



Real-world Efficacy and Safety of Trastuzumab Deruxtecan in HER2-positive Metastatic Breast Cancer: A Multicenter Retrospective Study from Türkiye

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ABSTRACT

Objective: Trastuzumab deruxtecan (T-DXd) is a novel human epidermal growth factor receptor 2 (HER2)-directed antibody-drug conjugate that has demonstrated significant clinical activity in patients with HER2-positive metastatic breast cancer (mBC) in multiple pivotal trials. However, data regarding its effectiveness and safety in real-world settings, particularly from underrepresented regions such as Türkiye, remain limited.

Material and Methods: This retrospective, multicenter observational study included HER2-positive mBC patients [immunohistochemistry (IHC) score of 3+, or IHC score of 2+ with *in situ* hybridization-positive gene amplification] who received T-DXd after at least one prior line of systemic therapy. Clinical outcomes, including objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS), were evaluated. Subgroup and univariate Cox regression analyses were conducted to assess prognostic factors. Adverse events (AEs) were recorded and graded according to the Common Terminology Criteria for AEs version 5.0 (CTCAE v5.0).

Results: A total of 39 patients were included. The ORR was 89.7%, and the DCR was 100%. Median PFS and median OS were not reached at the time of analysis. In univariate analysis, a better Eastern Cooperative Oncology Group performance status and receipt of T-DXd in earlier treatment lines were associated with improved survival outcomes. AEs were generally manageable; grade ≥ 3 toxicity occurred in 15.4% of patients. Interstitial lung disease (ILD) was observed in 7.7% of patients, leading to treatment discontinuation in one patient.

Conclusion: T-DXd demonstrated high clinical efficacy and manageable toxicity in a real-world cohort of Turkish patients with HER2-positive mBC. These results are consistent with those reported in clinical trials and support the use of T-DXd as an effective treatment option in routine clinical practice. Our findings also highlight the importance of early identification and management of treatment-related AEs, particularly ILD.

Keywords: Trastuzumab deruxtecan; HER2-positive breast cancer; metastatic breast cancer; real-world evidence; antibody-drug conjugate; interstitial lung disease; progression-free survival

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 15-20% of breast cancers and is associated with increased tumor proliferation, aggressive clinical behavior, and a historically poor prognosis in the absence of targeted therapies.^{1,2} The introduction of HER2-directed agents such as trastuzumab, pertuzumab,

and trastuzumab emtansine (T-DM1) has revolutionized the management of HER2-positive metastatic breast cancer (mBC), significantly improving survival outcomes in both early-stage and advanced disease.³⁻⁵ Nonetheless, treatment resistance frequently develops, and a substantial proportion of patients ultimately progress after two or more lines of HER2-targeted therapies, highlighting the need for more effective agents in later lines of therapy.⁶

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Trastuzumab deruxtecan (T-DXd) is a novel antibody-drug conjugate (ADC) comprising a humanized anti-HER2 monoclonal antibody conjugated to a topoisomerase I inhibitor payload via a cleavable linker.⁷ Unlike earlier ADCs, T-DXd possesses a high drug-to-antibody ratio (~8:1) and exhibits a potent bystander killing effect, which enables it to target both HER2-overexpressing and neighboring low-HER2-expressing tumor cells.⁸ These pharmacological advantages have translated into favorable clinical outcomes across multiple trials. Although randomized clinical trials provide high-quality evidence under controlled conditions, their strict eligibility criteria may limit generalizability to routine clinical practice. Patients enrolled in pivotal trials often represent selected populations, whereas real-world patients are typically more heterogeneous in terms of age, performance status (PS), comorbidities, prior treatment exposure, and disease burden, including the presence of brain metastases. Consequently, real-world evidence (RWE) is crucial to validate the effectiveness and safety of T-DXd in broader and more representative patient populations.⁹

The clinical activity of T-DXd has been demonstrated in multiple pivotal trials. The phase II DESTINY-Breast01 study established its efficacy in heavily pretreated patients, while the phase III DESTINY-Breast03 trial confirmed its superiority over T-DM1 in the second-line setting. More recently, DESTINY-Breast02 further supported its benefit in patients previously treated with T-DM1, consolidating its role across multiple lines of therapy.¹⁰⁻¹²

Several observational studies have evaluated the real-world use of trastuzumab deruxtecan, supporting its effectiveness and manageable safety profile outside clinical trial settings. However, these reports originate primarily from Western European cohorts, and data from other geographic regions remain limited.¹³⁻¹⁶

Nevertheless, real-world data from Türkiye remain scarce, and no national-level study to date has reported the use of T-DXd in routine practice. Given the regional differences in treatment accessibility, sequencing strategies, and patient characteristics, it is essential to generate local data to inform clinicians and guide therapeutic decisions.

In this retrospective, multicenter study, we aimed to evaluate the real-world clinical outcomes of T-DXd in patients with HER2-positive mBC treated in Türkiye. Specifically, we assessed objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and treatment-related adverse events (AEs), including interstitial lung disease (ILD). Additionally, we investigated potential prognostic factors for survival outcomes in routine clinical practice. By providing multicenter data from an

underrepresented population, this study contributes region-specific evidence to the growing body of real-world literature on T-DXd.

MATERIAL AND METHODS

This retrospective multicenter observational study was conducted at three oncology centers in Türkiye between November 2025 and January 2026 to evaluate the real-world effectiveness and safety of T-DXd in patients with HER2-positive mBC. The study included adult patients (≥18 years) with histologically confirmed HER2-positive disease, defined as immunohistochemistry (IHC) 3+ or IHC 2+ with *in situ* hybridization (ISH) positivity, who had received at least one prior line of systemic therapy for metastatic disease. Patients were identified via electronic medical records, and treatment with T-DXd was administered in accordance with standard clinical practice. Patients were excluded if they had HER2-negative or HER2-low disease (i.e., IHC 0, 1+, or 2+ with ISH-negative), were enrolled in interventional clinical trials during T-DXd treatment, or had incomplete clinical documentation. T-DXd was administered intravenously at a starting dose of 5.4 mg/kg every three weeks (q3w), in accordance with standard clinical practice and the prescribing information. Dose reductions were implemented when clinically indicated, with the first dose reduction to 4.4 mg/kg and a second reduction to 3.2 mg/kg. Further dose reduction beyond 3.2 mg/kg led to treatment discontinuation. Treatment interruptions, dose adjustments, and permanent discontinuations were performed at the discretion of the treating physician based on toxicity severity and established safety recommendations. Treatment was continued until disease progression, unacceptable toxicity, or physician's decision.

Only patients with active brain metastases (defined as untreated lesions or lesions with radiological progression at the time of T-DXd initiation) were recorded as having central nervous system (CNS) involvement. Patients with previously treated and radiologically stable brain metastases were not included in this category.

Demographic and clinical data, including age, hormone receptor status, Eastern Cooperative Oncology Group (ECOG) PS, number and type of prior therapies, and presence of brain metastases, were collected at baseline. Treatment responses were assessed by the treating investigators at each participating center, based on radiological evaluations performed according to the Response Evaluation Criteria in Solid Tumors version 1.1. Radiological assessments were performed approximately every 8-12 weeks according to institutional practice. Given the retrospective, real-world design of the study, response assessments were not centrally reviewed or blinded. The primary outcome

measures included ORR and DCR. The secondary endpoints were PFS and OS. PFS was defined as the time from initiation of T-DXd to documented disease progression or death from any cause, whichever occurred first. OS was defined as the time from initiation of T-DXd to death from any cause. AEs were retrospectively collected through systematic review of electronic medical records, including physician notes, laboratory results, and imaging reports. ILD was defined based on the presence of new pulmonary symptoms and/or radiological findings suggestive of drug-related pneumonitis, as documented in medical records. Alternative causes such as infection, pulmonary embolism, or disease progression were excluded based on clinical and radiological evaluation where applicable. ILD severity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.¹⁷ Other toxicities were also graded according to the CTCAE, version 5.0.¹⁷ No prospective active safety monitoring was performed due to the retrospective design of the study.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as medians and ranges. Survival analyses (PFS and OS) were conducted using the Kaplan-Meier method, and subgroup comparisons were performed using the log-rank test. Associations between categorical variables were examined using the chi-square test or Fisher's exact test, where appropriate. A p-value <0.05 was considered statistically significant. Patients without documented progression or death at the time of data cut-off were censored on the date of their last follow-up. Because of the limited sample size and the small number of outcome events, multivariable modeling was not performed to avoid overfitting. Therefore, exploratory univariate Cox regression analyses were conducted. Data completeness was assessed prior to statistical analysis. A small proportion of missing data was identified for certain baseline variables. Therefore, analyses were performed using a complete-case approach without imputation.

The data cut-off date for survival analyses was January 31, 2026. Median follow-up time was calculated from the date of initiation of T-DXd to the date of last follow-up or death, whichever occurred first.

The study protocol was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of İstanbul Medipol University (approval no: 1322, date: 30.10.2025). All procedures were performed in accordance with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and

its later amendments. Due to the retrospective nature of the study, the requirement for informed consent was waived.

RESULTS

A total of 39 patients with HER2-positive breast cancer who received T-DXd were included in this real-world analysis. Baseline clinicopathological characteristics are summarized in Table 1. The median age at diagnosis was 46 years (range, 24-66). Most patients had a good PS, with 97.4% having an ECOG PS of 0-1.

The majority of tumors (97.4%) were invasive ductal carcinomas, and hormone receptor positivity was observed in 64.1% of patients. *De novo* metastatic disease was present in 30.8% of cases. Visceral metastases were observed in 64.1% of patients, including liver metastases in 33.3% of patients; active (untreated or radiologically progressing) brain metastases were present in 35.9% of patients at the time of T-DXd initiation.

All patients had previously received trastuzumab, and most had been treated with pertuzumab (89.7%) and T-DM1 (87.2%). T-DXd was most commonly administered in the third-line setting (53.8%), followed by $\geq 4^{\text{th}}$ line (35.9%). All patients received T-DXd at a starting dose of 5.4 mg/kg. The median number of treatment cycles was 12 (range, 3-71). At the data cut-off (January 31, 2026), the median follow-up from T-DXd initiation was 11.3 months (range, 2.2-28.2 months).

The best overall responses to T-DXd were complete response in 30.8% of patients, partial response in 59.0%, and stable disease in 10.3%. Accordingly, the ORR was 89.7%, and the DCR was 100%. At the time of analysis, disease progression was observed in 6 patients (15.4%). Median PFS was not reached. Kaplan-Meier estimates for PFS are shown in Figure 1.

During the follow-up period, 9 deaths (23.1%) were recorded. When OS was calculated from the time of metastatic diagnosis,

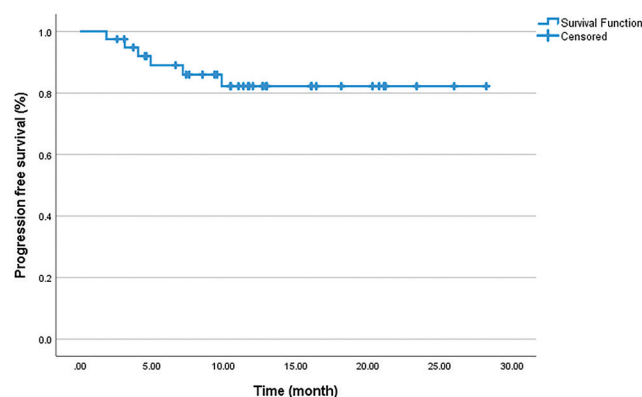


FIGURE 1: Kaplan-Meier curve for progression-free survival.

the median OS was not reached. OS from the initiation of T-DXd therapy was also evaluated. Median OS from T-DXd initiation was not reached. Kaplan-Meier curves for OS from metastatic diagnosis and from T-DXd initiation are presented in Figures 2 and 3, respectively.

TABLE 1: Baseline clinicopathological characteristics of patients with HER2-positive breast cancer treated with T-DXd in a real-world setting (n=39).

Variable	Total (n=39)
Age at diagnosis, years, median (range)	46 (24-66)
Menopausal status, n (%)	
Premenopausal	23 (59.0)
Postmenopausal	16 (41.0)
ECOG performance status, n (%)	
0	30 (76.9)
1	8 (20.5)
≥2	1 (2.6)
Histology, n (%)	
Invasive ductal carcinoma	38 (97.4)
Other	1 (2.6)
Hormone receptor status, n (%)	
ER-positive	25 (64.1)
PR-positive	16 (41.0)
HER2 status before T-DXd, n (%)	
IHC 3+	26 (66.7)
IHC 2+/ISH+	11 (28.2)
De novo metastatic disease, n (%)	12 (30.8)
Metastatic sites at baseline, n (%)	
Visceral metastasis (any)	25 (64.1)
Liver metastasis	13 (33.3)
Bone metastasis	19 (48.7)
Active (untreated/progressing) brain metastasis	14 (35.9)
Prior systemic treatments, n (%)	
Trastuzumab	39 (100)
Pertuzumab	35 (89.7)
Taxane	39 (100)
T-DM1	34 (87.2)
Capecitabine	12 (30.8)
Lapatinib	8 (21.1)
Line of T-DXd therapy, n (%)	
2 nd line	4 (10.3)
3 rd line	21 (53.8)
≥4 th line	14 (35.9)
T-DXd dose	5.4 mg/kg (100%)

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; HR: Hormone receptor; IHC: immunohistochemistry; ISH: *In situ* hybridization; PR: Progesterone receptor; T-DM1: Trastuzumab emtansine; T-DXd: Trastuzumab deruxtecan.

Univariate analyses for PFS and OS are summarized in Tables 2A and 2B, respectively. For PFS, no baseline clinical or treatment-related variables demonstrated a statistically significant association.

Several variables were significantly associated with OS in univariate analysis, including ECOG PS ($p=0.03$), prior exposure to T-DM1 ($p=0.02$), prior exposure to capecitabine ($p=0.023$), line of T-DXd therapy ($p=0.049$), and receipt of subsequent therapy after T-DXd ($p=0.032$). Other clinicopathological characteristics, such as comorbidity status, menopausal status, metastatic status at diagnosis, hormone receptor status, and metastatic site involvement, were not significantly associated with survival outcomes.

Treatment-related AEs are summarized in Table 3. Overall, T-DXd was well tolerated. The most frequently observed AEs of any grade were alopecia (74.4%), nausea (66.7%), leukopenia (56.4%), anemia (51.3%), and neutropenia (48.7%). Grade 3-4 AEs occurred in 15.4% of patients, with neutropenia,

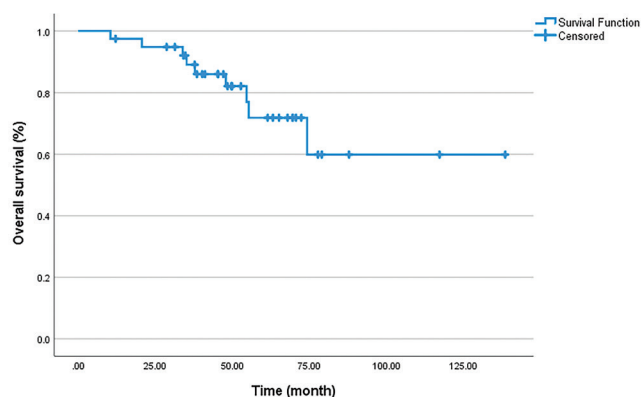


FIGURE 2: Kaplan-Meier curve for overall survival from metastatic diagnosis.

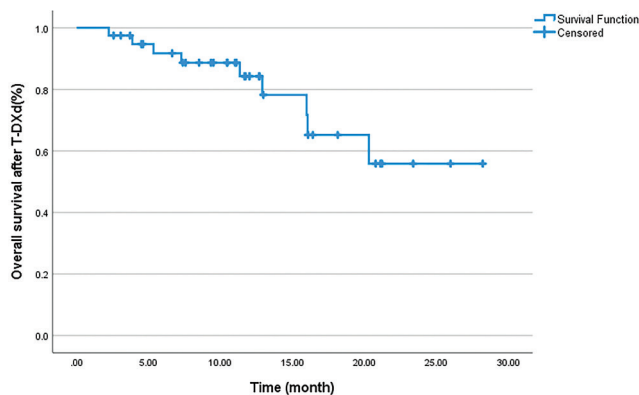


FIGURE 3: Kaplan-Meier curve for overall survival from trastuzumab deruxtecan initiation.

T-DXd: Trastuzumab deruxtecan.

leukopenia, anemia, thrombocytopenia, nausea, and ILD being the most common severe toxicities. Dose reductions due to treatment-related toxicity were required in 33.3% of patients, while treatment interruptions and permanent

treatment discontinuations occurred in 17.9% and 5.1% of patients, respectively. ILD was observed in 7.7% of patients and led to treatment discontinuation in one patient. No treatment-related deaths were recorded.

DISCUSSION

The high response rates observed in our cohort are consistent with those reported in pivotal DESTINY trials and emerging real-world studies.^{10,11} However, the ORR in our study appears numerically higher than in some controlled settings, which may reflect differences in patient selection, follow-up duration, and retrospective assessment.^{13,18,19}

The relatively short median follow-up duration and a limited number of progression and death events may have influenced survival estimates. Median PFS and OS were not reached at the time of analysis; therefore, long-term survival outcomes should be interpreted cautiously. The small sample size (n=39) further limits statistical precision and generalizability.

In our real-world cohort, median PFS was not reached at the time of analysis and appeared comparable to that reported in controlled trials, despite the inclusion of patients with a broad range of prior therapies and varying ECOG PS. This real-world effectiveness corroborates existing observational studies, including the DE-REAL study, which also reported meaningful clinical activity of T-DXd in routine practice albeit with somewhat lower median PFS and ORR than in trials.¹³

Real-world studies from France and Greece, as well as from multinational cohorts further support the generalizability of T-DXd efficacy across diverse populations and healthcare systems. These findings demonstrate that T-DXd maintains

TABLE 2A: Univariate analysis for progression-free survival.

Variable	p-value for PFS
Comorbidity (yes vs. no)	0.333
Menopausal status	0.622
Metastatic status at diagnosis (<i>de novo</i> vs. recurrent)	0.640
ECOG performance status	0.413
Prior pertuzumab exposure (yes vs. no)	0.781
Prior T-DM1 exposure (yes vs. no)	0.05
Prior capecitabine exposure (yes vs. no)	0.341
Prior lapatinib exposure (yes vs. no)	0.836
Hormone receptor status (positive vs. negative)	0.535
Line of T-DXd therapy	0.187
Liver metastasis	0.423
Lung metastasis	0.914
Bone metastasis	0.375
Active (untreated/progressing) brain metastasis	0.207

PFS: Progression-free survival; ECOG: Eastern Cooperative Oncology Group; T-DM1: Trastuzumab emtansine; T-DXd: Trastuzumab deruxtecan.

TABLE 2B: Univariate analysis for overall survival.

Variable	p-value for OS
Comorbidity (yes vs. no)	0.302
Menopausal status	0.949
Metastatic status at diagnosis (<i>de novo</i> vs. recurrent)	0.800
ECOG performance status	0.03
Prior pertuzumab exposure (yes vs. no)	0.781
Prior T-DM1 exposure (yes vs. no)	0.02
Prior capecitabine exposure (yes vs. no)	0.023
Prior lapatinib exposure (yes vs. no)	0.242
Hormone receptor status (positive vs. negative)	0.602
Line of T-DXd therapy	0.049
Liver metastasis	0.668
Lung metastasis	0.911
Bone metastasis	0.732
Active (untreated/progressing) brain metastasis	0.244
Subsequent therapy after T-DXd (yes vs. no)	0.032

OS: Overall survival; ECOG: Eastern Cooperative Oncology Group; T-DM1, Trastuzumab emtansine; T-DXd: Trastuzumab deruxtecan.

TABLE 3: Trastuzumab deruxtecan-related adverse events (n=39).

Adverse event	Any grade n (%)	Grade 3-4 n (%)
Anemia	20 (51.3)	1 (2.6)
Leukopenia	22 (56.4)	2 (5.1)
Neutropenia	19 (48.7)	1 (2.6)
Thrombocytopenia	14 (35.9)	2 (5.1)
Nausea	26 (66.7)	5 (12.8)
Vomiting	12 (30.8)	1 (2.6)
Diarrhea	11 (28.2)	0
Transaminase elevation	14 (35.9)	0
Alopecia	29 (74.4)	0
Interstitial lung disease	3 (7.7)	1 (2.6)
Any grade ≥ 3 adverse event	–	6 (15.4)
Dose reduction due to toxicity	–	13 (33.3)
Treatment interruption	–	7 (17.9)
Treatment discontinuation	–	2 (5.1)

high clinical utility beyond the controlled conditions of randomized clinical trials.^{14,15,20-23}

In our univariate analyses, factors such as ECOG PS, the number of prior therapies, and the presence of brain metastases were associated with variations in survival outcomes. Specifically, patients with better PS and fewer prior lines of treatment tended to show longer PFS and OS. These findings are consistent with other analyses showing that earlier integration of T-DXd in the treatment sequence may enhance outcomes, particularly in second-line settings as highlighted by DESTINYBreast03.¹¹

Although several associations were observed in univariate analysis, these findings should be interpreted with caution given the limited sample size and number of outcome events.¹⁹ Notably, the receipt of subsequent lines of therapy after T-DXd was associated with improved survival outcomes, suggesting that T-DXd can serve as a therapeutic bridge, enabling further treatment options. However, this finding should be interpreted cautiously due to the potential for time-dependent bias inherent in retrospective analyses.

Brain metastases represent a challenging clinical subgroup with a poorer prognosis. While DESTINY trials and pooled analyses have shown that T-DXd provides intracranial responses, albeit with lower magnitudes than extracranial disease, our cohort's outcomes in patients with baseline CNS involvement were acceptable and generally aligned with these observations.¹⁶ RWE increasingly recognizes the need for more focused studies on CNS disease management with ADCs, a priority area given the historical limitations of systemic therapies in controlling brain metastases.²⁴

Safety outcomes in our study were consistent with the known toxicity spectrum of T-DXd. Most AEs were low-grade and manageable, with grade ≥ 3 events observed in 15.4% of patients. This aligns with real-world and clinical trial safety data showing manageable toxicity profiles when appropriate monitoring and supportive care are provided.^{10,11,13} Dose reductions were required in a proportion of patients, reflecting clinical practice adjustments to ameliorate side effects while maintaining therapeutic effectiveness.

Of particular interest is the incidence of ILD/pneumonitis, a well-documented and potentially serious AE associated with T-DXd. Clinical trial data indicate ILD incidence ranging from 10-15% in some cohorts, with rare fatal outcomes.^{10,11,25} Meta-analyses also report ILD rates of approximately 11.7% across breast cancer patients treated with T-DXd, with higher risk potentially linked to dose intensity and patient characteristics.^{20,25} In our cohort, ILD occurred at a frequency consistent with these reports, confirming the necessity of vigilant pulmonary monitoring and early

intervention protocols in routine care. Additional real-world studies emphasize that while ILD remains a toxicity of concern, it is often manageable when recognized promptly, underlining the importance of multicenter experience and multidisciplinary approaches to toxicity management.^{18,20,26,27}

Cardiotoxicity and other ADC-related toxicities appear to be infrequent but are also under active investigation, with pooled analyses suggesting a low but measurable incidence that warrants clinical awareness and baseline cardiac assessment. Real-world safety data increasingly contribute to refining guidelines for dose modifications and supportive care to improve tolerability without compromising efficacy.^{28,29}

The accumulation of RWE, including this study and other international cohorts, complements phase III evidence by demonstrating the reproducibility of T-DXd's efficacy and safety in broader, everyday clinical settings. Narrative reviews of real-world studies underscore consistent activity of T-DXd and emphasize its favorable safety profile, while also identifying areas where evidence is limited — such as older patients, those with comorbidities, and HR-negative subgroups. Additionally, ongoing research explores T-DXd's potential in combination regimens, novel sequencing strategies, and emerging indications such as first-line treatment in combination with other targeted agents.^{13,30}

As ADC-based therapy continues to evolve, prospective registry studies and larger real-world databases will be crucial to optimize patient selection, mitigate toxicity, and determine sequencing strategies that maximize both survival and quality of life. Integrating molecular biomarkers and longitudinal patient-reported outcomes may further enhance the clinical applicability of these findings.

Study Limitations

Our study's retrospective design, relatively small sample size, and short follow-up duration represent important limitations. The limited number of outcome events reduces statistical power and precludes robust prognostic modeling. Additionally, the absence of centralized radiological review and the potential heterogeneity across participating centers may have influenced the outcome assessment. Therefore, the findings should be interpreted as exploratory and hypothesis-generating rather than definitive. Furthermore, while real-world data provide valuable insights, they are subject to potential confounding factors and heterogeneity in clinical practice. Despite these limitations, our findings add to a growing body of RWE that reinforces the role of T-DXd as a potent therapeutic agent for HER2-positive mBC in routine clinical settings. Given the limited sample size and number of outcome events, multivariable analyses were not performed

to avoid model overfitting; therefore, prognostic findings are exploratory in nature.

CONCLUSION

In this real-world multicenter study from Türkiye, T-DXd demonstrated substantial clinical benefit in patients with HER2-positive mBC who had previously received at least one line of systemic therapy. The high ORR and DCR, together with favorable PFS, are consistent with efficacy reported in randomized clinical trials and other real-world cohorts. Although certain clinical variables such as ECOG PS and treatment line were associated with survival outcomes in univariate analysis, these findings should be interpreted cautiously due to the limited sample size and number of events.

Importantly, the safety profile of T-DXd was manageable, with AEs comparable to those observed in larger studies, including a relatively low but clinically relevant incidence of ILD. Our study contributes valuable real-world data from an underrepresented population and supports the integration of T-DXd into standard care pathways for HER2-positive mBC. Further large-scale and prospective studies are warranted to refine patient selection, optimize treatment sequencing, and enhance the safe use of this potent therapeutic agent in diverse clinical settings.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (approval no: 1322, date: 30.10.2025).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: H.M., E.S., L.Ş.C., Ö.H., Ö.F.Ö., M.Ş., Concept: H.M., B.G., J.H., A.B., Design: H.M., B.Ç.D., Ö.A., A.B., Data Collection or Processing: H.M., E.S., L.Ş.C., Ö.H., B.Ç.D., Ö.A., Ö.F.Ö., M.Ş., Analysis or Interpretation: H.M., A.B., Literature Search: H.M., B.G., J.H., A.B., Writing: H.M.

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