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Real-World Evaluation of the Safety and Effectiveness of Trastuzumab Deruxtecan in Patients with Advanced Breast Cancer

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Abstract

Trastuzumab deruxtecan (T-DXd) offers substantial benefits for individuals with HER2-positive or HER2-low advanced breast cancer (ABC), though it carries a distinctive adverse event profile, notably interstitial lung disease (ILD). A retrospective observational cohort analysis was performed to assess the safety and effectiveness of T-DXd in patients with HER2-positive/low ABC managed at the European Institute of Oncology between December 2019 and April 2025. Key outcomes encompassed the cumulative ILD incidence, rates of grade ≥3 neutropenia across the cohort, and real-world progression-free survival (rwPFS) stratified by breast cancer subtype. ILD risks were evaluated in relation to factors such as age, smoking history, presence of lung metastases, subtype, previous immunotherapy exposure, and number of prior chemotherapy regimens. Grade ≥3 neutropenia was examined against age and neutrophil-to-lymphocyte ratio (NLR) measured on day 1 of cycle 3 (C3D1).
The study enrolled 112 patients, of whom 43% (n=48) had HER2-positive and 57% (n=64) had HER2-low ABC. Patients had received a median of 3.0 prior treatment lines for ABC [interquartile range (IQR) 2.0-5.0]. Previous antibody-drug conjugate therapy was noted in 58% (n=28) of HER2-positive cases and 17% (n=11) of HER2-low cases. De novo metastatic disease was present in 23% (n=26). With a median follow-up of 9 months (IQR 5.1-21.7 months), the 12-month cumulative ILD incidence reached 13 percent [95 percent confidence interval (CI) 7.2%-20.6%], including two fatal (grade 5) events (2%). Multivariable analysis indicated trends toward elevated ILD risk with prior immunotherapy (hazard ratio 3.22, 95 percent CI 1.06-9.72, P=0.052) and smoking history (hazard ratio 2.71, 95 percent CI 1.00-7.34, P=0.062). Grade ≥3 neutropenia affected 10 patients (9%) and was linked to lower NLR at C3D1 (hazard ratio 0.10, 95 percent CI 0.02-0.53, P<0.001). Real-world PFS was 21.82 months (95 percent CI 17.98-not reached) in HER2-positive ABC and 6.90 months (95 percent CI 4.93-10.19) in HER2-low ABC. This real-world evaluation supports the established safety and efficacy of T-DXd in advanced breast cancer. Potential ILD risk factors including prior immunotherapy and smoking, along with low NLR as a predictor of severe neutropenia, warrant additional research.

Keywords: Breast cancer, Trastuzumab deruxtecan, Interstitial lung disease, Toxicity

Introduction

In 2024, breast cancer was the most commonly diagnosed cancer and the second leading cause of cancer-related death among women in the United States [1]. Advanced breast cancer (ABC) remains incurable, even with the advent of innovative therapies such as antibody-drug conjugates (ADCs) [2]. These therapies utilize monoclonal antibodies to precisely target tumors and deliver highly potent cytotoxic agents that would be too toxic for systemic administration alone [3]. One such agent, the anti-HER2 antibody-drug conjugate trastuzumab deruxtecan (T-DXd), conjugates the topoisomerase I inhibitor deruxtecan (DXd) through a cleavable linker at a drug-to-antibody ratio of 8:1. T-DXd has demonstrated substantial efficacy in patients with ABC [1]. It is now indicated for a large proportion of ABC cases—up to approximately 85%—including those with HER2-positive disease (immunohistochemistry

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[IHC] 3+ or IHC 2+ with positive in situ hybridization [ISH]), luminal-type breast cancer or triple-negative breast cancer (TNBC) with HER2-low expression (IHC 1+ or IHC 2+ with negative ISH), and hormone receptor (HR)-positive disease with HER2-ultralow expression (IHC >0 but <1+) [1, 4–11].

Randomized trials of T-DXd in ABC have shown a generally tolerable safety profile, predominantly featuring mild-to-moderate gastrointestinal, hematological, and pulmonary treatment-related adverse events (TRAEs) [1, 4–12]. However, T-DXd can also cause significant TRAEs that result in treatment discontinuation in up to one-quarter of patients and dose reductions in as many as 27% of those receiving monotherapy [1, 4–12].

In these trials, some patients experienced interstitial lung disease (ILD)/pneumonitis, which can be life-threatening [1]. Current guidelines advocate for vigilant monitoring of T-DXd-treated patients, along with rapid diagnosis and treatment (including corticosteroids) for suspected or confirmed ILD/pneumonitis [13, 14]. Permanent discontinuation is recommended for events of grade 2 or higher, with limited evidence on the safety of rechallenge [13, 14]. To date, no validated biomarkers or clinical predictors for ILD/pneumonitis or other severe adverse events have been established, highlighting a key research priority.

Given T-DXd's toxicity profile and its expanding use across a broad patient population, there is a pressing need to identify predictive biomarkers for serious TRAEs. This would improve patient management by promoting better treatment compliance and reducing the risk of severe or fatal complications.

The Tox-DXd Retrospective Study gathered real-world clinical data from patients treated with T-DXd in routine practice to evaluate its safety and efficacy profiles and to explore possible predictors of significant TRAEs, particularly ILD/pneumonitis.

Materials and Methods

Study population

This was a single-center, retrospective, observational cohort study conducted at the European Institute of Oncology (IEO) in Milan, Italy. Data were retrospectively collected from consecutive adult patients (aged ≥18 years) with histologically confirmed invasive breast carcinoma and either HER2-positive or HER2-low status, as defined by American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (determined by local testing on the most recent biopsy specimen) [15, 16]. Patients received T-DXd in standard clinical practice between December 2019 and April 2025.

Eligibility required: age ≥18 years; administration of at least one cycle of T-DXd; and a diagnosis of advanced breast cancer (metastatic or unresectable locally advanced). Patients were excluded if they had received prior T-DXd in any setting, were concurrently enrolled in an interventional clinical trial, or had curable early-stage disease.

All patients underwent routine whole-body imaging (computed tomography in all cases, supplemented by positron emission tomography, magnetic resonance imaging, or combinations thereof in select patients) during treatment, aligned with IEO internal standards and international guidelines (approximately every 12 ± 2 weeks) [17]. In cases of respiratory symptoms, high-resolution chest computed tomography was performed as needed, and for suspected ILD, patients received pneumologist consultation and relevant laboratory tests, including complete blood count (CBC), liver and kidney function, electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase, infection-specific analyses (e.g., blood cultures, sputum, urinary antigens, β-D glucan), tumor markers, and autoimmune antibodies. ILD was graded according to Common Terminology Criteria for Adverse Events (CTCAE v.5.0): grade 1 (asymptomatic), grade 2 (symptomatic), and grades 3–4 (severe symptoms requiring oxygen). ILD management followed international guidelines [18].

Antiemetic prophylaxis consisted of dexamethasone (8 mg intravenous on day 1, followed by 4 mg orally from days 2 to 5), a 5-HT3 receptor antagonist (primarily granisetron 3 mg intravenous on day 1) in all patients, and an NK1 receptor antagonist in 95.5% of patients (107/112), either aprepitant (oral 125 mg on day 1, then 80 mg on days 2 and 3) or fosaprepitant (150 mg intravenous on day 1).

CBC was monitored before each T-DXd administration. Neutropenia was graded per CTCAE v.5.0 as grade 3 if neutrophil count was <1000–500/mm³ and managed according to international standards and the T-DXd Summary of Product Characteristics.

Collected variables included age, sex, body mass index, ethnicity, smoking history, comorbidities, concomitant medications, disease characteristics and sites, prior therapies, functional assessments (pulse oximetry, left

ventricular ejection fraction [LVEF], electrocardiogram, spirometry), blood tests (CBC, renal and liver function), T-DXd administration details (dose, cycles, reductions/interruptions, premedication), and toxicities (ILD, LVEF decline, neutropenia). Data were sourced from medical records. All patients were treated and followed at the IEO until T-DXd discontinuation for any reason.

The study was approved by the IEO institutional review board (Project Code: UID4802) and conducted in accordance with the Declaration of Helsinki and good clinical practice principles.

Endpoints

The primary objective was to evaluate the overall occurrence rate of interstitial lung disease (ILD) at any severity level during T-DXd therapy. Secondary objectives encompassed the occurrence rate of severe neutropenia (grade 3 or worse) while on treatment; real-world progression-free survival (rwPFS), calculated from the initiation of T-DXd to either disease progression or death from any cause (whichever happened first); and real-world overall survival (rwOS), calculated from the start of T-DXd to death from any cause.

Statistical analyses

Given the enrollment of 112 patients, a projected 6-month rate of any-grade ILD around 7.5% could be estimated with a 95% confidence interval spanning roughly 3.4% to 14.4% [19]. This degree of accuracy was judged suitable, considering previously documented ILD rates of 5% to 15% among patients with advanced solid tumours treated with T-DXd.

Baseline patient and tumour characteristics were described using summary statistics. Variables were categorised into typical groups whenever feasible. Continuous measures were presented as medians accompanied by interquartile ranges (IQR), and differences between groups were examined with the Wilcoxon signed-rank test. Categorical measures were shown as frequencies and percentages, with comparisons made via Fisher's exact test or chi-square test depending on the situation.

Occurrence rates of any-grade ILD and of severe neutropenia were determined using competing-risks methodology, reported per person-month through cumulative incidence functions (CIF) [20]. Competing events included death, disease progression, or cessation of T-DXd for any reason. Variations in these rates between groups were assessed with Gray's test [21].

Rates of any-grade ILD were investigated across predefined patient subgroups via Gray's test, covering HER2 status (positive versus low), smoking history (ever versus never), presence of pulmonary metastases (yes versus no), prior exposure to immunotherapy (yes versus no), extent of previous chemotherapy (2 or fewer lines versus more than 2), and patient age (below 65 versus 65 and above). Variables demonstrating suggestive associations in univariable testing (Gray's test $P < 0.10$) were included in a multivariable Fine-Gray competing-risks regression to obtain adjusted hazard ratios along with 95% confidence intervals.

Rates of severe neutropenia were likewise explored in subgroups based on HER2 status, neutrophil counts at the beginning of cycle 3, neutrophil-to-lymphocyte ratio (NLR) at that point (dichotomised at the median of 1.97), and prior chemotherapy burden. An additional multivariable Fine-Gray model incorporated starting age and NLR as continuous predictors to produce adjusted hazard ratios.

Real-world PFS and OS were derived using Kaplan–Meier estimates. The median duration of follow-up was derived from the reverse Kaplan–Meier method applied to overall survival. Potential differences in PFS according to HER2 status were evaluated with the log-rank test.

Testing was two-sided throughout, with a threshold for significance of $P < 0.05$. All computations were conducted using R Studio (version 4.2.2, released 31 October 2022).

Results and Discussion

Patient and disease characteristics

From December 2019 through April 2025, 112 patients received T-DXd as monotherapy in standard clinical practice at the European Institute of Oncology, Milan, Italy **(Tables 1 and 2)**. Among them, 48 patients (43%) had HER2-positive advanced breast cancer and 64 (57%) had HER2-low disease, encompassing both hormone receptor-positive and triple-negative cases. Approximately one-quarter (26 patients; 23.2%) had metastatic disease from the outset, while around one-fifth (22 patients; 19.6%) reported a smoking history.

Within the HER2-low subgroup, the majority (49 patients; 77%) were hormone receptor-positive, and 15 patients (23%) had triple-negative breast cancer. The

median age when beginning T-DXd was 58.5 years (IQR 48.0–67.0), following a median of 3 prior treatment regimens for advanced disease (IQR 2.0–5.0).

Prior treatment with another antibody-drug conjugate occurred in 28 HER2-positive patients (58.3%), predominantly trastuzumab emtansine (T-DM1; all 28) and occasionally trastuzumab duocarmazine (3 cases). Among HER2-low patients, 11 (17.2%) had received a prior ADC, exclusively sacituzumab govitecan in those with triple-negative disease. Chemotherapy exposure before T-DXd was universal, with 46 patients (41.1%) having undergone three or more chemotherapy regimens. Previous use of immune checkpoint inhibitors was noted in 10 patients (8.9%).

Table 1. Baseline patient characteristics

Characteristics	Overall (N = 112)	HER2-positive (N = 48)	HER2-low (N = 64)	P-value*
Age, years [median (Q1–Q3)]	58.5 (48.0–67.0)	53.5 (44.0–65.5)	61.0 (51.0–68.0)	0.022
Stage at initial diagnosis				0.674
Early or locally advanced	86 (76.8%)	35 (72.9%)	51 (79.7%)	
De novo unresectable/metastatic	26 (23.2%)	13 (27.1%)	13 (20.3%)	
Smoking history				0.607
No	90 (80.4%)	37 (77.1%)	53 (82.8%)	
Yes	22 (19.6%)	11 (22.9%)	11 (17.2%)	
Number of prior treatment lines [median (Q1–Q3)]	3.0 (2.0–5.0)	2.5 (1.0–4.0)	3.0 (3.0–5.0)	0.006
Prior antibody–drug conjugate (ADC)				<0.001
No	73 (65.2%)	20 (41.7%)	53 (82.8%)	
Yes	39 (34.8%)	28 (58.3%)	11 (17.2%)	
Prior immunotherapy				0.062
No	102 (91.1%)	47 (97.9%)	55 (85.9%)	
Yes	10 (8.9%)	1 (2.1%)	9 (14.1%)	
Prior chemotherapy ≥2 lines				0.280
No	66 (58.9%)	25 (52.1%)	41 (64.1%)	
Yes	46 (41.1%)	23 (47.9%)	23 (35.9%)	
T-DXd starting dose				0.015
5.4 mg/kg	72 (64.3%)	38 (79.2%)	34 (53.1%)	
4.4 mg/kg	27 (24.1%)	6 (12.5%)	21 (32.8%)	
3.2 mg/kg	13 (11.6%)	4 (8.3%)	9 (14.1%)	
Lung metastases at baseline				0.589
No	72 (64.3%)	29 (60.4%)	43 (67.2%)	
Yes	40 (35.7%)	19 (39.6%)	21 (32.8%)	

ADC, antibody–drug conjugate; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; IT, immunotherapy; Q, quartile; T-DXd, trastuzumab deruxtecan. *Wilcoxon rank-sum test for continuous variables; Pearson's chi-square test for categorical variables.

Table 2. Detailed breakdown of HER2-low histological subtypes and prior treatment history across patient groups

Characteristics	n/N (%)
HER2-low breast cancer (N = 64)	
Luminal-like	49/64 (77%)
Triple-negative	15/64 (23%)
Prior antibody–drug conjugate (ADC)	
Luminal-like subgroup[1]	1/49 (2%)

Triple-negative subgroup[2]	10/15 (68%)
HER2-positive group[3]	28/48 (58%)
Prior immunotherapy (IT)	
Triple-negative subgroup[4]	9/15 (60%)
HER2-positive group[5]	1/48 (2%)
11 (17.2%)	

ADC= antibody–drug conjugate; BC= breast cancer; HER2= human epidermal growth factor receptor 2; IT= immunotherapy. [1]One patient in the luminal-like group received sacituzumab govitecan. [2]All 10 patients in the triple-negative group received sacituzumab govitecan. [3]All 28 patients in the HER2-positive group received trastuzumab emtansine, and 10.7% (3/28) also received trastuzumab duocarmazine. [4]Among the 9 patients: 44% (4/9) received pembrolizumab, 44% (4/9) received atezolizumab, and 11% (1/9) received canakinumab (anti-IL-1β), spartalizumab (anti-PD-1), LAG525 (anti-LAG3), and IL12/L19L19. [5]One patient received atezolizumab for non-small-cell lung cancer diagnosed 2 years after completing adjuvant trastuzumab, continuing until metastatic progression of the HER2-positive breast cancer was documented.

Overall toxicity profile

Following a median follow-up period of nine months (IQR 5.1–21.7 months), severe treatment-related adverse events (grade ≥3) were observed in 27.7% of patients (n = 31). The most frequently reported severe events were neutropenia, affecting 7.1 percent (n = 8), and fatigue, affecting 6.3 percent (n = 7) **(Table 3)**.

Dose reductions of T-DXd due to adverse events were required in 31.3% of patients (n = 35), while permanent discontinuation because of toxicity occurred in 7.1 percent (n = 8). Interstitial lung disease/pneumonitis was the leading cause of treatment discontinuation (n = 3 cases).

Nausea of any grade was reported in 50.9% of patients (n = 57).

Table 3. General safety profile of T-DXd in all patients and by breast cancer subtype

Characteristics	HER2-low (N = 64a)	HER2-positive (N = 48a)	Overall (N = 112a)
Patients with AE grade ≥3			
No	48/64 (75.0)	33/48 (68.8)	81/112 (72.3)
Yes	16/64 (25.0)	15/48 (31.3)	31/112 (27.7)
Type of AE grade ≥3			
ILD	1/16 (6.3)	0/15 (0)	1/31 (3.2)
Hematologic	5/16 (31)	7/15 (47)	12/31 (39)
GI	3/16 (19)	3/15 (20)	6/31 (19)
Others	7/16 (44)	5/15 (33)	12/31 (39)
First dose reduction			
No	48/64 (75.0)	29/48 (60.4)	77/112 (68.8)
Yes	16/64 (25.0)	19/48 (39.6)	35/112 (31.3)
AE causing first dose reduction			
ILD	1/16 (6.3)	1/19 (5.3)	2/35 (5.7)
Hematologic	3/16 (19)	5/19 (26)	8/35 (23)
GI	4/16 (25)	8/19 (42)	12/35 (34)
Others	8/16 (50)	5/19 (26)	13/35 (37)
Second dose reduction			
No	64/64 (100.0)	42/48 (87.5)	106/112 (94.6)
Yes	0/64 (0.0)	6/48 (12.5)	6/112 (5.4)
AE causing second dose reduction			
ILD	0/0 (NA)	2/6 (33)	2/6 (33)
Hematologic	0/0 (NA)	2/6 (33)	2/6 (33)

GI	0/0 (NA)	1/6 (17)	1/6 (17)
Others	0/0 (NA)	1/6 (17)	1/6 (17)
Treatment discontinuation due to AE			
No	60/64 (93.8)	44/48 (91.7)	104/112 (92.9)
Yes	4/64 (6.3)	4/48 (8.3)	8/112 (7.1)
AE leading to discontinuation			
ILD	2/4 (50)	1/4 (25)	3/8 (38)
Hematologic	0/4 (0)	1/4 (25)	1/8 (13)
GI	0/4 (0)	1/4 (25)	1/8 (13)
Others	2/4 (50)	1/4 (25)	3/8 (38)
Nausea			
No	35/64 (54.7)	20/48 (41.7)	55/112 (49.1)
Yes	29/64 (45.3)	28/48 (58.3)	57/112 (50.9)

Abbreviations: AE= adverse event; GI= gastrointestinal; ILD= interstitial lung disease; NA= not available. a n/N (%).

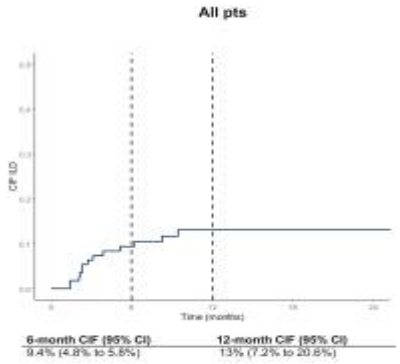
Interstitial lung disease/pneumonitis

The estimated 12-month cumulative incidence of any-grade ILD/pneumonitis was 13 percent (95 percent CI 7.2%–20.6%). The median time from T-DXd initiation to the onset of ILD/pneumonitis was 2.9 months (IQR 2.1–6.2 months). Two fatal (grade 5) events were recorded, corresponding to 1.8% of the cohort.

Cumulative incidences of ILD/pneumonitis were evaluated according to age, prior immunotherapy exposure, breast cancer subtype, smoking history, presence of lung metastases, and number of prior chemotherapy lines **(Figure 1)**.

In the multivariable competing-risks model that incorporated smoking status, prior immunotherapy, and lung metastases, both prior immunotherapy (hazard ratio 3.22, 95 percent CI 1.06–9.72, P = 0.052) and smoking history (hazard ratio 2.71, 95 percent CI 1.00–7.34, P = 0.062) emerged as potential risk factors for ILD/pneumonitis. Notably, none of the patients with prior immunotherapy exposure had experienced pulmonary toxicity related to that earlier treatment.

Ten patients who fully resolved a grade 1 ILD/pneumonitis event were subsequently rechallenged with T-DXd; of these, two (20%) developed recurrent ILD.



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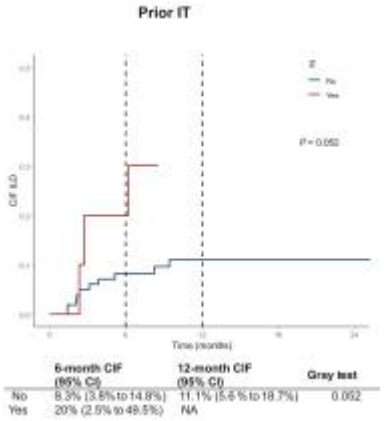

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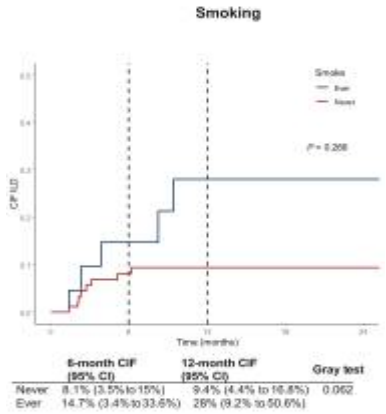

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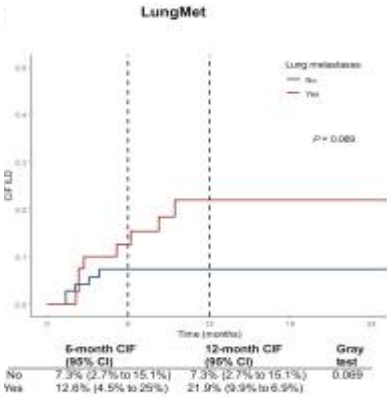

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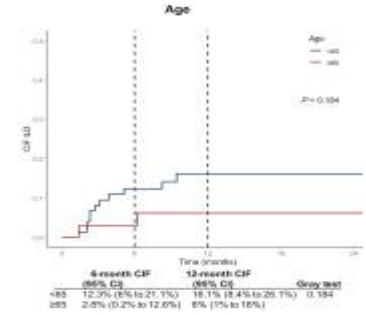

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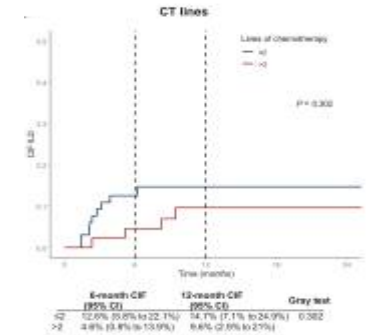

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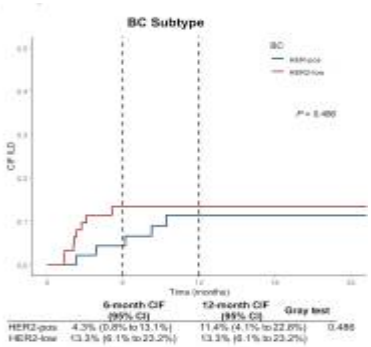

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Multivariable analysis	6-months CIF Rates (95% CI)	P value (Gray test)	HR (Cox regression)
Prior IT (yes; no)	No: 8.3% (3.8% to 14.8%); Yes: 20% (2.5% to 49.5%)	0.052	3.22 (1.06-9.72)
Smoking (yes; no)	No: 8.1% (3.5% to 15%); Yes: 14.7% (3.4% to 33.6%)	0.062	2.71 (1.00-7.34)
LungMet (yes; no)	No: 7.3% (2.7% to 15.1%); Yes: 12.8% (4.5% to 25%)	0.069	2.95 (0.99-8.86)
Age (<65; ≥65)	<65: 12.3% (6% to 21.1%); ≥65: 2.8% (0.2% to 12.6%)	0.18	
Prior CT (≤2; >2)	≤2: 12.6% (5.8% to 22.1%); >2: 4.8 (0.8% to 13.9%)	0.32	
Subtype (HER2-pos; HER2-low)	HER2-pos: 4.3% (0.8% to 13.1%); HER2-low: 13.3% (6.1% to 23.2%)	0.49	

'n / N (%)

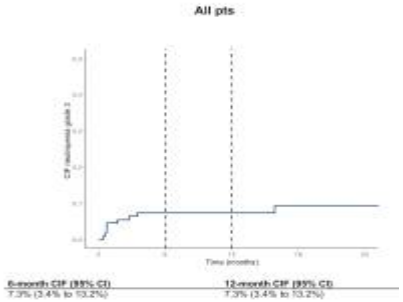
h)

Figure 1. Cumulative incidence of interstitial lung disease (ILD)/pneumonitis in real-world patients with HER2-positive or HER2-low advanced breast cancer treated with T-DXd. Panel a shows the overall cumulative incidence function (CIF) across all patients. Panels b through g display CIF stratified by selected baseline factors. Panel h presents the results of the multivariable competing-risks analysis identifying potential risk factors.
ABC= advanced breast cancer; CI= confidence interval; CIF= cumulative incidence function; CT= chemotherapy; HER2= human epidermal growth factor receptor 2; HR= hazard ratio; ILD= interstitial lung disease; IT= immunotherapy; LungMet= lung metastases; NA= not applicable; pos= positive; pts= patients.

Neutropenia

Neutropenia of any grade occurred in 32.1% of patients (n = 36), including severe (grade ≥3) cases in 8.9 percent (n = 10) and febrile neutropenia in two patients (1.8%). The median interval to the development of grade ≥3 neutropenia was 1.2 months (IQR 0.7–3.5 months).
Cumulative incidences of grade ≥3 neutropenia were examined according to breast cancer subtype, extent of prior chemotherapy, neutrophil-to-lymphocyte ratio (NLR) at the start of cycle 3, and absolute neutrophil count at that timepoint **(Figure 2)**.

In multivariable analysis, a lower NLR at cycle 3 day 1 (≤1.97) was confirmed as an independent protective factor against severe neutropenia (hazard ratio 0.10 per unit increase, 95% CI 0.02–0.53, P < 0.001), whereas low neutrophil count alone was not.



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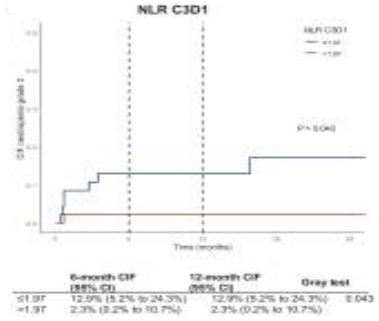

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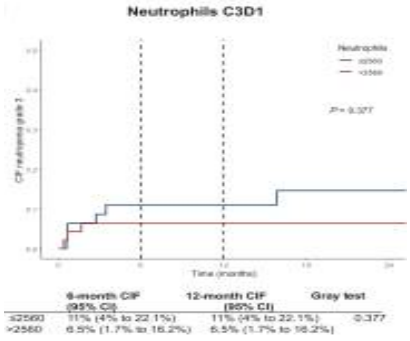

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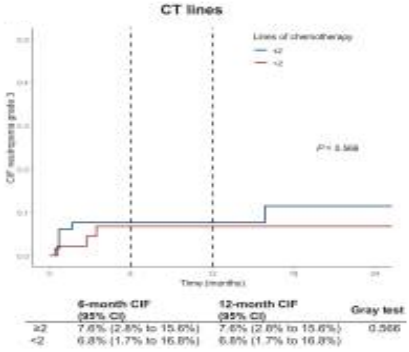

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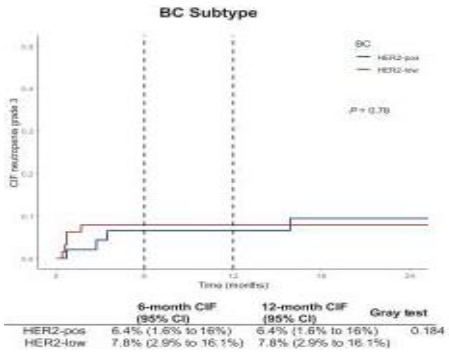


e)

Multivariable analysis	Level	P value (Gray test)	HR (Cox regression)
NLR at C3D1 (≤1.97 versus >1.97)	+1*log	<0.001	0.10 (0.02-0.53)
Age (<65 years; ≥65 years)	+1 year	0.3	1.03 (0.98-1.08)

f)

Figure 2. Real-world cumulative incidence of grade ≥3 neutropenia in patients with HER2-positive or HER2-low advanced breast cancer receiving T-DXd. Panel a presents the overall cumulative incidence function (CIF) for severe neutropenia across all patients. Panels b through e show CIF stratified by selected baseline and on-treatment variables. Panel f displays the results of the multivariable competing-risks analysis for risk factors.
ABC= advanced breast cancer; C= cycle; C3D1= cycle 3 day 1; CI, confidence interval; CIF= cumulative incidence function; CT= chemotherapy; D= day; HR= hazard ratio; NA= not applicable; NLR= neutrophil-to-lymphocyte ratio; pts= patients.

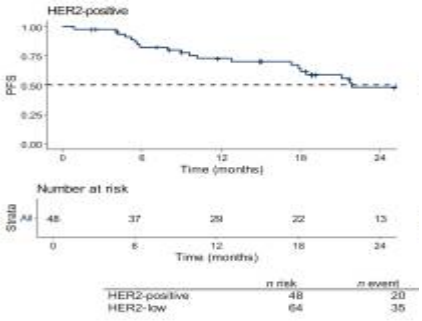
Efficacy outcomes

The median real-world progression-free survival (rwPFS) was 21.82 months (95 percent CI 17.98 months–not reached) in patients with HER2-positive advanced breast cancer and 6.90 months (95 percent CI 4.93–10.19 months) in those with HER2-low disease **(Figures 3a and 3b)**.

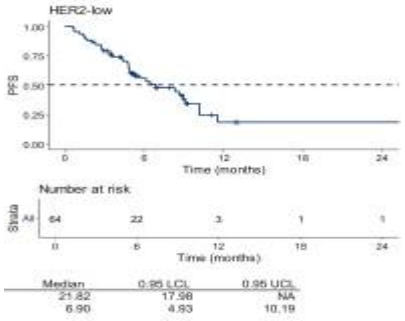
Within the HER2-low subgroup, patients previously exposed to an antibody-drug conjugate (ADC) had a median rwPFS of 2.86 months (95% CI 1.58 months–not reached), compared with 8.31 months (95 percent CI 5.72–11.60 months) for those without prior ADC treatment **(Figure 3c)**.

Among patients with HER2-low advanced breast cancer, the median rwPFS was 8.31 months (95 percent CI 5.72–11.57 months) in the hormone receptor (HR)-positive cohort and 4.77 months (95 percent CI 2.76 months–not

available) in the triple-negative breast cancer (TNBC) cohort **(Figure 3d)**.



a)



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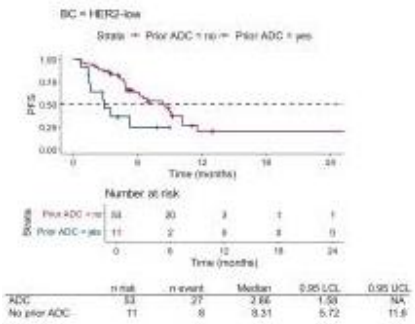

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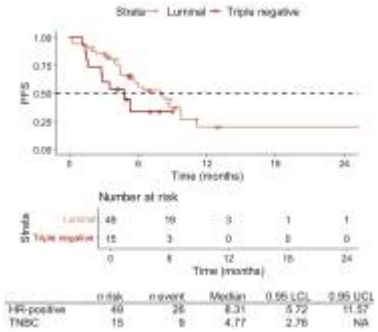

d)

Figure 3. Real-world efficacy of T-DXd in patients with HER2-positive or HER2-low advanced breast cancer. Kaplan–Meier curves for real-world progression-free survival (rwPFS) stratified by (a–b) breast cancer subtype across all patients; (c) prior exposure to antibody–drug conjugate (ADC) therapy in the HER2-low subgroup; and (d) hormone receptor (HR) status within the HER2-low subgroup. ADC= antibody–drug conjugate; BC= breast cancer; HR= hormone receptor; LCL= lower confidence limit; n= number; NA= not available; PFS= progression-free survival; pts= patients; TNBC= triple-negative breast cancer; UCL= upper confidence limit.

This single-center, retrospective real-world study of patients with HER2-positive or HER2-low advanced breast cancer treated with T-DXd in routine clinical practice revealed a 12-month cumulative incidence of any-grade ILD/pneumonitis of 13%, aligning closely with the established safety and efficacy patterns observed for T-DXd.

In the DESTINY-Breast series of trials involving patients with HER2-positive, HER2-low, or HER2-ultralow advanced breast cancer, treatment-related adverse events prompting dose reductions of T-DXd ranged from 16% to 27% (and reached 45.9% when combined with pertuzumab) [4-11], somewhat lower than the 31% observed in our real-world cohort. This difference may reflect a broader range of patient fitness levels and comorbidities in everyday practice compared to trial populations [4-11]. Additionally, trial participants typically undergo more frequent clinical assessments and imaging surveillance. Conversely, the rate of grade ≥3 treatment-related adverse events appeared higher in the clinical trials (49%–56% vs 28% in our study), potentially attributable to the retrospective nature of our analysis and possible underreporting in routine medical records [4-11]. Consistent with this, treatment discontinuations due to adverse events in our series were 7%, compared to 9.5%–20.7% across the DESTINY-Breast trials [4-11].

The rate of ILD/pneumonitis in our real-world setting (any grade: 13%; grade 5: 2%) mirrored findings from pivotal trials, where any-grade events occurred in 10%–16% of patients and fatal (grade 5) cases in 0%–2.3% [4-11]. These observations are noteworthy, as they validate the pulmonary safety profile of T-DXd outside strictly controlled trial environments, where monitoring and imaging adhere less rigidly to protocol schedules,

particularly for this serious and potentially irreversible toxicity lacking predictive biomarkers.

A comprehensive pooled analysis of 1150 patients enrolled in nine T-DXd monotherapy trials (predominantly Japanese patients at 44%, with 44% having advanced breast cancer) reported comparable ILD/pneumonitis rates (any grade: 15.4%; grade 5: 2.2%), identifying possible risk factors including age under 65 years, Japanese ethnicity, preexisting lung conditions, impaired renal function, prolonged time from initial diagnosis (>4 years), and baseline oxygen saturation <95% [19].

A large retrospective real-world analysis presented at the 2024 European Society for Medical Oncology Congress evaluated T-DXd-associated ILD/pneumonitis in 600 French patients with HER2-expressing advanced malignancies (93% breast cancer), documenting an incidence of 11.3% and highlighting prior ILD, smoking history, and baseline lung metastases as key risk associations [22].

Our dataset, uniquely restricted to breast cancer patients, corroborated smoking as a risk factor for ILD/pneumonitis and represents the first published evidence suggesting prior immunotherapy as an additional potential contributor. Given the approval of T-DXd for HER2-low triple-negative breast cancer—supported primarily by data from only 58 patients in DESTINY-Breast04 (40 in the T-DXd arm and 18 in the chemotherapy arm)—and considering that approximately 40% of advanced triple-negative cases receive frontline immunotherapy, these findings underscore the importance of further validation in larger prospective studies [23, 24].

Beyond retrospective analyses, genomic profiling is increasingly recognized as a promising approach to identify biomarkers of T-DXd-related toxicities. For instance, pharmacogenomic evaluation of 329 patients with ABC receiving T-DXd monotherapy revealed genomic loci associated with ILD/pneumonitis (unadjusted $P < 5 \times 10^{-5}$), including genes implicated in lung inflammation and fibrosis, such as interleukin-4 and interleukin-2 receptors, as well as variants in the human leukocyte antigen (HLA) region on chromosome 6p21.3 [25]. These findings indicate that, despite the absence of clinically validated T-DXd toxicity biomarkers, ongoing research is actively addressing their identification.

In our cohort, the overall incidence of any-grade neutropenia was 32%, consistent with previous clinical trial reports ranging from 20% to 45.5% [1]. Notably, grade ≥3 neutropenia occurred in 9% of patients, which is slightly lower than the 11%–27% reported in DESTINY-Breast trials [4–11], possibly reflecting the higher frequency of T-DXd dose reductions in routine clinical practice. Interestingly, we observed that a low neutrophil-to-lymphocyte ratio (NLR), rather than absolute neutrophil count, after two cycles of T-DXd may serve as a predictive marker for clinically relevant (grade ≥3) neutropenia, potentially reflecting limited bone marrow capacity to sustain granulopoiesis during treatment. However, the observed association between NLR at C3D1 and grade ≥3 neutropenia should be interpreted cautiously, as reverse causation cannot be excluded; treatment-induced neutropenia may itself influence NLR values. These findings warrant validation in larger, prospective cohorts to guide potential prophylactic strategies.

Despite patients having received a median of three prior treatment lines, the clinical efficacy of T-DXd in our cohort was comparable to that observed in DESTINY-Breast trials [4–11]. Among patients with HER2-positive ABC—58.3% of whom had previously received an ADC (all T-DM1)—the median real-world progression-free survival (rwPFS) was 21.82 months, consistent with the median PFS of 17.8 and 28.8 months reported in DESTINY-Breast02 and 03, respectively [6–8]. In these trials, patients had received a median of two prior lines, with all patients in DESTINY-Breast02 and <1% in DESTINY-Breast03 previously exposed to an ADC [6–8]. Among patients with HER2-low ABC, the median rwPFS in our study was slightly lower than the 9.9 months mPFS reported in DESTINY-Breast04 [6], particularly in TNBC patients (rwPFS 4.77 months vs. 8.5 months in the trial), likely reflecting prior ADC exposure (sacituzumab govitecan) in almost two-thirds of our cohort, which was absent in DESTINY-Breast04. These findings align with prior real-world observations showing reduced T-DXd efficacy in both HER2-positive and HER2-low ABC patients previously treated with ADCs [26–28], highlighting the need for additional real-world data, especially in TNBC patients with HER2-low disease, who represent an unmet medical need.

Several limitations must be acknowledged: the retrospective collection of clinical data may underreport non-clinically relevant adverse events, the single-center nature of the study limits generalizability, and the relatively small sample size restricts statistical power. Additionally, the observational design inherently constrains causal interpretation. Consequently, results

should be viewed cautiously and validated in larger, prospective studies, such as the ongoing Tox-DXd Study (NCT07049133). Nevertheless, all patients were treated at a comprehensive cancer center (IEO, Milan, Italy) using standardized protocols that ensure high-quality clinical documentation, and the observed efficacy outcomes, consistent with randomized clinical trials, support the reliability of the dataset.

Conclusion

In summary, the Tox-DXd Retrospective Study indicates that T-DXd safety and efficacy are consistent with pivotal phase III RCTs. Prior immune therapy exposure and smoking history emerged as potential risk factors for ILD/pneumonitis, while a low NLR after two cycles correlated with increased risk of clinically significant neutropenia. These findings warrant further exploration in larger, prospective studies, potentially extending beyond ABC.

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Conflict of Interest: None

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Ethics Statement: None

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