation focused on patients with HER2-positive metastatic breast cancer (MBC) complicated by brain metastases and/or leptomeningeal involvement (ROSET-BM trial) [18]. This report provided updated efficacy findings from an earlier publication and encompassed 104 patients in total [26]. Most participants had asymptomatic brain metastases (72 patients, 69.2%) and had undergone local therapy (99 patients, 95.2%), leaving only 5 patients (4.8%) without local treatment for brain metastases. Local interventions consisted primarily of

stereotactic radiotherapy (SRT) in 64 patients (61.5%) and whole-brain radiotherapy (WBRT) in 56 patients (53.8%). The median PFS reached 14.6 months, while median OS was not attained, with a 24-month OS rate of 56.0%. Subgroup evaluation indicated a median PFS of 13.2 months among patients with active brain metastases, 17.5 months among those with leptomeningeal carcinomatosis, and not reached among those with stable brain metastases (corresponding 24-month PFS rates were 32.7%, 25.1%, and 60.8%, respectively). Median OS stood at 27.0 months for patients with active brain metastases and was not reached for those with leptomeningeal carcinomatosis or stable brain metastases (24-month OS rates were 52.0%, 61.6%, and 71.6%, respectively).

In the analysis by Fountzilas *et al*., 59 patients (23.5%) harbored brain metastases upon commencing T-DXd, and this cohort achieved a median PFS of 13.24 months (considering either extracranial or intracranial progression) [16]. During T-DXd administration, central nervous system progression was documented in 10 patients (18.5%), including 7 (16.7%) with HER2-positive disease and 3 (25%) with HER2-low disease.

In the report by Sang *et al*., brain metastases were present in 7 (24.14%) patients with HER2-low disease and 10 (31.25%) with HER2-positive disease [22]. The objective response rate was 28.6%, and over half of the responding patients displayed HER2-low status. For individuals with HER2-positive MBC and brain metastases, those treated with three or fewer prior regimens exhibited prolonged PFS (reaching 10.55 months, 95% CI, 6.37–NE). Conversely, those exposed to more than three previous lines showed markedly reduced median PFS (reaching 3.88 months; 95% CI, 1.81–10.18). An analogous pattern emerged in patients with HER2-low MBC.

In the trial reported by Lanzarotos *et al*., 15 patients with central nervous system (CNS) metastases were enrolled, all of whom had received local treatment (radiation and/or surgery) before starting T-DXd [21]. Among them, 10 patients (66.7%) underwent brain radiotherapy alone, while 5 (33.3%) received both surgery and brain radiotherapy. Prior to T-DXd initiation, 6 of 15 patients (40%) had experienced progression of brain lesions despite earlier local therapy; responses included complete response in 2 patients (13.3%), partial response in 7 (46.7%), stable disease in 1 (6.7%), and progressive brain/leptomeningeal disease in 1 (6.7%). Objective response rates showed no meaningful difference between HER2-positive and HER2-low subgroups. Two patients free of brain metastases at baseline developed leptomeningeal disease while on T-DXd (5.3%). Among those with brain involvement, median PFS was not reached and median OS was 420 days, without notable differences in PFS or OS according to HER2 status. Furthermore, no significant disparities in PFS or OS emerged between patients with versus without brain metastases.

Another large cohort study included 1079 patients with HER2-positive breast cancer (BC) and 419 patients with HER2-low BC who had brain metastases [17]. Multivariate Cox regression analysis confirmed brain metastases as an independent prognostic factor for both overall survival and cause-specific hospitalization, alongside comorbidities.

In the extensive trial led by Petit and colleagues, among 57 patients with assessable intracranial tumors, 35.7% achieved complete or partial intracranial response, whereas 5.4% demonstrated progression [14].

In the investigation by Botticelli *et al*., brain involvement was noted in 36 patients (25%), though specific outcomes for this subset were not detailed separately [15].

Overall, these findings suggest that, in everyday clinical settings, locoregional therapies—including surgery or radiation—continue to represent the standard first-line management for brain metastases in HER2-positive breast cancer prior to commencing T-DXd. This practice aligns with existing guidelines focused on achieving intracranial control and relieving neurologic symptoms before systemic treatment. Nevertheless, growing data indicate that, in carefully selected patients lacking active brain metastases, locoregional procedures can be safely postponed, enabling earlier initiation of T-DXd. Such an approach could reduce treatment-associated complications while preserving robust systemic disease control. It appears especially suitable for individuals with stable or previously treated brain lesions under close surveillance for intracranial progression. Notably, real-world evidence repeatedly confirms strong efficacy of T-DXd even when central nervous system involvement is present. Patients receiving T-DXd achieve substantial disease control and symptomatic relief, demonstrating the agent's activity beyond extracranial sites. Additionally, no novel or unforeseen toxicities have emerged in these observational settings, supporting the consistent favorable safety profile seen in pivotal trials. These observations reinforce the expanding role of T-DXd as an essential systemic option for HER2-positive breast cancer patients with brain metastases, emphasizing the importance of personalized therapeutic strategies. Upcoming investigations should focus on defining the ideal timing and integration of locoregional and systemic treatments to optimize outcomes, alongside further evaluating long-term safety and effectiveness of T-DXd in this challenging population.

Elderly

The elderly population unquestionably warrants particular consideration in oncology care and when introducing novel therapies, given the inherent vulnerability often seen in these individuals. The ongoing TREX-Old retrospective multicenter European registry is dedicated to assessing T-DXd toxicity in patients aged ≥70 years [27]. Although the study remains active, only interim findings have been released thus far. From the analyses reviewed here, limited specific data are available for this age group. In the investigation by Fountzilas *et al*., no notable differences emerged in grade 3/4 adverse events, dose reduction frequencies, or treatment discontinuation rates between patients younger than 70 years and those aged ≥70 years [16]. Journain and colleagues reported that their real-world cohort treated with T-DXd was older compared to participants in pivotal randomized trials, with median ages of 60 years for HER2-positive cases and 61 years for HER2-low cases [17]. Moreover, 13.8% of patients had cardiovascular comorbidities (either active or monitored), despite exclusion of active cardiac disease in the randomized studies. Diabetes and respiratory disorders affected 9.6% and 7.6% of the cohort, respectively. These observations imply that T-DXd can be administered safely to older individuals without excessive risk of severe toxicities. Nonetheless, the retrospective design and possible selection bias—favoring healthier elderly patients for treatment—should be acknowledged. Dedicated prospective trials incorporating thorough geriatric evaluations are essential to validate these results and inform clinical decision-making.

Interstitial lung disease (ILD)

Interstitial lung disease (ILD) encompasses a spectrum of disorders characterized by inflammation and fibrosis of pulmonary tissue, potentially compromising gas exchange. ILD represents a recognized and potentially grave toxicity associated with T-DXd. In phase III randomized trials, ILD occurred in roughly 12.0% of patients, predominantly low-grade events (13.6%, 10.4%, and 15.2% in DESTINY-Breast01, -Breast02, and -Breast03, respectively) [6-8].

In the real-world analysis by Fountzilas *et al*., ILD developed in 17 patients (6.7%), with grade 3/4 events in 1.2% [16]. Affected patients had received a median of four prior treatment lines (excluding T-DXd) before ILD onset. Imaging follow-up via computed tomography (CT) occurred at median intervals of 13 weeks. Median time from T-DXd start to ILD diagnosis was 4.58 months (IQR 2.48–8 months). Hospital admission for pneumonitis was needed in 9 patients (56.2%), and resolution occurred in 15/17 cases (88.2%) following corticosteroid therapy. Dose adjustments were required in three patients (1.2%), and permanent discontinuation of T-DXd occurred in eight patients. In two cases with grade 2 ILD, rechallenge with T-DXd after resolution was successful without recurrence. One potentially ILD-related death was recorded in a patient on T-DXd.

Across additional reports, ILD rates were 2% in the Botticelli *et al*. study, 3.7% in the Petit *et al*. study, and 10% in the Sang *et al*. study, with no fatalities attributed to ILD [14, 15, 22].

In the Nakayama *et al*. investigation, ILD affected 23.1% of patients and was the leading cause of T-DXd discontinuation [18]. Median time to ILD onset was 5.3 months (95% CI 4.0, 8.8). Grade 1 ILD predominated (14 cases, 13.5%), exceeding higher grades (grade 2: 3 cases, 2.9%; grade 3: 5 cases, 4.8%; grade 4: 2 cases, 1.9%). No deaths related to ILD were reported.

In the analysis conducted by Bizarro *et al*., interstitial lung disease (ILD) of any grade was documented in 12% of participants (of whom 3% experienced grade 3 or higher) [20]. For any-grade ILD cases, oral corticosteroid treatment was administered to seven patients (58%), and intravenous corticosteroids to five patients (42%). One individual progressed despite receiving invasive mechanical ventilation and subsequently succumbed.

In the investigation by Lazarotos and colleagues, pneumonitis/ILD was identified in four participants, leading to permanent cessation of T-DXd in three cases (7.9%) because of grade 2 pneumonitis/ILD [21].

In the report from Jourdain *et al*., ILD emerged in 36 individuals (1.1%) with HER2-positive breast cancer and in 23 individuals (0.9%) with HER2-low breast cancer. Severity grading was not detailed, but hospitalization occurred in 1.1% of instances [17].

To summarize, ILD constitutes an acknowledged and noteworthy adverse reaction that is integrated into the risk mitigation strategy for T-DXd. Evidence from routine clinical practice indicates fluctuating ILD rates, yet these do not surpass the frequencies seen in registrational randomized studies. An increasing body of literature also outlines practical approaches to handling this complication. Rigorous patient oversight remains critical to avert severe-grade ILD, particularly by employing routine CT imaging and swift assessment of incipient pulmonary symptoms. In line with established toxicity management protocols, irreversible termination of T-DXd is indicated

for ILD reaching grade 2 or above [28]. Reinstating therapy might be contemplated for individuals who encountered grade 1 or 2 ILD, possibly incorporating dose alterations to achieve an acceptable risk-benefit equilibrium.

Safety and dose modifications

Toxicity data were captured in every examined study apart from the Nakayama *et al*. publication, which exclusively detailed ILD occurrence. Predominant side effects encompassed fatigue (roughly 9%), nausea (roughly 5%), and neutropenia (roughly 8%), whereas grade 3–4 occurrences were infrequent **(Table 2).** Rates of hair loss displayed considerable variation across investigations, from as low as 2.5% in the Petit *et al*. series to as high as 59% in the Fabi *et al*. series [14, 19]. These discrepancies could stem from differences in patient populations and, especially, the nature of antecedent therapies.

In the Botticelli *et al*. cohort, both the overall frequency of adverse reactions and the proportion of high-grade events were inferior to figures from registered trials [15]. Notably, even with an elevated median patient age, the team documented diminished myelosuppression (including anemia and neutrophil reductions) relative to randomized trial benchmarks, alongside reduced nausea and vomiting. Contributing elements might involve under-capture of adverse reaction frequency and intensity in observational designs; enhanced prophylactic and therapeutic measures for T-DXd-associated effects in daily practice, informed by trial outcomes; and greater utilization of dose attenuation in observational contexts owing to more adaptable guidelines, thereby mitigating toxicity severity. Moreover, patient-reported symptoms in non-interventional research may suffer from incomplete documentation in charts, a phenomenon already highlighted in prior reports [29]. Interestingly, response rates proved equivalent irrespective of the presence of any-grade adverse effects (67% versus 68%, $p = 0.74$) or when contrasting mild versus severe toxicities (68% versus 66%, $p = 0.63$).

In the Sang *et al*. cohort, decisions regarding starting dose were influenced by ECOG performance status, body weight, and socioeconomic factors, resulting in reduced initial dosing for the majority (54 patients, 88.52%), with subsequent modifications in 5 patients (8.20%) prompted by gastrointestinal or hematologic complications [22]. Side effects manifested in 59 participants, predominantly nausea affecting 48 (78.69%), reduced appetite in 45 (73.77%), leukopenia in 21 (34.43%), anemia in 18 (29.51%), hair loss in 14 (22.95%), vomiting in 12 (19.67%), diarrhea in 9 (14.75%), thrombocytopenia in 9 (14.75%), and constipation in 6 (9.84%).

In the cohort described by Bizarro and colleagues, toxicities of any severity were noted in 83 female participants [20]. Leading complaints included nausea in 49 cases (49%), neutropenia in 37 (37%), and alopecia in 34 (34%). Events of grade 3 or worse involved 16 individuals, distributed as neutropenia in 10 (10%), fatigue in 3 (3%), and ILD in 3 (3%). Declines in ejection fraction of any degree occurred in 5% of the population. Toxicity prompted dose lowering or therapy cessation in 46 participants (46%).

In the Petit *et al*. series, toxicities arose in 97 of 459 recipients, including 41 classified as serious [14]. A total of thirteen fatalities were logged (three deemed treatment-associated, nine unrelated, and one indeterminate). The treatment-linked deaths comprised: profound deterioration in performance with neurologic compromise and cachexia; combined pulmonary and cardiac issues (distinct from ILD); and unavailable details for the remaining case. Frequently encountered toxicities were nausea (grade 1–2: 17.7%, grade ≥ 3: 5.5%), neutropenia (grade 1–2: 4.5%), fatigue (grade 1–2: 10.1%), and appetite loss (grade 1–2: 2.5%, grade ≥ 3: 0.5%). Of the 459 enrolled, the intended regimen was full dose for 452 (98.5%) and a one-level reduction (4.4 mg/kg) for 6, attributable to hepatic abnormalities (n = 2), low body mass (n = 1), prior toxicity alongside comorbidities (n = 1), and ECOG PS 2 (n = 1). A further patient received a planned 3.2 mg/kg dose due to intolerance of earlier chemotherapies. Therapy was halted in 39 cases owing to tumor advancement (n = 14), mortality (n = 13), patient decision (n = 4), toxicity (n = 3), mixed progression/toxicity/patient choice (n = 1), and miscellaneous (n = 2). End-of-therapy documentation was provided for seventeen instances (twelve absent), while dose alterations were noted in twenty-one (eleven absent).

The investigation by Jourdain and colleagues revealed elevated rates of hospitalization among both HER2-positive and HER2-low cohorts for respiratory, gastrointestinal, and hematological issues following the start of T-DXd, relative to the preceding interval [17]. Nevertheless, hospital admissions might not be wholly attributable to T-DXd itself, but could also stem from the progressive metastatic condition and concomitant health issues. Given the characteristics of the database employed, the investigators could not access details regarding treatment

administration, adverse reactions, therapy cessation, or tumor advancement. Furthermore, no dose adjustments were documented in response to toxic effects.

In the Lazarotos study, treatment discontinuation due to grade 2 pneumonitis occurred in only 3/38 patients, while 14 experienced delays in drug administration and 12 underwent dose reductions owing to side effects. The specifics of the reduced dosing regimen were not detailed in the publication [21].

To summarize, across the evaluated investigations, T-DXd exhibited a tolerable safety profile, with the majority of side effects aligning with those characteristic of antibody–drug conjugates and those documented in pivotal randomized studies. The predominant non-ILD adverse reactions encompassed gastrointestinal complaints (including nausea, vomiting, and loss of appetite), blood-related anomalies (particularly neutropenia and anemia), and fatigue. Such reactions are typically mild to moderate in intensity and frequently amenable to supportive interventions or dose alterations. That said, notable constraints are apparent. Substantial discrepancies in reporting adverse reactions—for instance, alopecia frequencies spanning 2.5% to 59%—point to irregularities in data gathering and underscore the inherent difficulties of observational study formats. Incomplete reporting, lack of uniform toxicity assessment, and deficient recording represent persistent problems, probably resulting in an understatement of actual toxicity incidence. In addition, routine clinical adaptations, such as common upfront dose tailoring or reductions (for example, in frail patients or those with poorer ECOG performance status), diverge from protocols in registrational trials. These modifications might lessen toxicity but hinder direct comparisons of effectiveness. The higher hospitalization rates noted in certain groups additionally highlight the importance of distinguishing therapy-induced impacts from the inherent progression of late-stage illness and associated health burdens.

The emergence of antibody-drug conjugates (ADCs), especially T-DXd, is broadly viewed as among the foremost breakthroughs in contemporary management of HER2-positive breast cancer. ADCs distinctively merge targeted antigen recognition with strong cytotoxic potency, yielding robust and precisely directed therapeutic actions [30]. T-DXd stands as a HER2-directed ADC featuring an elevated drug-to-antibody ratio (DAR), facilitating the targeted release of high levels of its payload—DXd, a powerful topoisomerase I inhibitor—straight into cancer cells. Payload liberation occurs via a stable linker cleaved exclusively by lysosomal enzymes after ADC internalization in the intended cell. Additionally, DXd's ability to permeate cell membranes enables a bystander antitumor effect, allowing impact on neighboring cancer cells irrespective of their HER2 status. This property distinguishes T-DXd from other authorized HER2-targeted ADCs and accounts for its proven effectiveness in HER2-low and heterogeneous neoplasms alongside HER2-positive ones.

The marked enhancement in median progression-free survival seen throughout the DESTINY-Breast series of trials remained uniform across all patient subsets, regardless of grouping criteria or initial features. Multiple active randomized phase III studies are presently investigating T-DXd across diverse metastatic scenarios, with early findings already reported **(Table 3)** [31-34].

Table 3. Ongoing randomized phase III clinical trial with T-DXd in the metastatic breast cancer setting.

Characteristic	DESTINY-Breast 06(Completion expected 2026) [31]	DESTINY-Breast 07(Completion expected 2030) [32]	DESTINY-Breast 08(Completion expected 12/2025) [33]	DESTINY-Breast 09(Completion expected 2029) [34]
Study phase and design	Phase III, open-label, randomized (1:1)	Phase Ib/II	Phase I, non-randomized	Phase III, open-label, interventional, randomized
Line of therapy	≥2nd line (1 or 2 prior lines)	Second line (previous anti-HER2 therapy)	≥2nd line	First line
Treatment regimens	T-DXd compared with investigator's choice chemotherapy in HER2-low and ultra-low, HR-positive patients with disease progression following endocrine therapy	T-DXd administered in combination with other anticancer therapies in HER2-positive metastatic breast cancer	T-DXd-based combinations in HER2-low advanced or metastatic breast cancer	T-DXd plus pertuzumab-matched placebo versus T-DXd plus pertuzumab versus standard treatment (docetaxel or paclitaxel with trastuzumab and pertuzumab)

Primary endpoint(s)	Progression-free survival (PFS)	Adverse events (AEs), safety, and tolerability	Adverse events (AEs) and serious adverse events (SAEs)	PFS
Secondary endpoint(s)	PFS in the intention-to-treat population, overall survival (OS), objective response rate (ORR), duration of response (DoR), and safety	OS, ORR, and PFS	ORR, PFS, DoR, OS, and immunogenicity of T-DXd	OS, ORR, DoR, second progression-free survival (PFS2), pain progression, symptom assessment, tolerability, serum concentrations of T-DXd and pertuzumab, immunogenicity of T-DXd, and safety

Abbreviations: AEs, adverse events; DoR, duration of treatment; HR, hormone receptor; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PFS2, progression free survival to 2° line of treatment; SAEs, serious adverse events; T-DXd, trastuzumab–deruxtecan.

Although treatment recommendations primarily draw from randomized trial evidence, everyday oncology care frequently encounters individuals with more diverse disease manifestations and concomitant conditions. Within this framework, the accumulating real-world data provide essential perspectives on T-DXd's behavior in standard practice. The present work represents the initial published review synthesizing real-world experience with T-DXd in individuals affected by HER2-positive and HER2-low breast cancer. Findings from our review affirm that outcomes in routine settings substantially mirror those from key phase III registrational studies. Predictably, therapeutic potency and effectiveness appear linked to the treatment sequence in which T-DXd is deployed.

For instance, the peak overall response rate (68%) in the HER2-positive subset was described by Botticelli *et al*., whereas the most extended progression-free survival was noted by Bizzaro *et al*. (13 months) and Fabi *et al*. (intracranial PFS 15.6 months) [15, 19, 20]. The strongest overall survival figures came from Jourdain *et al*., reporting a median OS of 30.2 months among HER2-positive cases and 16.8 months among HER2-low cases [17]. Furthermore, treatment effectiveness also appears tied to the degree of HER2 expression, as individuals with HER2-low status exhibited less profound responses, briefer periods of benefit, and faster progression to subsequent regimens compared to those with HER2-positive metastatic breast cancer.

Regarding safety aspects, the toxicities documented in observational studies closely resembled those from registrational trials, with nausea, vomiting, asthenia, and neutropenia ranking as the predominant adverse reactions. The occurrence of interstitial lung disease (ILD) displayed marked variation between investigations, spanning from 1.2% in the Fountzilas *et al*. cohort to 23.1% in the Nakayama *et al*. cohort, emphasizing the necessity for vigilant patient surveillance via routine CT imaging and rapid evaluation of any incipient pulmonary symptoms [16, 18]. No particular subgroup—defined by age, previous therapies, sites of disease, or disease burden—emerged as having distinct risks for efficacy endpoints or toxicities. Furthermore, in individuals with brain metastases, T-DXd exhibited substantial antitumor activity alongside an acceptable tolerability profile, indicating that, in appropriately chosen patients without symptomatic or active intracranial lesions, local treatments could potentially be postponed safely to permit earlier commencement of T-DXd. Although limited information exists for elderly individuals, evidence from the reviewed real-world investigations suggests that T-DXd can be delivered securely to older populations without heightened rates of adverse reactions.

Multiple domains warrant additional investigation. Primarily, refining the application of T-DXd and mitigating its associated toxicities remains crucial. This encompasses establishing protocols for reintroducing therapy in patients who previously developed asymptomatic or completely resolved grade 2 ILD. Moreover, initiatives should target enhanced preventive measures and therapeutic options for T-DXd-related nausea and vomiting, especially those with delayed presentation. To achieve treatment optimization and tailored management, a more structured framework appears essential for discovering dependable predictive biomarkers of response and resistance, in addition to determining the optimal ordering of therapeutic agents to enhance patient outcomes.

Although valuable, observational studies carry inherent constraints. Frequent challenges include absent or partial data, potentially introducing biases and analytical discrepancies, while the retrospective design elevates susceptibility to recall bias and unmeasured confounders. Additionally, comparatively brief observation durations might underrepresent the full scope and frequency of toxicities, particularly delayed-onset events. Further drawbacks involve the absence of randomization, along with non-centralized tumor evaluations and non-uniform

response criteria, which can compromise the uniformity and dependability of efficacy measures due to inter-institutional or inter-observer differences. Patient cohorts, therapeutic protocols, and clinical environments also exhibit considerable diversity, generating variability that hinders result interpretation and broader applicability. Acknowledging these shortcomings in real-world evidence is vital for properly framing observations, delineating the boundaries of such data, and advocating prudent comparisons with randomized trial results. Nonetheless, the alignment between observational outcomes and pivotal trial data bolsters assurance in the effectiveness and tolerability of T-DXd for metastatic breast cancer. Furthermore, real-world investigations capture results in broader, more complicated patient groups—frequently older, with concomitant illnesses or greater disease extent—who are commonly underrepresented in controlled trials and tend to fare worse.

At present, no observational evidence addresses patient-reported outcomes or management of oligometastatic disease, constituting notable deficiencies in current knowledge. Another priority for progress lies in pinpointing biomarkers capable of forecasting response to T-DXd. One encouraging modality under exploration is HER2-directed positron emission tomography (PET), which may facilitate detection of HER2-low metastatic sites and inform customized therapeutic approaches [35].

Given the encouraging results from controlled studies, T-DXd is anticipated to shift toward earlier positions in the treatment algorithm for breast cancer. It is presently under evaluation as first-line therapy in metastatic disease (DESTINY-Breast09) and in adjuvant or neoadjuvant roles for early-stage settings (DESTINY-Breast05 and DESTINY-Breast11). Owing to its robust activity, prolonged exposure periods are foreseeable, highlighting the importance of intensified supportive care to maintain patient well-being.

Conclusion

T-DXd has demonstrated enhanced clinical outcomes for women with metastatic HER2-low or HER2-positive breast cancer. As a comparatively new agent in the armamentarium, substantial lessons can be derived from assessing its application in routine practice, including administration patterns and toxicity handling across centers experienced with the compound. The present review supports a favorable tolerability profile, featuring adverse reactions that are predominantly controllable and seldom necessitate permanent cessation. Nevertheless, ongoing hurdles persist in toxicity mitigation, biomarker discovery, and incorporation into earlier lines of therapy. Overcoming these deficiencies will be critical to optimizing patient advantages and refining individualized approaches within this dynamic field.

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References

1. IARC. WHO. Available online: https://gco.iarc.who.int/today/en/fact-sheets-cancers (accessed on 5 February 2025).
2. Zhu K, Yang X, Tai H, Zhong X, Luo T, Zheng H. HER2-Targeted Therapies in Cancer: A Systematic Review. Biomark Res. 2024;12:16.
3. National Breast Cancer. Available online: https://www.nationalbreastcancer.org/breast-cancer-facts/ (accessed on 5 February 2025).
4. Agostinetto E, Curigliano G, Piccart M. Emerging Treatments in HER2-Positive Advanced Breast Cancer: Keep Raising the Bar. Cell Rep Med. 2024;5:101575.
5. Swain SM, Miles D, Kim SB, Im Y-H, Im SA, Semiglazov V, et al. Pertuzumab, Trastuzumab, and Docetaxel for HER2-Positive Metastatic Breast Cancer (CLEOPATRA): End-of-Study Results from a

Double-Blind, Randomised, Placebo-Controlled, Phase 3 Study. Lancet Oncol. 2020;21:519–30.
6. Hurvitz SA, Hegg R, Chung WP, Im S-A, 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;401:105–17.
7. Modi S, Saura C, Yamashita T, Park YH, Kim S-B, Tamura K, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2020;382:610–21.
8. André F, Hee Park Y, Kim SB, Takano T, Im SA, Borges G, et al. Trastuzumab Deruxtecan versus Treatment of Physician's Choice in Patients with HER2-Positive Metastatic Breast Cancer (DESTINY-Breast02): A Randomised, Open-Label, Multicentre, Phase 3 Trial. Lancet. 2023;401:1773–85.
9. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022;387:9–20.
10. Harbeck N, Ciruelos E, Jerusalem G, Müller V, Niikura N, Viale G, et al. Trastuzumab Deruxtecan in HER2-Positive Advanced Breast Cancer with or without Brain Metastases: A Phase 3b/4 Trial. Nat Med. 2024;30:3717–27.
11. Murthy R, Borges VF, Conlin A, Chaves J, Chamberlain M, Gray T, et al. Tucatinib with Capecitabine and Trastuzumab in Advanced HER2-Positive Metastatic Breast Cancer with and without Brain Metastases: A Non-Randomised, Open-Label, Phase 1b Study. Lancet Oncol. 2018;19:880–8.
12. Curigliano G, Mueller V, Borges V, Hamilton E, Hurvitz S, Loi S, et al. Tucatinib versus Placebo Added to Trastuzumab and Capecitabine for Patients with Pretreated HER2+ Metastatic Breast Cancer with and without Brain Metastases (HER2CLIMB): Final Overall Survival Analysis. Ann Oncol. 2022;33:321–9.
13. Das G, Wong STC, Zhao H. Beyond Primary HER2 Expression: Trastuzumab Deruxtecan's Efficacy in Brain Metastasis. Cancers. 2024;16:3525.
14. Petit T, Hajjaji N, Antoine EC, Benderra MA, Gozy M, Foa C, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Metastatic or Unresectable Breast Cancer: Real-Life Data from the Temporary Use Authorization Program in France. Cancer Med. 2024;13:e7168.
15. Botticelli A, Caputo R, Scagnoli S, Pisegna S, De Laurentiis M, Curigliano G, et al. Real-World Outcomes of Trastuzumab Deruxtecan in Patients with HER2+ Metastatic Breast Cancer: The DE-REAL Study. Oncologist. 2024;29:303–10.
16. Fountzilas E, Karageorgopoulou S, Karakatsoulis G, Tryfonopoulos D, Papazisis K, Koutras A, et al. Real-world safety and effectiveness data of trastuzumab deruxtecan and sacituzumab govitecan in breast cancer: A Hellenic Cooperative Oncology Group study. ESMO Real World Data Digit Oncol. 2025;7:100095.
17. Jourdain H, Di Meglio A, Mansouri I, Desplas D, Zureik M, Haddy N. Use and Outcomes of Trastuzumab Deruxtecan in HER2-Positive and HER2-Low Metastatic Breast Cancer in a Real-World Setting: A Nationwide Cohort Study. ESMO Open. 2024;9:104083.
18. Nakayama T, Niikura N, Yamanaka T, Yamamoto M, Matsuura K, Inoue K, et al. Trastuzumab Deruxtecan for the Treatment of Patients with HER2-Positive Breast Cancer with Brain and/or Leptomeningeal Metastases: An Updated Overall Survival Analysis Using Data from a Multicenter Retrospective Study (ROSET-BM). Breast Cancer. 2024;31:1167–75.
19. Fabi A, Rossi A, Caputo R, Pisegna S, Scagnoli S, Pantano F, D'Auria G, Fedele P, Fabbri A, Vernieri C, et al. Real Life Outcome Analysis of Breast Cancer Brain Metastases Treated with Trastuzumab Deruxtecan. NPJ Precis Oncol. 2025;9:22.
20. Bizarro R, Pazos I, Teixeira A, Pereira M, Gonçalves J, Abreu C, Ferreira R, Oliveira S, Duarte Mendes A, Eiriz I, et al. Real-Life Experience of HER2-Positive Advanced Breast Cancer Patients Treated with T-DXd (Trastuzumab Deruxtecan): A Multicentric Portuguese Study. Cureus. 2025;17:e79734.
21. Lazaratos A-M, Dankner M, Hamouda A, Labidi S, Cohen V, Panasci L, Friedmann JE, Patenaude F, Ferrario C, Basik M, et al. The Real-World Clinical Outcomes of Heavily Pretreated HER2+ and HER2-Low Metastatic Breast Cancer Patients Treated with Trastuzumab Deruxtecan at a Single Centre. Curr Oncol. 2024;32:1.
22. Sang D, Su Y, Zhang Y, Guan Y, Fan S, Zhang J, Zheng L, Wang Y, Guo Y, Lei Z, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Chinese Patients with HER2-Positive and HER2-Low Advanced Breast

Cancer: A Multicenter, Observational, Real-World Study. Ther Adv Med Oncol. 2025;17:17588359251318853.
23. West HJ, Jin JO. Performance Status in Patients with Cancer. JAMA Oncol. 2015;1:998.
24. Pérez-García JM, Vaz Batista M, Cortez P, Ruiz-Borrego M, Cejalvo JM, de la Haba-Rodriguez J, Garrigós L, Racca F, Servitja S, Blanch S, et al. Trastuzumab Deruxtecan in Patients with Central Nervous System Involvement from HER2-Positive Breast Cancer: The DEBBRAH Trial. Neuro Oncol. 2023;25:157–166.
25. Bartsch R, Berghoff AS, Furtner J, Marhold M, Bergen ES, Roider-Schur S, Starzer AM, Forstner H, Rottenmanner B, Dieckmann K, et al. Trastuzumab Deruxtecan in HER2-Positive Breast Cancer with Brain Metastases: A Single-Arm, Phase 2 Trial. Nat Med. 2022;28:1840–1847.
26. Niikura N, Yamanaka T, Nomura H, Shiraishi K, Kusama H, Yamamoto M, Matsuura K, Inoue K, Takahara S, Kita S, et al. Treatment with Trastuzumab Deruxtecan in Patients with HER2-Positive Breast Cancer and Brain Metastases and/or Leptomeningeal Disease (ROSET-BM). NPJ Breast Cancer. 2023;9:82.
27. Buono G, Deleuze A, Klocker EV, Nardin S, Eiriz IF, Luz PJC, Braga S, Harbeck N, Dieras VC. 237P Real-World Safety and Efficacy of Trastuzumab-Deruxtecan (T-DXd) in HER2-Positive Advanced Breast Cancer (ABC) Elderly Patients (Pts): The TREX-Old Retrospective Registry. ESMO Open. 2023;8:101425.
28. Chiu JWY, Lee SC, Ho JC-M, Park YH, Chao T-C, Kim S-B, Lim E, Lin C-H, Loi S, Low SY, et al. Clinical Guidance on the Monitoring and Management of Trastuzumab Deruxtecan (T-DXd)-Related Adverse Events: Insights from an Asia-Pacific Multidisciplinary Panel. Drug Saf. 2023;46:927–949.
29. Di Maio M, Perrone F, Conte P. Real-World Evidence in Oncology: Opportunities and Limitations. Oncologist. 2020;25:e746–e752.
30. Martín M, Pandiella A, Vargas-Castrillón E, Díaz-Rodríguez E, Iglesias-Hernangómez T, Martínez Cano C, Fernández-Cuesta I, Winkow E, Perelló MF. Trastuzumab Deruxtecan in Breast Cancer. Crit Rev Oncol Hematol. 2024;198:104355.
31. Curigliano G, Hu X, Dent RA, Yonemori K, Barrios CH, O'Shaughnessy J, Wildiers H, Zhang Q, Im S-A, Saura C, et al. Trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): Primary results from DESTINY-Breast06 (DB-06). J Clin Oncol. 2024;42:LBA1000.
32. Andre F, Hamilton EP, Loi S, Anders CK, Schmid P, Stroyakovskiy D, Villanueva R, Pedrini JL, Doval DC, Zurawski B, et al. DESTINY-Breast07: Dose-expansion interim analysis of T-DXd monotherapy and T-DXd + pertuzumab in patients with previously untreated HER2+ mBC. J Clin Oncol. 2024;42:1009.
33. Jhaveri KL, André F, Hamilton EP, Schmid P, Anders CK, Testa L, Ganshina IP, Lu Y, Im S, Young RR, et al. Abstract RF02-03: Trastuzumab deruxtecan (T-DXd) in combination with anastrozole or fulvestrant in patients with HER2-low HR+ advanced/metastatic breast cancer: A Phase 1b, open-label, multicenter, dose-expansion study (DESTINY-Breast08). Cancer Res. 2024;84:RF02-03.
34. Tolaney SM, Jiang Z, Zhang Q, Barroso-Sousa R, Park YH, Rimawi MF, Manich CS, Schneeweiss A, Toi M, Chae YS, et al. Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for first-line (1L) treatment of patients (pts) with human epidermal growth factor receptor 2–positive (HER2+) advanced/metastatic breast cancer (a/mBC): Interim results from DESTINY-Breast09. J Clin Oncol. 2025;43:LBA1008.
35. Seban RD, Champion L, Bellesoeur A, Vincent-Salomon A, Bidard FC. Clinical Potential of HER2 PET as a Predictive Biomarker to Guide the Use of Trastuzumab Deruxtecan in Breast Cancer Patients. J Nucl Med. 2023;64:1164–1165.