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ORIGINAL RESEARCH

Real-World Safety of Trastuzumab Deruxtecan in Patients with HER2-Positive and HER2-Low Metastatic Breast Cancer in Saudi Arabia: A Retrospective Cohort Study

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Introduction: Trastuzumab deruxtecan (T-DXd) has become an important treatment option for patients with HER2-positive and HER2-low solid tumors, yet real-world evidence on its safety remains limited, particularly in Middle Eastern populations. This study evaluates the safety profile of T-DXd in routine clinical practice at a major tertiary center in Makkah, Saudi Arabia.

Methods: A retrospective cohort study was conducted at King Abdullah Medical City and included adults with HER2-positive or HER2-low metastatic breast cancer who received at least one dose of T-DXd between 2022 and 2024. Electronic medical records were reviewed for demographic data, prior treatments, and adverse events. Toxicities were graded according to CTCAE v5.0. The primary outcome was the incidence and severity of T-DXd–related adverse events. Secondary outcomes included treatment discontinuation rates and adherence to recommended interstitial lung disease (ILD) monitoring protocols.

Results: Thirty-one patients were included (93.5% female; median age 50–59 years). Hematologic toxicities were most common, occurring in 87.1% of patients. Respiratory events including ILD and pneumonitis were documented in 28% of patients. Among patients who underwent imaging according to recommended intervals, respiratory events were identified more frequently (36%) than in those with less consistent monitoring (11%), likely reflecting increased detection of subclinical events rather than a true difference in incidence. Treatment discontinuation occurred in 25.8% of patients, primarily due to adverse events or progression.

Conclusion: T-DXd was generally tolerable in this small Saudi cohort, with hematologic and respiratory toxicities being the most frequent. The relatively higher frequency of respiratory events and the observed differences by monitoring adherence should be interpreted cautiously given the descriptive design. Larger multicenter studies are needed to better define safety patterns and optimal monitoring strategies.

Keywords: trastuzumab deruxtecan, HER2-positive, HER2-low, interstitial lung disease, real-world evidence, metastatic breast cancer, Saudi Arabia

Introduction

Trastuzumab deruxtecan (T-DXd) has emerged as one of the most important recent advances in the management of HER2-positive and HER2-low solid tumors. As an antibody–drug conjugate (ADC), T-DXd combines a humanized anti-HER2 monoclonal antibody with a cleavable linker and a potent topoisomerase I inhibitor payload, enabling selective drug delivery and minimizing off-target toxicity.[1,2] The drug was first approved by the U.S. Food and Drug Administration in 2019 for HER2-positive metastatic breast cancer, and subsequent evidence expanded its indications

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to HER2-low breast cancer, HER2-positive gastric cancer, and HER2-mutant non-small cell lung cancer (NSCLC).[3–7] These approvals were largely driven by the DESTINY clinical trial program, which consistently demonstrated improved outcomes across multiple tumor types. In HER2-positive metastatic breast cancer, the DESTINY-Breast03 trial reported significantly longer progression-free survival and overall survival with T-DXd compared with trastuzumab emtansine (T-DM1), establishing it as a preferred second-line treatment.[8] The DESTINY-Breast04 trial subsequently expanded the therapeutic role of T-DXd to patients with HER2-low metastatic breast cancer, showing meaningful survival improvements and defining a new disease category.[9] Beyond breast cancer, the DESTINY-Gastric01 trial demonstrated superior response rates and overall survival in HER2-positive advanced gastric cancer compared with traditional chemotherapy.[10] The DESTINY-Lung01 study further highlighted its activity in HER2-mutated NSCLC, leading to regulatory approval and adding a new therapeutic option for this molecularly defined population.[11] Alongside these benefits, safety concerns —particularly interstitial lung disease (ILD) and pneumonitis have become a defining feature of T-DXd's clinical profile. A pooled analysis of T-DXd studies reported ILD in approximately 20% of treated patients, including rare but life-threatening grade 4–5 cases.[2,6] Most ILD events occur within the first six months of therapy and may be asymptomatic, underscoring the importance of structured surveillance with chest CT or high-resolution CT.[2,6,12] International guidelines emphasize prompt recognition and early corticosteroid treatment to prevent progression.[13] Other notable toxicities include neutropenia, thrombocytopenia, anemia, leukopenia, and gastrointestinal events such as nausea, vomiting, and diarrhea.[9,14,15] Although cardiovascular events appear less frequent than with earlier HER2-directed therapies, routine cardiac monitoring remains recommended.[16] Despite the growing body of evidence from global clinical trials, real-world data remain limited, particularly from the Middle East. Treatment practices and patient characteristics in Saudi Arabia such as higher rates of obesity, diabetes, and hypertension may influence toxicity patterns and tolerability.[11] Despite the growing evidence from global clinical trials, real-world safety data on trastuzumab deruxtecan from Middle Eastern populations remain very limited. In Saudi Arabia and the wider region, patient characteristics and comorbidity patterns including obesity, diabetes, and hypertension may influence treatment tolerability and adverse event detection in routine practice. In addition to describing the safety profile of trastuzumab deruxtecan, this study also explores adherence to recommended interstitial lung disease surveillance in real-world care, an area that has not been well characterized in regional practice. Accordingly, this study aimed to evaluate the real-world safety profile of trastuzumab deruxtecan among patients with HER2-positive and HER2-low metastatic breast cancer treated at King Abdullah Medical City in Makkah, Saudi Arabia, with particular focus on the incidence and severity of adverse events and a descriptive assessment of adherence to interstitial lung disease monitoring recommendations.

Methods

This retrospective cohort study was conducted at King Abdullah Medical City (KAMC), Makkah, Saudi Arabia. The study included all adult patients (≥18 years) with confirmed HER2-positive or HER2-low metastatic breast cancer who received at least one dose of trastuzumab deruxtecan (T-DXd) between January 1, 2022 and November 30, 2024. Patients were excluded if they did not receive T-DXd or if essential clinical data were missing from their medical records. Data were collected from the hospital's electronic medical record system (TrackCare) using a standardized extraction form to ensure consistency. Adverse events were identified through structured review of physician progress notes, oncology clinic documentation, laboratory results, and radiology reports. The collected variables included demographic data (age, sex, BMI), clinical characteristics (cancer stage, HER2 expression level, ECOG performance status, comorbidities), and treatment history (previous lines of therapy, prior chemotherapy, radiotherapy, endocrine therapy, and targeted therapy). Treatment-related variables included T-DXd start date, number of administered cycles, dose modifications, treatment interruptions, and reasons for discontinuation. Follow-up duration was defined from the initiation of T-DXd to the last documented clinical encounter or treatment discontinuation, whichever occurred first. The primary outcome was the incidence and severity of adverse events associated with T-DXd. Adverse events were classified and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Interstitial lung disease (ILD) and pneumonitis were defined based on radiologic findings (chest CT or HRCT) consistent with interstitial changes, with or without corresponding clinical symptoms, as documented by treating physicians or radiology reports. Events were considered present if documented by treating physicians and/or confirmed by radiologic assessment. Secondary outcomes

included treatment tolerability (measured by dose reductions, dose delays, or permanent discontinuation) and adherence to recommended interstitial lung disease (ILD) surveillance. For ILD monitoring, adherence was defined as undergoing chest CT or HRCT imaging at baseline and at intervals of approximately 6–12 weeks, consistent with international recommendations. Patients were categorized into "adherent" and "non-adherent" groups based on compliance with these imaging intervals. The incidence of ILD or pneumonitis was compared between groups to evaluate whether monitoring adherence was associated with earlier detection. Descriptive statistics were used to summarize the data. Categorical variables were presented as frequencies and percentages. Where applicable, 95% confidence intervals were calculated for key proportions to provide an estimate of precision. The association between HER2 status (positive vs low) and specific toxicities was also explored. Given the small number of HER2-low patients (n=4), subgroup comparisons were considered descriptive only and not intended for inferential interpretation. Given the small sample size and exploratory nature of the study, analyses were limited to descriptive statistics. No inferential hypothesis testing was performed, and findings should be interpreted as hypothesis-generating. Statistical analyses were performed using IBM SPSS Statistics software. Ethical approval was obtained from the Institutional Review Board of King Abdullah Medical City (IRB Approval No.: 25-1371). All patient information was anonymized and handled confidentially in compliance with institutional and national research ethics guidelines.

Results

Patient Demographics and Clinical Characteristics

A total of 31 patients met the inclusion criteria for this retrospective cohort as shown in Table 1. Nearly half of the cohort (48.4%) were between 50 and 59 years old, while 32.3% were aged 40–49 years. Smaller proportions were older than 60 years (12.9%) or between 30 and 39 years (6.5%). The study population was predominantly female, with only two male

Table 1 Patient Demographics and Baseline Clinical Characteristics (n = 31)

Characteristic	Category	Frequency	Percentage
Age (years)	30–39	2	6.4%
	40–49	10	32.3%
	50–59	15	48.4%
	>60	4	12.9%
Gender	Female	29	93.5%
	Male	2	6.5%
BMI classification	Underweight	1	3.2%
	Normal weight	6	19.4%
	Overweight	12	38.7%
	Obese	12	38.7%
Smoking status	No	31	100%
	Yes	0	0%
Cancer type	Breast cancer	31	100%
HER2 expression level	HER2-positive	27	87.1%
	HER2-low	4	12.9%
Stage of cancer	Stage IV (metastatic)	31	100%
ECOG performance status	0–1	22	71.0%
	2–4	9	29.0%
Comorbidities	Type 2 diabetes mellitus	9	29.0%
	Hypertension	12	38.7%
Number of previous lines of therapy	One line	2	6.4%
	Two lines	4	12.9%
	Three lines	15	48.4%
	More than three	8	25.8%

(*Continued*)

Table 1 (Continued).

Characteristic	Category	Frequency	Percentage
Previous treatments	Chemotherapy	26	83.9%
	Radiotherapy	8	25.8%
	Hormonal therapy	16	51.6%
	Targeted therapy	31	100%
	Immune checkpoint inhibitors	1	3.2%
	Surgery	7	22.5%

patients (6.5%). In terms of body mass index, most patients were either overweight (38.7%) or obese (38.7%). Normal BMI was recorded in 19.4% of the cohort, while one patient (3.2%) was underweight. None of the included patients reported current or prior tobacco use. All patients had metastatic (stage IV) breast cancer at the time of T-DXd initiation. HER2-positive disease accounted for 87.1% of cases, whereas 12.9% were classified as HER2-low. Functional status was generally preserved; 71% had an ECOG performance score of 0–1, while the remaining 29% had scores of 2–4. Hypertension (38.7%) and type 2 diabetes mellitus (29%) were the most frequently documented comorbidities. Treatment history showed that nearly half of the cohort (48.4%) had received three prior lines of systemic therapy, and one-quarter (25.8%) had undergone more than three lines. All patients had previously been treated with HER2-directed therapy. Chemotherapy exposure was documented in 83.9% of cases, while 51.6% had received hormonal therapy; 25.8% had undergone radiotherapy.

Treatment Details and Outcome of Trastuzumab Deruxtecan Therapy

As presented in Table 2, the majority of patients (51.6%) had a follow-up duration of 0 to 6 months, followed by 32.3% with 6 to 12 months, and 16.1% with 12 to 18 months. At the end of the study period, 25.8% (n = 8) of patients had discontinued trastuzumab deruxtecan (T-DXd) therapy, while 74.2% (n = 23) continued treatment. Treatment discontinuation was mainly attributed to adverse events (37%), followed by disease progression (25%), and patient preference or poor compliance (25%). (Figure 1).

Safety and Adverse Events

Hematological toxicities were the most commonly observed adverse events, occurring in 87.1% of patients as shown in Table 3. These included neutropenia, anemia, and thrombocytopenia, and were observed primarily in the HER2-positive subgroup (85.2%). Respiratory events, including interstitial lung disease (ILD) and pneumonitis, were reported in 28% of patients. Gastrointestinal toxicities occurred in 25.8%, followed by hepatobiliary events in 12.9%. General adverse events, mainly fatigue, were reported in 9.6%. No dermatologic, hypersensitivity, musculoskeletal, or cardiovascular events were documented. Echocardiographic monitoring was performed in 83.8% of the cohort. Figure 2 presents the distribution of hematologic adverse events among patients.

Table 2 Trastuzumab Deruxtecan Treatment Details and Patient Outcomes. n = 31

Characteristic	Category	Frequency	Percentage
Duration of Follow-up (Months)	0–6 months	16	51.6%
	6–12 months	10	32.3%
	12–18 months	5	16.1%
Discontinuation of treatment	Yes	8	25.8%
	No	23	74.2%
Final status of the patient	Alive	28	90.3%
	Dead	3	9.7%

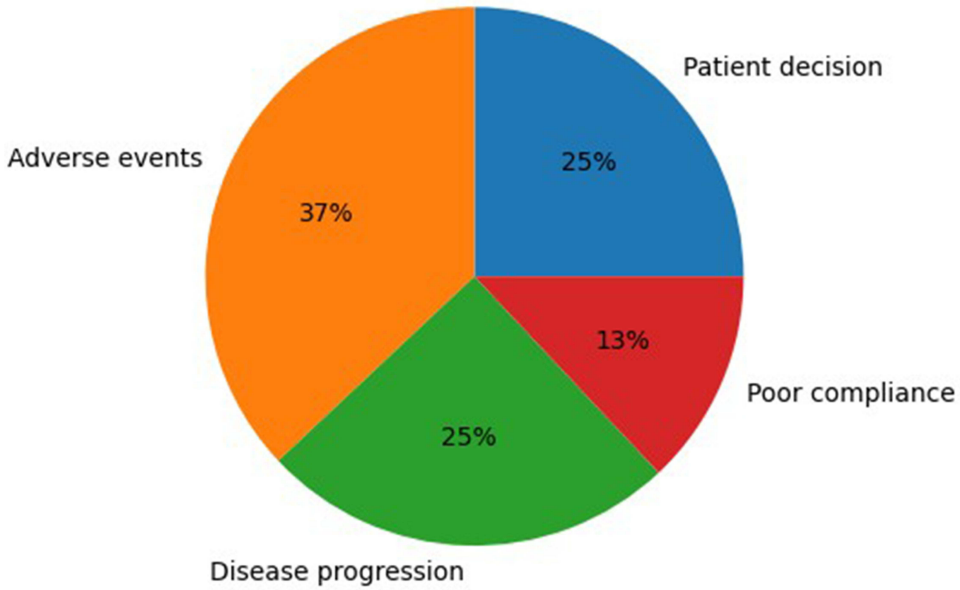

Figure 1 Reasons for discontinuation of trastuzumab deruxtecan therapy. n = 8.

Adverse Event Management and Outcomes

Management strategies and outcomes of adverse events are summarized in Table 4. Most adverse events were manageable with supportive care. Hematologic toxicities were predominantly mild to moderate (CTCAE grade 1 to 2 in 85.2%), and were treated with supportive measures (92.6%), interruptions of treatment (11.1%), and dose reductions (3.7%). Approximately half of these events resolved by the end of follow-up (51.8%), while (48.1%) were ongoing.

Respiratory events were managed primarily by interruptions of treatment (77.8%) and supportive care (33.3%), with 88.9% of cases resolving. Gastrointestinal toxicities required combined management strategies including dose reductions (50%), treatment interruptions (25%), and supportive care (75%). Hepatobiliary events were equally managed with supportive care and treatment modifications. All cases of fatigue were grade 3 or higher and managed through a combination of supportive care, treatment interruption, and dose modification.

Additionally, hypokalemia (22.5%), cough (16.1%), and fever (12.9%) were among the most frequent "other" adverse events.

Table 3 Comparative Examination of Adverse Events Between HER2-Positive and HER2- Low Patient Groups

System	Adverse Event	Total Count (%)	HER2 Expression Level	
			HER2+	HER2-Low
Hematological	Neutropenia, Anemia, Thrombocytopenia	27 (87.1%)	23 (85.2%)	4 (14.8%)
Respiratory	ILD, Pneumonitis, Pulmonary Effects	9 (28.0%)	7 (77.8%)	2 (22.2%)
Gastrointestinal	Nausea, Vomiting, Diarrhea, Constipation, Abdominal pain	8 (25.8%)	7 (87.5%)	1 (12.5%)
Hepatobiliary	Elevated liver enzymes, Increased ALP, and Ascites	4 (12.9%)	4 (100%)	0 (0.0%)
General	Fatigue	3 (9.6%)	3 (100%)	0 (0.0%)
Dermatological	Rash, Pruritus, Hyperpigmentation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypersensitivity	Infusion-related Reactions	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal	Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiovascular	Heart Failure, Ejection Fraction Decline	0 (0.0%)	0 (0.0%)	0 (0.0%)

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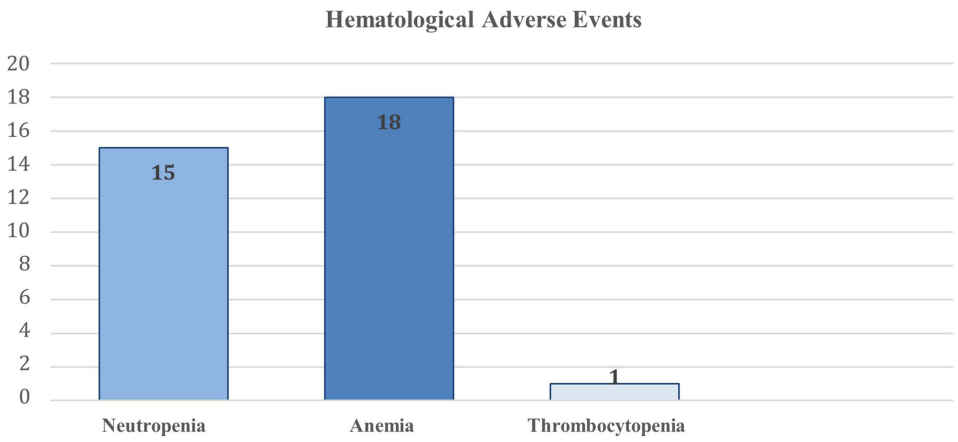

Figure 2 Counts of Hematologic Adverse Events. n = 27.

Effectiveness of ILD Monitoring Protocols in Detecting and Managing Interstitial Lung Disease/Pneumonitis

All Adherence to ILD monitoring protocols was assessed among all patients. According to recommended guidelines, baseline imaging followed by repeat chest CT or non-contrast high- resolution CT (HRCT) every 6 to 12 weeks was advised. Among the cohort, 71% (n=22) adhered to the recommended monitoring frequency, undergoing baseline imaging followed by scans at regular intervals within the 6 to12 week window. The remaining 29% (n=9) were classified as non- adherent due to infrequent imaging, delayed follow-ups, or insufficient data to assess compliance. Among patients who adhered to the monitoring guidelines, 36% (n=8) were diagnosed with respiratory conditions suggestive of ILD or pneumonitis. On the contrary, only 11% (n=1) of the non-adherent cohort acquired such a diagnosis. This finding may reflect increased detection of subclinical events rather than a true difference in incidence, and causal inference is not possible. Further research is needed to evaluate its impact on clinical outcomes.;

Discussion

This study provides one of the first descriptions of trastuzumab deruxtecan (T-DXd) safety outcomes among patients with metastatic HER2-positive and HER2-low breast cancer in Saudi Arabia. Although clinical trials have established the drug's clinical benefit across multiple tumor types,[1–5] the real-world experience—particularly in Middle Eastern populations—remains scarce. Our findings generally align with international reports but also reveal several important differences that merit consideration when applying T-DXd in routine practice. Hematologic toxicities were the most common adverse events in our cohort, affecting 87.1% of patients. This trend mirrors the high rate of cytopenias reported in major trials, including DESTINY-Breast03 and pooled meta-analyses.[8,9] The pattern is biologically plausible, as the membrane-permeable payload of T-DXd is known to exert a strong by-stander effect that may intensify bone marrow suppression.[14] Most hematologic events in our study were mild to moderate and manageable with supportive measures or

Table 4 Frequency, Severity, Management, and Outcomes of Adverse Events Related to Trastuzumab deruxtecan (T-DXd)

Adverse Events	Total Count	Severity (CTCAE Grade)		Management Intervention			Outcome	
		Grade 1–2	Grade 3–5	Dose Reduction	Treatment Interruption	Supportive Care	Resolved	Ongoing
Hematological	27	23 (85.2%)	4 (14.8%)	1 (3.7%)	3 (11.1%)	25 (92.6%)	14 (51.8%)	13 (48.1%)
Respiratory	9	9 (100%)	0 (0.0%)	1 (11.1%)	7 (77.8%)	3 (33.3%)	8 (88.9%)	1 (11.1%)
Gastrointestinal	8	6 (75.0%)	2 (25.0%)	4 (50.0%)	2 (25.0%)	6 (75.0%)	7 (87.5%)	1 (12.5%)
Hepatobiliary	4	3 (75.0%)	1 (25.0%)	1 (25.0%)	1 (25.0%)	2 (50.0%)	2 (50.0%)	2 (50.0%)
Fatigue	3	0 (0.0%)	3 (100%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (100%)	0 (0.0%)
Other adverse events	17	–	–	3 (17.6%)	15 (88.2%)	7 (41.2%)	15 (88.2%)	2 (11.8%)

short treatment delays, consistent with expert recommendations.[13] The limited need for dose reductions (3.7%) suggests that with careful monitoring, T-DXd is tolerable even in heavily pretreated patients. One of the most notable findings is the higher incidence of interstitial lung disease (ILD) and pneumonitis compared with clinical trial data. In our cohort, ILD occurred in 28% of patients, whereas published trials have reported rates between 10% and 13.6%.[6,8,17] Several explanations are possible: differences in comorbidity profiles, variable thresholds for radiologic evaluation, or earlier detection due to more frequent imaging. Similar observations were reported in a recent nationwide real-world study, where ILD rates exceeded those seen in controlled trials.[18] Importantly, no cases of grade 4 or 5 ILD were identified in our cohort. The absence of severe events may reflect adherence to early detection and prompt drug interruption, as recommended by international panels.[2,6,12] Differences in ILD detection between monitoring groups may reflect increased identification of subclinical events rather than a true difference in incidence. Among patients who underwent regular imaging, ILD was identified more frequently (36%) than in those with irregular surveillance (11%). Although this might appear counterintuitive, it likely reflects detection of subclinical or early-stage ILD, which is often radiologic rather than symptomatic.[12,19] These findings are consistent with guideline recommendations emphasizing routine CT or HRCT at baseline and every 6–12 weeks during therapy.[13] Without such surveillance, asymptomatic disease could progress unnoticed to severe or fatal toxicity.

Gastrointestinal and general toxicities were less frequent than expected when compared with pooled analyses, where nausea and vomiting affect more than 70% of patients.[9,14–16] This difference may relate to consistent use of prophylactic antiemetics or variation in documentation within retrospective datasets. Fatigue—commonly reported in clinical trials—was also less frequent in our cohort. As with GI symptoms, this may reflect underreporting rather than a true difference in tolerability. Cardiovascular toxicity was not observed, which supports evidence that T-DXd carries a relatively lower cardiac risk compared with earlier HER2-targeted therapies.[10] Treatment discontinuation occurred in approximately one-quarter of patients, a rate comparable to real-world cohorts and later-line breast cancer populations.[17,18] The majority of discontinuations were due to disease progression or toxicity, highlighting the need for individualized treatment planning, especially for patients with multiple comorbidities or limited functional status. The growing use of T-DXd in HER2-positive, HER2-low, and HER2-mutated tumors underscores the need for region-specific data. Our findings contribute meaningful insights to help clinicians balance efficacy and safety, particularly in populations with high prevalence of obesity, diabetes, and hypertension—factors that may influence toxicity risk.[11] This study also reinforces the importance of structured ILD monitoring programs, which have shown benefit in early detection and reducing severe events in international settings.[19] This study has several limitations. It was a single-center retrospective study with a small sample size, limiting generalizability. The HER2-low subgroup was particularly small, precluding meaningful subgroup comparisons.[20,21] Follow-up duration varied across patients, and reliance on retrospective documentation may have resulted in under-reporting of mild adverse events. Additionally, the descriptive design limits the ability to infer causality, particularly regarding ILD monitoring adherence.

Conclusion

T-DXd demonstrated a generally manageable safety profile in this small Saudi cohort, with hematologic and respiratory toxicities being the most frequently observed adverse events. The relatively higher frequency of respiratory events and the descriptive findings related to ILD monitoring should be interpreted cautiously. Larger multicenter studies are needed to better define safety patterns and optimize monitoring strategies.

Data Sharing Statement

The datasets generated and/or analyzed in this study are not publicly available due to institutional privacy regulations governing patient health information. Data may be made available by the corresponding author upon reasonable request, subject to IRB and institutional approval.

Ethical Considerations

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of King Abdullah Medical City (KAMC), Makkah, Saudi Arabia (IRB Approval No.: 25-1371). The KAMC IRB is registered with the National

BioMedical Ethics Committee at King Abdulaziz City for Science and Technology (KACST) (Registration No.: H-02-K-001). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation, Good Clinical Practice (ICH-GCP) guidelines. Given the retrospective observational design of the study and the use of anonymized clinical data, the requirement for informed consent was waived by the Institutional Review Board.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests related to this research.

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