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Real-world effectiveness of trastuzumab deruxtecan in heavily pretreated HER2-positive metastatic breast cancer: A single-center experience

Yoğun tedavi almış HER2-pozitif metastatik meme kanserinde trastuzumab derukstekan'ın gerçek yaşam etkinliği: Tek merkez deneyimi

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ABSTRACT

Aim: Trastuzumab deruxtecan (T-DXd) has shown substantial activity in trials of HER2-positive metastatic breast cancer (mBC), but real-world data in heavily pretreated patients, in those with CNS metastases, and in patients started at reduced doses remain limited. To evaluate real-world efficacy and safety of T-DXd in HER2-positive mBC, focusing on late-line use, CNS disease, and reduced-dose initiation.

Material and Methods: This retrospective single-center cohort included 42 consecutive HER2-positive mBC patients treated with T-DXd between September 2023 and December 2025. HER2 positivity required IHC 3+ or IHC 2+/ISH-positive. Baseline CNS metastases were present in 16 patients (38.1%); 81.0% received T-DXd as fourth-line therapy or later. T-DXd was initiated at 3.6 mg/kg in 34 patients (81.0%) and at 5.4 mg/kg in 8 (19.0%). Primary endpoints were real-world progression-free (rwPFS) and overall survival (rwOS); secondary endpoints were disease control rate (DCR) and safety.

Results: At a median follow-up of 16.2 months, median rwPFS was 14.4 months (95% CI: 10.8–18.0) and median rwOS was not reached. ORR was 67.5% and DCR 90.0% (n=40 evaluable). In the CNS subgroup, ORR was 62.5% and rwPFS 13.2 months; in the 3.6 mg/kg subgroup, ORR was 64.7% and rwPFS 14.1 months. Any-grade adverse events occurred in 59.5%, grade ≥3 in 11.9%; ILD/pneumonitis in 4.8% (all grade 1–2).

Conclusion: T-DXd showed meaningful, sustained real-world activity in heavily pretreated HER2-positive mBC, including CNS disease and reduced-dose initiation, warranting prospective confirmation.

Keywords: Trastuzumab deruxtecan, HER2-positive breast cancer, Metastatic breast cancer, Real-world evidence

ÖZ

Amaç: Trastuzumab deruxtecan (T-DXd), HER2-pozitif metastatik meme kanserinde (mBC) klinik çalışmalarda güçlü aktivite göstermiştir. Ancak yoğun ön tedavi almış hastalarda, merkezi sinir sistemi (MSS) metastazı bulunanlarda ve düşük başlangıç dozuyla tedaviye başlanan olgularda gerçek dünya verileri sınırlıdır. Bu çalışmada amaç, HER2-pozitif mBC hastalarında T-DXd'nin gerçek dünya etkinliği ve güvenliğini; geç basamak kullanımı, MSS hastalığı ve düşük doz başlangıcına odaklanarak değerlendirmektir.

Gereç ve Yöntemler: Eylül 2023 – Aralık 2025 arasında T-DXd ile tedavi edilen 42 ardışık HER2-pozitif mBC hastası geriye dönük incelendi. HER2 pozitifliği IHC 3+ veya IHC 2+/ISH-pozitif olarak tanımlandı. Başlangıçta 16 hastada (%38,1) MSS metastazı vardı; %81,0'i T-DXd'yi dördüncü veya sonraki basamakta aldı. T-DXd, 34 hastada (%81,0) 3,6 mg/kg, 8 hastada (%19,0) 5,4 mg/kg dozunda başlatıldı. Birincil sonlanımlar gerçek dünya progresyonsuz sağkalım (rwPFS) ve genel sağkalımdı (rwOS); ikincil sonlanımlar hastalık kontrol oranı (DCR) ve güvenlikti.

Bulgular: Ortanca 16,2 aylık takipte ortanca rwPFS 14,4 ay (%95 GA: 10,8–18,0) idi; ortanca rwOS'e ulaşılamadı. Yanıt değerlendirilebilen 40 hastada ORR %67,5, DCR %90,0 bulundu. MSS alt grubunda ORR %62,5 ve rwPFS 13,2 ay; 3,6 mg/kg alt grubunda ORR %64,7 ve rwPFS 14,1 aydı. Herhangi derece advers olay %59,5'inde, ≥3. derece %11,9'unda; interstisyel akciğer hastalığı/pnömoni %4,8 (tümü 1–2. derece).

Sonuç: T-DXd; yoğun ön tedavi almış, MSS tutulumu olan ve sıklıkla düşük dozda başlatılan HER2-pozitif mBC popülasyonunda klinik olarak anlamlı ve sürekli gerçek dünya aktivitesi göstermiştir; prospektif çalışmalarla doğrulanması gerekmektedir.

Anahtar Kelimeler: Trastuzumab derukstekan, HER2-pozitif meme kanseri, Metastatik meme kanseri, Gerçek yaşam verileri

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Highlights

- Trastuzumab deruxtecan showed meaningful real-world activity in heavily pretreated HER2-positive metastatic breast cancer.
- Clinical activity was maintained in patients with baseline brain metastases.
- Most patients received T-DXd in the fourth line or later, reflecting a highly pretreated cohort.
- Reduced-dose initiation retained activity in selected patients, but this finding should be considered hypothesis-generatin.

INTRODUCTION

HER2-positive disease accounts for approximately 15% to 20% of all breast cancers and has historically been associated with aggressive clinical behavior and poor outcomes in the absence of HER2-directed treatment. The development of HER2-targeted therapies, including monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates, has substantially improved outcomes in this subtype.

One such agent is trastuzumab deruxtecan (T-DXd), a next-generation HER2-directed antibody-drug conjugate composed of a trastuzumab backbone linked to a cleavable topoisomerase I inhibitor payload (1,2). The pivotal DESTINY-Breast clinical trial program has established the efficacy of T-DXd across multiple treatment settings. In DESTINY-Breast01, conducted in a heavily pretreated HER2-positive metastatic population, T-DXd produced an objective response rate (ORR) of 60.9% and a median progression-free survival (PFS) of 16.4 months, with durable benefit in later analyses (3).

DESTINY-Breast02 subsequently demonstrated superiority over treatment of physician's choice after trastuzumab emtansine (4). In DESTINY-Breast03, T-DXd significantly improved progression-free and overall survival compared with trastuzumab emtansine in the second-line setting (5,6).

More recently, the clinical role of T-DXd expanded further in hormone receptor-positive HER2-low and HER2-ultralow metastatic breast cancer (7). Subgroup analyses of DESTINY-Breast01 reported an ORR of 58.3% and a median PFS of 18.1 months in patients with previously treated brain metastases (8). Pooled analyses from DESTINY-Breast studies showed intracranial response rates of approximately 45% in patients with stable or active brain metastases (9). Prospective data from TUXEDO-1 further demonstrated strong intracranial activity, with an ORR of 73.3% in patients with active brain metastases (10). These findings were reinforced by DESTINY-Breast12, the largest prospective study in this setting, which demonstrated durable intracranial and systemic activity (11).

Although such encouraging efficacy results are expected, such safety concerns as interstitial lung disease (ILD)/pneumonitis are still clinically significant. In clinical trials, ILD/pneumonitis has been reported in approximately 10% to 15% of patients, with severe events occurring less frequently (5). Early detection and appropriate management are essential to reduce treatment-related morbidity and mortality (12). Moreover, the need to reduce doses and interrupt treatment is common in everyday clinical practice, especially in patients who are highly pretreated or patients who are weak.

These findings have been mostly supported by real-world data. In a multicenter study from the Turkish Oncology Group, median real-world PFS (rwPFS) was 17.9 months, median real-world overall survival (rwOS) was 35.7 months, and ORR was 71.4% (13).

Other retrospective studies have also shown consistent effectiveness in patients with brain metastases and in later-line settings (14).

Nevertheless, there are significant gaps especially with respect to the outcomes in very late-line settings and also in patients who were started on lower starting doses because of frailty or tolerability issues.

In this respect, single-center studies are a good complement that may offer a more consistent treatment, follow-up, and toxicity management. The current study therefore sought to assess the efficacy and safety of T-DXd in patients with HER2-positive metastatic breast cancer treated at a tertiary referral center, with particular focus on three clinically relevant real-world features: frequent use in the fourth line or beyond, a high prevalence of brain metastases, and frequent initiation at a reduced nonstandard starting dose.

MATERIAL and METHODS

Study Design and Setting

It was a retrospective and observational cohort study conducted in the Department of Medical Oncology, a tertiary referral center. The trial was a comparison of the real clinical outcomes of patients with metastatic breast cancer of HER2-positive and treated with trastuzumab deruxtecan (T-DXd) in the real clinical practice. The study period was

September 2023 to December 2025, and the follow-up data collection was done up to the last clinical contact or death.

Patient Population

Institutional electronic medical records were used to identify eligible patients sequentially. Inclusion criteria were: (1) the age was 18 years or older; (2) known to have breast cancer and it was historically diagnosed; (3) known to have HER2-positive metastatic disease; (4) one cycle of T-DXd had been received within the study period. HER2 positivity was defined as immunohistochemistry (IHC) 3+ or IHC 2+ with in situ hybridization positivity, consistent with criteria used in prior clinical trials.

The elimination criterion of the patients was that they lacked complete baseline or follow-up information, the indeterminate status of HER2, and lacked sufficient information to determine the response to treatment or survival outcomes. There were no limitations based on previous lines of therapy, the presence of brain metastases or performance status which was a reflection of a real-world population.

Treatment Exposure and Dose Modifications

T-DXd was given intravenously after every 3 weeks as per the practice in the institution. This therapy was discontinued until disease progression, unbearable toxicity, patient withdrawal, demise or a physician ruling.

Unlike clinical trial protocols, which consistently used a starting dose of 5.4 mg/kg, the starting dose in this cohort was individualized. Higher percentage of patients (81.0%) started their treatment with lower dose of 3.6 mg/kg, and only a small percentage (19.0) of patients started with the standard dose. Selection of the dose was done on a clinical basis, considering the cumulative toxicity of previous treatment, the number of previous treatment lines, Eastern Cooperative Oncology Group (ECOG) performance status, age, comorbidities, and overall frailty.

Reductions in dose, delays, and interruptions were documented and instituted on the basis of toxicity, tolerability and discretion of the physicians. Antiemetics and growth factor support were used as clinically deemed necessary.

Variables and Data Collection

The electronic health records were reviewed to retrieve data through a standardized data abstraction method. The baseline demographic and clinical variables were age at T-DXd initiation, menopausal status, ECOG performance status, hormone receptor status, HER2 status and disease presentation (de novo metastatic disease vs. recurrent disease).

The variables pertaining to tumor and treatment were also the number of previous lines of systemic therapy, previous exposure to the HER2-directed therapy (trastuzumab, pertuzumab, trastuzumab emtansine), existence and location of metastatic disease (including involvement of central nervous system), and the quantity of T-DXd cycles given. The variables of outcome were best radiologic response, time to response, progression status, survival status, adverse events, dose adjustments, and discontinuation of treatment.

Response Assessment

Radiological evaluation of tumor response was done using computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET)/CT, depending on the institutional practice. The imaging tests were usually conducted after every 8-12 weeks or sooner whenever it was clinically necessary.

Though formal criteria based on the RECIST version 1.1 were not uniformly applied in the study since it was retrospective, responses were given in terms of the radiologic report; complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as would be done in real-life assessment.

Endpoints

The major endpoints were real-world progression-free survival (rwPFS) and real-world overall survival (rwOS).

- rwPFS was defined as the duration between the beginning of T-DXd and radiologically defined disease progression or death of any cause, the first occurred.
- This time was characterized as the rwOS as the period of T-DXd to any death.
- The objective response rate (ORR), disease control rate (DCR), time to best response, duration of response (DoR) and safety were considered as secondary endpoints.
- ORR was the rate of patients who attained CR or PR.
- DCR was called the percentage-population obtaining CR, PR or SD.
- Time to best response was defined as the period between the time of starting treatment and the first time when best response was recorded.
- The responders were defined by DoR which was the duration between first recorded response and disease progression or death.

Safety Assessment

Clinical documentation and laboratory findings were reviewed to evaluate adverse events (AEs), which were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (15). The focus was made on interstitial lung disease (ILD)/pneumonitis, their time to onset, grade, management, and outcomes.

Statistical Analysis

Basic statistics was used to characterize baseline variables and treatment patterns. Continuous variables were reported

using medians and interquartile ranges (IQRs), and categorical variables were reported using frequencies and percentages. Kaplan-Meier was applied to conduct survival analysis of rwPFS and rwOS and with 95% confidence interval (CI) calculated. Differences between subgroups (i.e. starting dose, brain metastases, line of therapy) were compared log-rank. The sample size was limited and the number of progression and death events was relatively small. Therefore, multivariable regression modeling was not performed because it would not satisfy accepted events-per-variable requirements and could result in unstable estimates and overfitted models. Consequently, the subgroup analyses were considered exploratory and hypothesis-generating. All the statistical tests were of the two-sided type with a p-value of below 0.05 was considered statistically significant. The analyses were done by using IBM SPSS Statistics.

As a retrospective real-world study, no formal sample size calculation was performed. All consecutive eligible patients who met the inclusion criteria and received trastuzumab deruxtecan during the predefined study period were included in the analysis.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki and applicable national regulations. The study protocol was approved by the Istinye University Clinical Research Ethics Committee before data collection. Because of the retrospective design of the study, the requirement for informed consent was waived in accordance with local regulations where applicable.

RESULTS

Patient Characteristics

A total of 42 patients were included in the analysis, and all were female. The median age at T-DXd initiation was 51 years (IQR, 44-59). The majority of the patients were in good performance with an Eastern Cooperative Oncology Group (ECOG) score of 0-1 (39 patients, 92.8%), and few (3) had an ECOG score of 2.

Hormone receptor-positive disease was present in 26 patients (61.9%), whereas 16 patients (38.1%) had hormone receptor-negative tumors. HER2 status was IHC 3+ in 31 patients (73.8%) and IHC 2+/ISH-positive in 11 patients (26.2%). When the disease presented, 19(45.2%) were metastatic disease that were de novo and 23 (54.8%) were recurrent diseases. The most predominant sites of metastasis were bone (50.0%), lung (42.9%), liver (40.5%) and brain (38.1%). It should be noted, though, that the proportion of brain metastases in this group was considerably higher than the proportion of the Turkish Oncology Group (38.1% vs. 21.6%), which represented a more sophisticated clinical group. Similarly, the proportion of patients that were treated with T-DXd in the fourth or later line was also far higher (81.0% vs. 40.1%) which again demonstrates the highly pretreated nature of the cohort.

Trastuzumab was previously used by all patients. Pertuzumab (92.9%) and trastuzumab emtansine (78.6%) were also found to be used in high rates. T-DXd was used as second-line therapy in 3 patients (7.1%), third-line therapy in 5 patients (11.9%), and in the fourth line or more in most patients (81.0%). The median of previous therapy lines in the metastatic population was 4 (IQR, 3-5), which validated the wide pretreatment coverage in the population (Table 1).

Treatment Exposure

Patients received a median of 8 cycles of T-DXd (IQR, 4-14) at a median follow-up of 16.2 months (IQR, 9.8-22.1). At the data cutoff, 25 patients (59.5%) had experienced disease progression and 16 patients (38.1%) had died.

Table 1: Baseline clinicopathologic characteristics of the study population

Characteristic	Value
Total patients	42
Age, median (IQR), y	51 (44-59)
Female sex	42 (100.0)
ECOG performance status 0	24 (57.1)
ECOG performance status 1	15 (35.7)
ECOG performance status 2	3 (7.1)
Hormone receptor-positive disease	26 (61.9)
Hormone receptor-negative disease	16 (38.1)
HER2 IHC 3+	31 (73.8)
HER2 IHC 2+/ISH-positive	11 (26.2)
De novo metastatic disease	19 (45.2)
Recurrent metastatic disease	23 (54.8)
Bone metastases	21 (50.0)
Lung metastases	18 (42.9)
Liver metastases	17 (40.5)
Brain metastases	16 (38.1)
Prior trastuzumab exposure	42 (100.0)
Prior pertuzumab exposure	39 (92.9)
Prior trastuzumab emtansine exposure	33 (78.6)
T-DXd as second line	3 (7.1)
T-DXd as third line	5 (11.9)
T-DXd as fourth line or later	34 (81.0)
Starting dose 3.6 mg/kg	34 (81.0)
Starting dose 5.4 mg/kg	8 (19.0)

Data are presented as n (%) unless otherwise indicated.

Efficacy Outcomes

Median rwPFS was 14.4 months (95% CI, 10.8-18.0). The 6-month and 12-month rwPFS rates were 78.4% and 56.8%, respectively. Median real-world overall survival (rwOS) was not reached at the time of analysis. The 12-month and 18-month overall survival rates were 83.1% and 66.4%, respectively (Table 2, Figure 1, Figure 2).

Out of 40 patients that could be evaluated to respond, the optimal response was complete response (CR) (4 patients, 10.0%), and partial response (PR) in 23 patients (57.5%), which led to an objective response rate (ORR) of 67.5%. A disease control rate (DCR) of 90.0 was found with 9 patients having stable disease (SD). The most appropriate response was progressive disease (PD) and was noted in 4 patients (10.0%). Median time of best response was 3.1 months (IQR, 1.9–4.7), indicating a rather quick antitumor response (Table 2).

Table 2: Treatment exposure and efficacy outcomes

Outcome	Value
Median follow-up, mo (IQR)	16.2 (9.8-22.1)
Median number of T-DXd cycles (IQR)	8 (4-14)
Documented progression events	25 (59.5)
Death events	16 (38.1)
Median rwPFS, mo (95% CI)	14.4 (10.8-18.0)
6-month rwPFS rate, %	78.4
12-month rwPFS rate, %	56.8
Median rwOS	Not reached
12-month OS rate, %	83.1
18-month OS rate, %	66.4
Response-evaluable patients, No.	40
Complete response	4 (10.0)
Partial response	23 (57.5)
Stable disease	9 (22.5)
Progressive disease	4 (10.0)
Objective response rate, %	67.5 (95% CI: 50.9–81.4)
Disease control rate, %	90.0 (95% CI, 76.3–97.2)
Median time to best response, mo (IQR)	3.1 (1.9-4.7)

Percentages for best overall response were calculated among response-evaluable patients.

Exploratory Subgroup Analyses

Line of therapy

The efficacy results were also considered in clinically relevant subgroups such as line of therapy, presence of brain metastases and starting dose (Table 3, Figure 3).

In terms of line of treatment, patients undergoing T-DXd in second or third line showed better results than their counterparts undergoing other later lines. The earlier-line group achieved 87.5 percent response rate which is compared to 62.5 percent of patients who were treated in the fourth line or above. In the same way, the median rwPFS was greater in patients that had previously received treatment (20.1 months vs. 13.6 months), and this was statistically significant (log-rank p=0.032). This noted ineffectiveness increase with lines of treatment was accompanied with preservation of clinical meaningful activity in highly treated individuals.

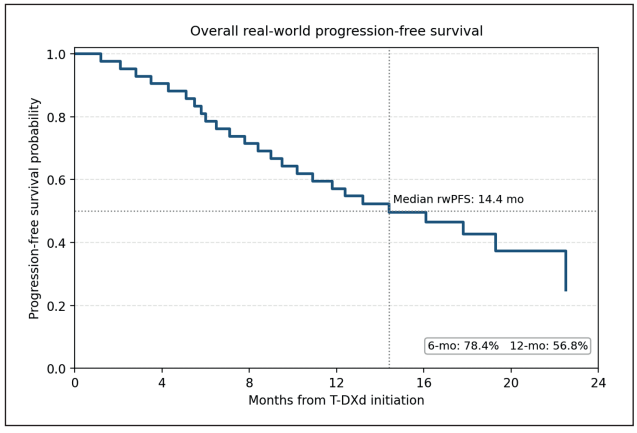

Figure 1: Kaplan-Meier estimate of real-world progression-free survival in the overall cohort.

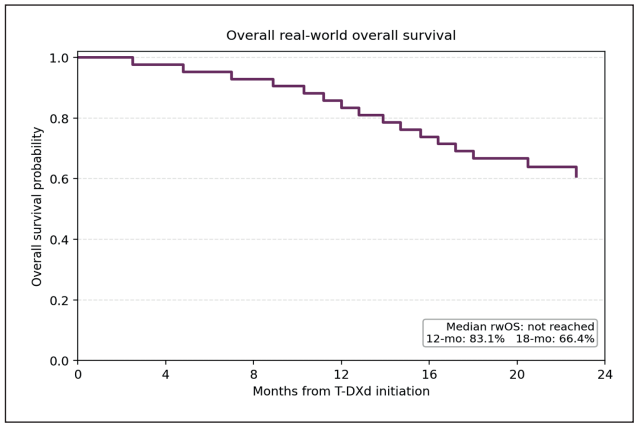

Figure 2: Kaplan-Meier estimate of real-world overall survival in the overall cohort.

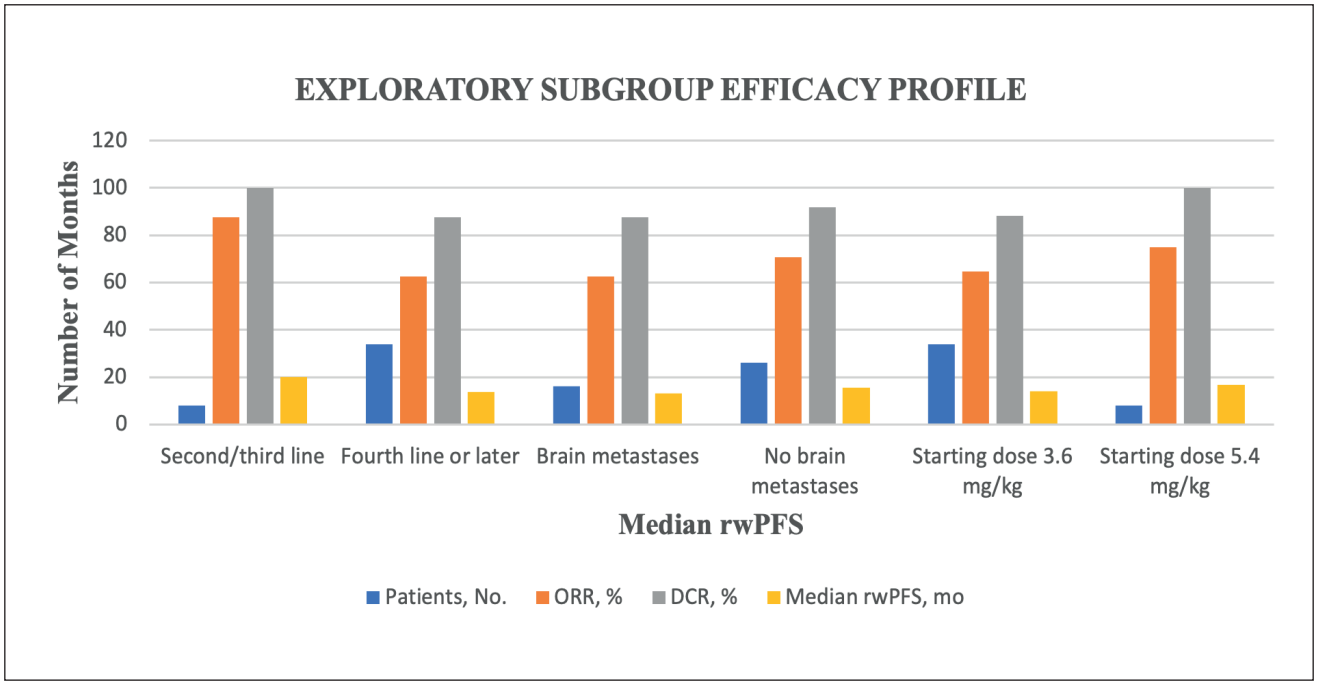

Figure 3: Exploratory subgroup efficacy profile summarizing median rwPFS and objective response rates across clinically relevant subgroups.

Table 3: Exploratory subgroup efficacy outcomes

Subgroup	Patients, No.	ORR, %	DCR, %	Median rwPFS, mo
Second/third line	8	87.5	100.0	20.1
Fourth line or later	34	62.5	87.5	13.6
Brain metastases	16	62.5	87.5	13.2
No brain metastases	26	70.8	91.7	15.4
Starting dose 3.6 mg/kg	34	64.7	88.2	14.1
Starting dose 5.4 mg/kg	8	75.0	100.0	16.8

Subgroup outcomes are exploratory and should be interpreted cautiously because of the small cohort size and non-randomized treatment selection.

Brain metastases

16 patients (38.1%) had brain metastases at baseline. The ORR in this subgroup was 62.5% and the median rwPFS was 13.2 months. Compared to that, patients without brain metastases had an ORR of 70.8% and a median rwPFS of 15.4 months. Though the results were lower numerically in patients with CNS involvement, the differences were not significant (p=0.287), probably due to the small number of patients. Significantly, these results indicate that T-DXd can be continued to be used in patients with brain metastases.

Starting dose

Dose-adjusted analysis showed that patients who initiated at 3.6mg/kg were released at an ORR of 64.7 and a median rwPFS of 14.1 months. Conversely, patients receiving the standard dose of 5.4 mg /kg showed an ORR of 75.0% and median rwPFS of 16.8 months. Whereas the efficacy outcomes were higher numerically in the standard-dose, the differences were not found significant (p=0.418). The results of this study must be approached carefully since the allocation of doses was not random and also because of the limited numbers of the sample. Nevertheless, it is important to mention that the antitumor activity was maintained in the reduced dose group.

Safety

T-DXd was largely tolerable. Unfavorable events of any-grade and grade 59.5% and 11.9% occurred among patients respectively. Nausea (33.3%), neutropenia (26.2%), anemia (21.4%), alopecia (21.4%), and vomiting (16.7%) are the most commonly reported adverse events.

Grade 3 toxicities were infrequent and they were neutropenia (4.8%), thrombocytopenia (2.4%), nausea (2.4%), and fatigue (2.4%). Two patients developed interstitial lung disease (ILD)/pneumonitis (4.8%), both of which were grade 1-2 events; no grade 4 or fatal ILD events were observed. A patient (2.4%) suffered an asymptomatic loss of left ventricular ejection fraction.

A wihdrawal of the dose was needed in only a small portion of the patients with 9.5% of patients having dose lowered, 14.3% having temporary disruptions of their treatment, and 7.1% of patients having to withdraw permanently because of toxicity. Generally, the safety profile was still controllable and in line with previously observed toxicity profiles of T-DXd and had no novel safety signals (Table 4, Figure 4).

DISCUSSION

The present study is a single-center analysis, which is a real-world study study that demonstrates that trastuzumab deruxtecan (T-DXd) exhibits a high degree of clinical activity in a well-pretreated and at-risk population of metastatic breast cancer patients, i.e., the HER2-positive group (16,17). Three characteristics that are distinguishable to this group as compared to what normally appears in clinical trials are the high rate of late-line therapy, the high rate of central nervous system (CNS) disease, and high rate of patients upon initial lower dose of 3.6 mg/kg. Whereas these preset conditions of both baseline and treatment-related conditions are not desirable, this objective response rate (ORR) of 67.5% and a median real-world progression-free survival (rwPFS) of 14.4 months still indicates maintained antitumor efficacy in clinical practice (18,19).

The study is relevant in the late-line treatment situation, as far as its interpretation is concerned. A 60.9% ORR and 16.4-month median progression-free survival (PFS) accompanied by a T-DXd in the landmark phase-DESTINY-Breast01 study with more than half of the patients being heavily pretreated demonstrated an improvement in the survival with a revised data. The trials such as DES-

Table 4: Treatment-related adverse events

Adverse event	All grades, No. (%)	Grade ≥3, No. (%)
Any adverse event	25 (59.5)	5 (11.9)
Nausea	14 (33.3)	1 (2.4)
Neutropenia	11 (26.2)	2 (4.8)
Anemia	9 (21.4)	0
Alopecia	9 (21.4)	0
Vomiting	7 (16.7)	0
Thrombocytopenia	5 (11.9)	1 (2.4)
Diarrhea	4 (9.5)	0
Fatigue	3 (7.1)	1 (2.4)
ILD/pneumonitis	2 (4.8)	0
Left ventricular ejection fraction decline	1 (2.4)	0
Dose reduction after initiation	4 (9.5)	—
Temporary treatment interruption	6 (14.3)	—
Permanent discontinuation due to toxicity	3 (7.1)	—

ILD indicates interstitial lung disease

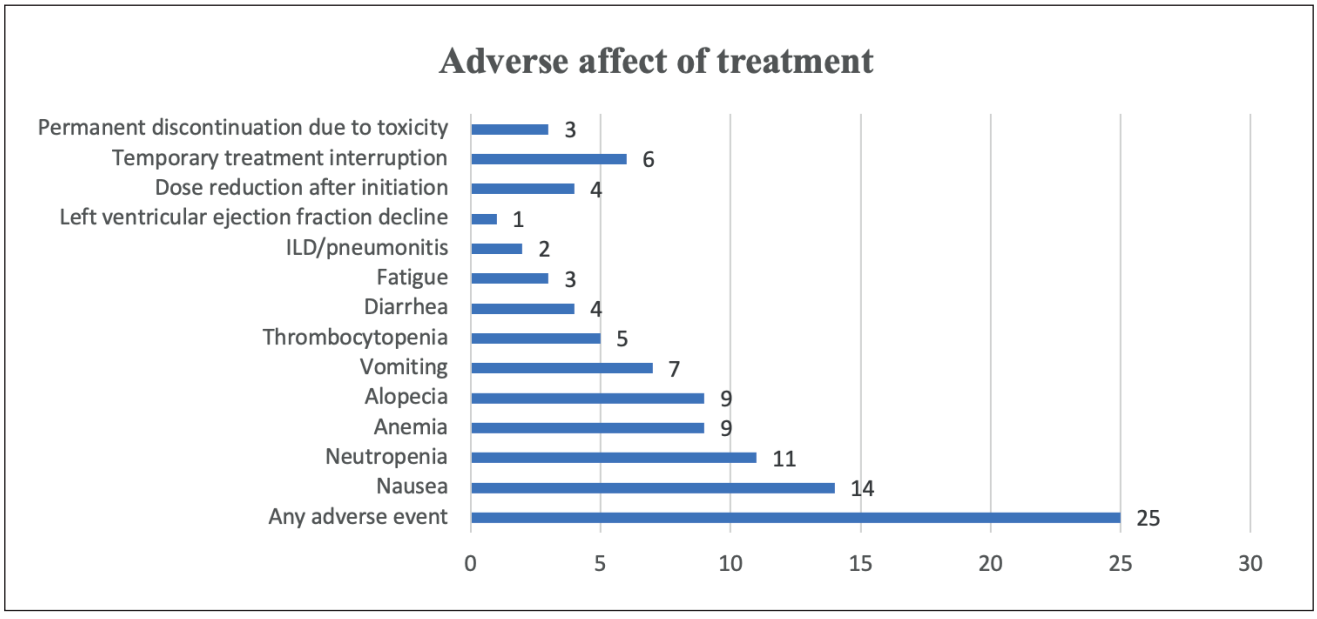

Figure 4: Adverse effects of treatment exposure.

TINY-Breast02 and DESTINY-Breast03 also proved the effectiveness of T-DXd and its use in the earlier lines of treatment, which is more effective than physician choice and trastuzumab emtansine. According to the outcomes of real-life cases provided by the Turkish Oncology Group, median rwPFS was 17.9 months, and ORR was 71.4 percent but only 40.1 percent of the respondents used T-DXd during the fourth or later line of treatment. On the other hand, 81.0 percent of the current cohort patients had 4th or more line and yet a median rwPFS of 14.4 months. This finding confirms the hypothesis that even in the settings of attenuated efficacy such as can be anticipated and may be experienced with later-line dosage, T-DXd is still able to exert a clinically significant effect on the patient even following extended pretreatment.

The prevalence rates of the brain metastases high in this cohort also contribute to the further complications of the clinical picture. The baseline CNS involvement proportion amounted to 38.1, and it is much higher than the prior values in real-life research. However, the ORR of 62.5 percent and median rwPFS of 13.2 months of this subgroup are consistent with the emerging evidence that points to the intracranial activity in T-DXd. In DESTINY-Breast01, the ORR of brain metastases with previous treatment therapy in patients was 58.3% and the median PFS was 18.1 months (20,21). Results of the combination of trials of DESTINY have intracranial response rates of approximately 45 percent in consistent and inactive CNS disease. Intracranial ORR was also observed in the prospective data reported by TUXEDO-1 study (73.3% in patients with active brain metastases) but it was confirmed by DESTINY-Breast12 in a broad population (22). Together with the results given above, the interpretation can be made that T-DXd remains a highly effective intervention in the patients with brain metastases, and the outcome of the present research is in agreement with this fact (23,24).

Another point of interest is that the efficacy was maintained using low starting dose of 3.6 mg/kg. T-DXd 5.4mg/kg has been licensed as a dose in breast cancer in all of their landmark studies on the DESTINY-Breast (25,26). Therefore, the dose response in the reduced-dose sub-group of the current study cannot be considered as dosage equivalence. Nevertheless, the ORR of 64.7 percent and median rwPFS of 14.1 months in patients initiating treatment at 3.6mg/kg suggest that clinical meaningful benefit of lower starting doses remains in the selected patients, particularly in frailty, older and highly burdened patients. The observation should be considered as the hypothesis generating one and should be investigated in the further research in more extensive real-world data or new studies, which will include dose-intensity studies and the appropriate evaluation of the confounding factors (27).

This study demonstrated a net positive safety and appears to have a less favorable rate, quantitatively, compared to clinical trials and other real-life studies. With interstitial lung disease (ILD)/pneumonitis 4.8 of which were low-grade, 59.5 percent of patients had any-grade adverse events, and grade 3 in 11.9 percent. Oncology Group study in Türkiye has reported higher rates of any-grade toxicity (68.4%) and ILD (7.8%); however, the DESTINY-Breast12 study provided 13%-16% rate of ILD according to CNS involvement (28). Although low dose strength may also be among the factors contributing to the difference in the toxicity burden observed, care should be taken to make cross-study comparisons. Data collection differences in the retrospective, the frequency of imaging, the reporting of adverse events, and the sample size may be a critical part of toxicity estimates. In that matter, the findings imply that the tolerability profile may be potentially positive in this group, however, there is no data regarding the presence of dose toxicity relationships.

Treatment line is one of the outcome determinants in this study as has been mentioned in the previous literature. T-DXd-treated patients who received treatment on earlier lines had synonymous response rates and rwPFS as compared to those who received treatment on later lines. This finding is consistent with the findings of DESTINY-Breast03 and real-life studies, which demonstrate better results in all cases of earlier use of T-DXd (29). Importantly, however, in the present study, it is also interesting to note that there is no actual annihilation of meaningful clinical benefit in subsequent lines. Response rates and survival rates in patients who received T-DXd in the fourth (or subsequent) line were also clinically significant and this justifies the utility of the drug in relation to the application in different treatment lines.

There are several weaknesses to be accepted. First, the retrospective design has the risk of selection bias, incomplete reporting of adverse events and variance of imaging intervals. Second, the size of the sample is not very large and this imposes certain limitations on the statistical might of subgroup analyses and also fails to enable conducting a powerful multivariable adjustment. Third, the most popular is reduced-dose initiation, which makes it difficult to compare patients who are put on lower dosing with those who are put on regular dosing. Fourth, the responses analysis was not centralized and based on the RECIST but based on the routine clinical practice. Therefore, the findings cannot be considered the evidence of dose equivalence or a factor to alter the dosing resemblances. Rather they provide clinical experience regarding the outcomes of treatment in less controlled and more heterogeneous clinical environments.

Limitations and Future Directions

Despite the clinical importance of the current study findings, there are several limitations that should be mentioned

when speaking about the findings. First, the retrospective single-center design may be also a cause of bias, in particular, selection bias, information bias, and unmeasured confounding. The decision making on therapies like the initial dose and the time of treatment was not conducted in line with the standard protocols but rather at the will of the physicians, this will probably engage the internal validity of the findings. Retrospective data collection can also contribute to incomplete or inconsistent reporting particularly when adverse event is considered as likelihood of under-reporting of low-grade toxicities such as early interstitial lung disease (ILD) may not be reported at all due to lack of systematic screening protocols, nor uniform structures of reporting.

Second, the sample size of the study is rather limited, and this decreases its statistical power, particularly subgroup analysis of patients with metastases to the central nervous system, and reduced-dose therapy. The latter is also constrained by the lack of multivariate statistical adjustment that would be useful in regulating the presence of important confounding factors of the performance status, comorbid conditions, prior exposure to treatment, and the overall disease burden. The correlations that exist between the properties of treatments and the outcomes as a result must be viewed with caution.

Third, the initiation is high (3.6 mg/kg) which poses a severe threat of confounding by indication. It is most likely that patients who start lower doses will be a more clinically vulnerable group, including frail patients, old patients, or prior treatment, and the results of both efficacy and safety interpretation will be difficult. Therefore, it is not possible to maintain clinical activity in this subgroup as a measure of dose equivalence to the approved regimen of 5. 4mg/kg.

Additionally, the response appraisals were also not conducted in the dynamic of the routine clinical practice and were not conducted in a centralized and blinded assessment on standardized RECIST standards. The estimation of objective response rates and progression-free survival can have been estimated because of imaging frequency, radiologic interpretation and documentation variability. Similarly, there was no equal measure of CNS-specific results in terms of specific intracranial response criteria, which limits the accuracy of results regarding the efficacy of trastuzumab deruxtecan in brain metastases patients.

Finally, the variability of clinical outcomes could have been caused by heterogeneity of former treatment methods, treatment lines and supportive care treatments. The study also lacks mature overall survival data, which is also one of the key endpoints that will be used to assess the long-term therapeutic benefit. Such limitations highlight the nature of cautious interpretation and the descriptive nature of the findings.

A last drawback of this study is that it was not possible to conduct extensive multivariable regression analyses. Care was taken to ensure the relatively small number of outcome events and the small sample size would not lead to unstable estimates or models being over-fitted by the inclusion of multiple covariates. Thus, the results are presented with the understanding that they are mainly descriptive and hypothesis generating. Essentially larger studies with adequate statistical power should be conducted to assess independent prognostic and predictive factors of treatment outcomes.

These flaws need to be overcome by the next generation of research that should implement properly designed prospective and multicenter studies that could provide stronger and more generalizable evidence. Larger real-world datasets using standardized data collection methods would be useful in making appropriate adjustment of confounding factors and stronger subgroup analyses. In particular the problem of dose optimization strategies needs to be discussed further to obtain a deeper understanding of the relationship between the dose intensity and clinical outcome, especially in especially vulnerable patients. Moreover, certain research to determine the degree of intracranial efficiency using standardized CNS-related standards of answer ought to be performed to better describe the role of trastuzumab deruxtecan in patients with metastases in the brain. Integration of the real world evidence and the information of randomized clinical trials may lead to the improved level of knowledge on treatment effectiveness in different clinical settings and assist in creating more personalized treatment plans.

Conclusion

In conclusion, this clinical trial that only assessed a single center suggests that trastuzumab deruxtecan continues to have significant and clinical antitumor activity in a high-risk patient population with metastatic breast cancer (HER2 +) with a high prevalence of central nervous system metastases and an initial lower dose. These are not good clinical features, nevertheless, the obtained response rates and progress-free survival rates are consistent with the findings of a clinical trial and other realistic studies, which demonstrates the external validity of findings.

Importantly, the outcomes confirmed the fact that despite the later stages of the treatment, trastuzumab deruxtecan has preserved the clinically relevant efficacy, which supports the premise that this type of therapy could be used as an option even in the conditions that do not presuppose the first-line setting. The comparative activity of patients with brain metastases contributes to the growing body of evidence to prove its efficacy in such a difficult patient group. Although this cohort indicated that lower dose-initiation was not associated with poorer clinical outcome, the result is merely hypothesis-generating and cannot be considered as evidence of dose equivalence.

Overall, this evidence demonstrates a high potential of trastuzumab deruxtecan as a therapeutic agent in diverse and clinically complicated populations of patients and the need of further research that can improve dosing regimens and better delimit intracranial activity and simplify the selection of patients in clinical practice.

Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: **Orcun Can,** data collection, analysis and interpretation of results, and draft manuscript preparation: **Orcun Can** and **Osman Gokhan Demir**. The authors reviewed the results and approved the final version of the article.

Conflicts of Interest

The authors declare that there is no conflict of interest to disclose.

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Ethical Approval

The study was approved by the Republic of Türkiye Istinye University Clinical Research Ethics Committee (date: 06.12.2025, number: (2024-KAEK-120) / 2/2025.G-109).

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