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Real-world outcomes of trastuzumab deruxtecan in HR-negative HER2-low metastatic breast cancer

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This real-world, multicenter study evaluated trastuzumab deruxtecan (T-DXd) in 64 patients with HR-negative, HER2-low metastatic breast cancer between May 2022 and May 2025. The median lines of therapy were 3 (range 1–7). The objective response rate (ORR) was 35.9%, and the disease control rate was 75%. Median real-world progression-free survival (rwPFS) and overall survival were 5.0 months and 14.9 months, respectively. Multivariate analysis identified brain metastases and prior Trop-2 ADC treatment as independent predictors of shorter rwPFS. The most common adverse events were nausea (71.9%), fatigue (39.1%), anorexia (31.3%), and neutropenia (31.3%). Grade 3/4 adverse events were primarily neutropenia (9.4%), thrombocytopenia (7.8%), and nausea (3.1%). Despite lower ORRs in patients with *BRCA1* mutations or *MYC* amplifications, the differences were not statistically significant. This study confirms the clinical efficacy and manageable safety profile of T-DXd in this population, identifying high-risk subgroups and potential resistance biomarkers to inform treatment decisions.

HER2-low breast cancer (BC), defined by an immunohistochemical (IHC) score of 1+ or 2+ in the absence of HER2 gene amplification, has emerged as a distinct clinical entity following the demonstrated efficacy of trastuzumab deruxtecan (T-DXd)[1,2]. This subtype is present in approximately 50–60% of hormone receptor (HR)-positive BC and about 12–20% of HR-negative cases[3,4], representing a heterogenous population with diverse prognostic outcomes and treatment response.

The landmark DESTINY-Breast 04 (DB-04) trial, the first phase III trial to establish efficacy of T-DXd in HER2-low metastatic breast cancer (mBC), enrolled 557 patients who had received one to two prior lines of chemotherapy for metastatic disease. T-DXd significantly improved outcomes compared with physician's choice treatment, with median progression-free survival (PFS) of 9.9 months vs. 5.1 months (hazard ratio (HR): 0.50, $P < 0.001$), and median overall survival (OS) of 23.4 months vs. 16.8 months (HR: 0.64, $P = 0.001$)[5]. These findings were further extended by the DB-06 trial, which also demonstrated survival benefits with T-DXd in both HER2-low and HER2-ultralow (IHC zero with any membrane staining) mBC populations[6].

However, both trials included limited representation of HR-negative HER2-low mBC patients. DB-04 trial enrolled only 58 HR-negative patients, with 40 receiving T-DXd, while DB-06 excluded this subgroup entirely[5,6]. This underrepresentation has left a critical evidence gap regarding the efficacy of T-DXd in HR-negative HER2-low mBC, particularly relative to other treatment options such as the anti-trop 2 antibody-drug conjugate (ADC) Sacituzumab govitecan (SG)[7].

To address this unmet need, we conducted a multicenter real-world study to evaluate the clinical performance of T-DXd in HR-negative HER2-low mBC.

Results

Patient characteristics

Between May 2022 and May 2025, a total of 64 patients were included in this study. The patient selection process was detailed in Supplementary Fig. 1. Baseline characteristics were summarized in Table 1. All patients were female, with a median age of 47 years (range 30–80). Of these, 34 (53.1%) had primary HR-negative disease, while 30 (46.9%) had converted from HR-positive to HR-negative status. Fifty-two (81.2%) patients presented with primary HER2-low BC, and 12 (18.8%) had converted from HER2-zero to HER2-low disease. HER2 expression levels were equally distributed,

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Table 1 | Characteristics of the patients

Characteristics	Patients, no. (%)
Age	
Median (range), years	47 (30–80)
Sex, female	64 (100)
ECOG	
0	19 (29.7)
≥1	45 (70.3)
HR expression	
Primary HR-negative	34 (53.1)
Converted to HR-negative	30 (46.9)
HER2 low status	
Primary HER2-low	52 (81.2)
Converted to HER2-low	12 (18.8)
HER2 expression	
IHC 1+	32 (50.0)
IHC 2+ and FISH-negative	32 (50.0)
PD-L1 expression	
Negative (CPS < 1)	10 (15.6)
Positive (CPS ≥ 1)	21 (32.8)
Unknown	33 (51.6)
Metastatic sites	
Visceral metastasis	47 (73.4)
Liver	29 (45.3)
Lung	27 (42.2)
Brain	11 (17.2)
Line of therapy in metastatic disease	
Median (range)	3 (1–7)
1st	3 (4.7)
2nd	18 (28.1)
≥3rd	43 (67.2)
Endocrine therapy in metastatic stage	13 (20.3)
Chemotherapy in metastatic stage	
Taxanes	60 (93.8)
Anthracyclines	58 (90.6)
Platinum	30 (46.9)
Capecitabine	23 (35.9)
Vinorelbine	14 (21.9)
Gemcitabine	9 (14.1)
Utidellone	6 (9.4)
Targeted therapy in metastatic stage	
Immunotherapy	34 (53.1)
Bevacizumab	18 (28.1)
CDK4/6 inhibitor	13 (20.3)
Trop-2 ADC	10 (15.6)
PARP inhibitor	5 (7.8)
PAM pathway inhibitor	2 (3.1)

HR hormone receptor, *IHC* immunohistochemistry, *FISH* fluorescence in situ hybridization, *CDK4/6* Cyclin-Dependent Kinase 4/6, *ADC* antibody-drug conjugate, *PARP* poly ADP-ribose polymerase, *PAM PI3K/AKT/mTOR*.

with 50% of patients showing HER2 1+ and 50% HER2 2+. Visceral metastases were presented in 47 (73.4%) patients, including liver metastases in 29 (45.3%), lung metastases in 27 (42.2%), and brain metastases (BM) in 11 (17.2%). T-DXd was administered as first- or second-line in 21 (32.8%) patients, and third-line or later treatment in 43 (67.2%) patients. The median number of lines of therapy for metastatic disease was 3 (range 1–7). Thirteen (20.3%) patients had progressed after endocrine therapy (ET) and CDK4/6 inhibitors during an earlier HR-positive disease phase. Ten (15.6%) patients had received prior Trop-2 ADC therapy.

Table 2 | Evaluation of efficacy

Treatment response	Patients, no. (%) *N* = 64
CR	0
PR	23 (35.9)
SD	25 (39.1)
Duration of SD of ≥ 24 weeks	10 (15.6)
PD	16 (25.0)
ORR	23 (35.9)
DCR	48 (75.0)
Median rwPFS (95% CI)	5.0 (3.6–6.4)
Median OS (95% CI)	14.9 (12.5–17.3)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* objective response rate, *DCR* disease control rate, *rwPFS* real-world progression-free survival, *OS* overall survival, *CI* confidence interval.

Efficacy

Up to May 2025, the median number of T-DXd cycles administered was 6 (range 2–25). Treatment was discontinued in 53 (82.8%) patients, primarily due to disease progression ($n = 50$), followed by grade 3/4 AEs ($n = 2$), and loss to follow-up ($n = 1$) (Supplementary Table 1 and Supplementary Fig. 2a). A total of 31 (48.4%) deaths were recorded (Supplementary Fig. 2b). In the overall population, 23 (35.9%) patients achieved PR, 25 (39.1%) had SD, and 16 (25%) experienced PD, resulting an ORR of 35.9% and a DCR of 75% (Table 2). ORR and DCR were higher in patients with HER2 IHC 2+ compared to IHC 1+ (ORR: 40.6% vs. 31.2%; DCR: 84.4% vs. 65.6%). Among the 11 patients with BM, ORR and DCR were 18.2% and 63.6%. None of the 10 patients with prior Trop-2 ADC exposure achieved a PR, and the DCR in this subgroup was 50% (Supplementary Table 2).

After a median follow-up of 19.5 months (95% CI: 14.5–21.5 months), the median rwPFS and OS in the whole cohort were 5.0 and 14.9 months, respectively (Fig. 1). Subgroup analysis showed patients with HER2 2+ had significantly longer median rwPFS than those with HER2 1+ (6.0 vs. 3.9 months; HR: 0.54, 95% CI: 0.31–0.96, $P = 0.020$), though the OS did not differ significantly (18.1 vs. 14.0 months; HR. 0.65, 95% CI: 0.32–1.33, $P = 0.220$) (Fig. 2a, b, Supplementary Table 2). Patients with BM had shorter rwPFS (3.6 vs. 5.6 months; HR: 2.57, 95% CI: 0.97–6.82, $P = 0.004$) and OS (8.6 vs. 15.7 months; HR: 2.44, 95% CI: 0.78–7.65, $P = 0.030$) compared to those without BM (Fig. 2c, d, Supplementary Table 2). Similarly, prior exposure to Trop-2 ADC was associated with inferior rwPFS (3.1 vs. 5.5 months; HR: 2.51, 95% CI: 0.91–6.93, $P = 0.020$) and OS (11.1 vs. 15.7 months; HR: 2.46, 95% CI: 0.78–7.73, $P = 0.030$) compared to Trop-2 ADC-naïve patients (Fig. 2e, f, Supplementary Table 2).

Univariate and multivariate analyses of rwPFS and OS

Univariate analysis identified several factors associated with poor rwPFS, including BM, HER2 1+, PD-L1 CPS ≥ 1, prior Trop-2 ADC exposure. Multivariate analysis confirmed that BM (HR: 2.46, 95% CI: 1.15–5.29, $P = 0.021$) and prior Trop-2 ADC treatment (HR: 2.79, 95% CI: 1.28–6.08, $P = 0.010$) were independent negative prognostic factors for rwPFS (Fig. 3). Both factors were also significantly associated with worse OS in univariate and multivariate analyses (Supplementary Fig. 3).

Potential biomarkers from next-generation sequencing

Next-generation sequencing (NGS) was performed on tumor samples from 28 (43.8%) patients. An oncoplot summarizing genetic alterations

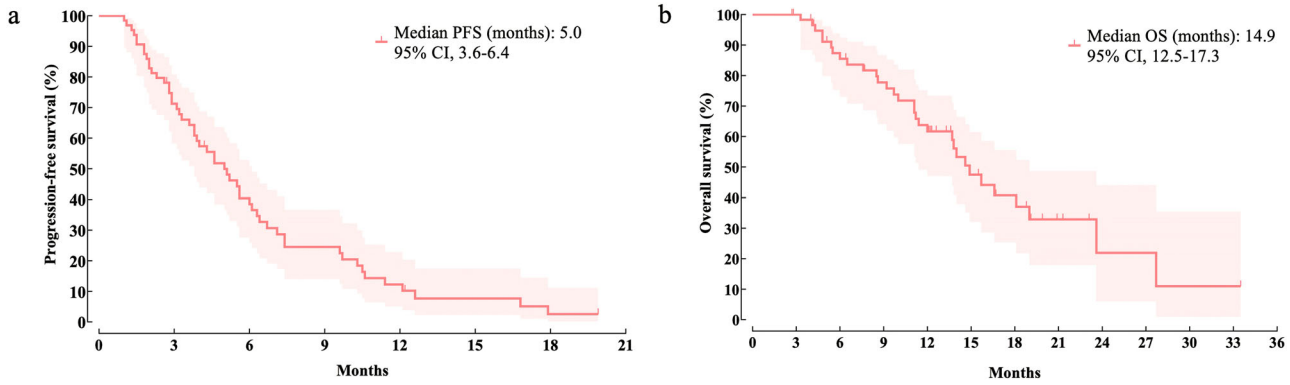


Fig. 1 | The treatment outcomes of the whole patients. The Kaplan-Meier curve for rwPFS of entire cohort (**a**); The Kaplan-Meier curve for OS of entire cohort (**b**). rwPFS, real-world progression-free survival; OS, overall survival.

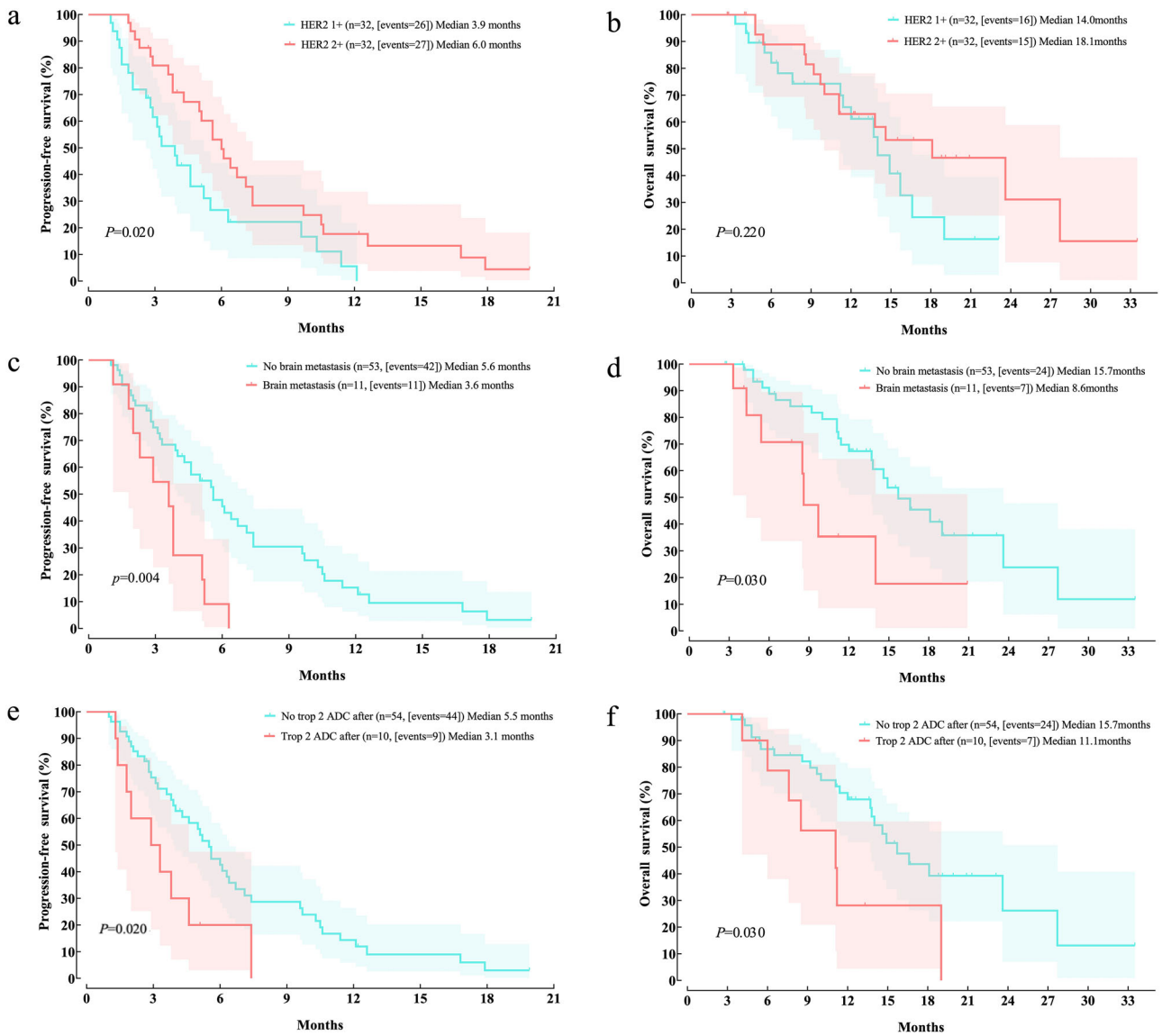
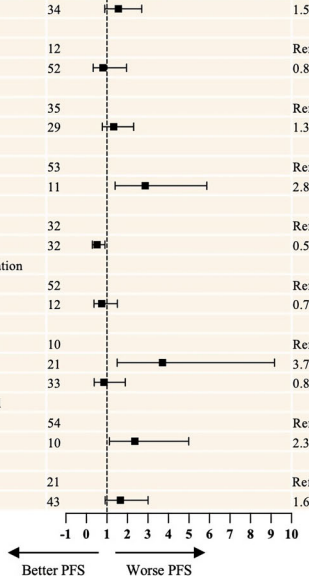


Fig. 2 | The treatment outcomes of patients in subgroups. The Kaplan-Meier curve for rwPFS (**a**) and OS (**b**) of patients with HER2 2+ and HER2 1+; The Kaplan-Meier curve for rwPFS (**c**) and OS (**d**) of brain metastasis patients; The Kaplan-Meier curve for rwPFS (**e**) and OS (**f**) of trop 2 ADC-treated and without trop 2 ADC-treated patients. rwPFS, real-world progression-free survival; OS, overall survival; ADC, antibody-drug conjugate.

a

Characteristic	Number	HR (95%CI)	P value
ECOG		Ref.	
0	19		
≥1	45	0.878 (0.478-1.613)	0.676
Primary HR negative			
No	30	Ref.	
Yes	34	1.558 (0.900-2.697)	0.113
Primary HER2 low			
No	12	Ref.	
Yes	52	0.812 (0.336-1.960)	0.643
Liver metastases			
No	35	Ref.	
Yes	29	1.336 (0.774-2.306)	0.299
Brain metastases			
No	53	Ref.	
Yes	11	2.873 (1.406-5.871)	**0.004**
HER2 status			
1+	32	Ref.	
2+	32	0.518 (0.295-0.911)	**0.022**
PAM pathway mutation			
No	52	Ref.	
Yes	12	0.750 (0.372-1.510)	0.420
PD-L1expression			
Negative (CPS < 1)	10	Ref. >	
Positive (CPS ≥ 1)	21	3.716 (1.506-9.169)	**0.004**
Unknow	33	0.857 (0.387-1.899)	0.704
Trop 2 ADC treated			
No	54	Ref.	
Yes	10	2.368 (1.124-4.988)	**0.023**
Treatment line			
≤ 2	21	Ref.	
> 2	43	1.661 (0.917-3.008)	0.094



b

Characteristic	Number	HR (95%CI)	P value
Brain metastases			
No	53	Ref.	
Yes	11	2.463 (1.146-5.294)	**0.021**
HER2 status			
1+	32	Ref.	
2+	32	0.633 (0.344-1.165)	0.142
PD-L1expression			
Negative (CPS < 1)	10	Ref.	
Positive (CPS ≥ 1)	21	2.443(0.911-6.552)	0.076
Unknow	33	0.702 (0.310-1.590)	0.397
Trop 2 ADC treated			
No	54	Ref.	
Yes	10	2.787 (1.277-6.080)	**0.010**

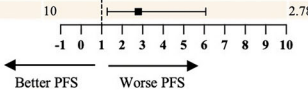


Fig. 3 | The rwPFS outcomes of Cox regression analysis. The rwPFS in univariable Cox regression analysis (**a**); The rwPFS in multivariable Cox regression analysis (**b**). rwPFS, real-world progression-free survival.

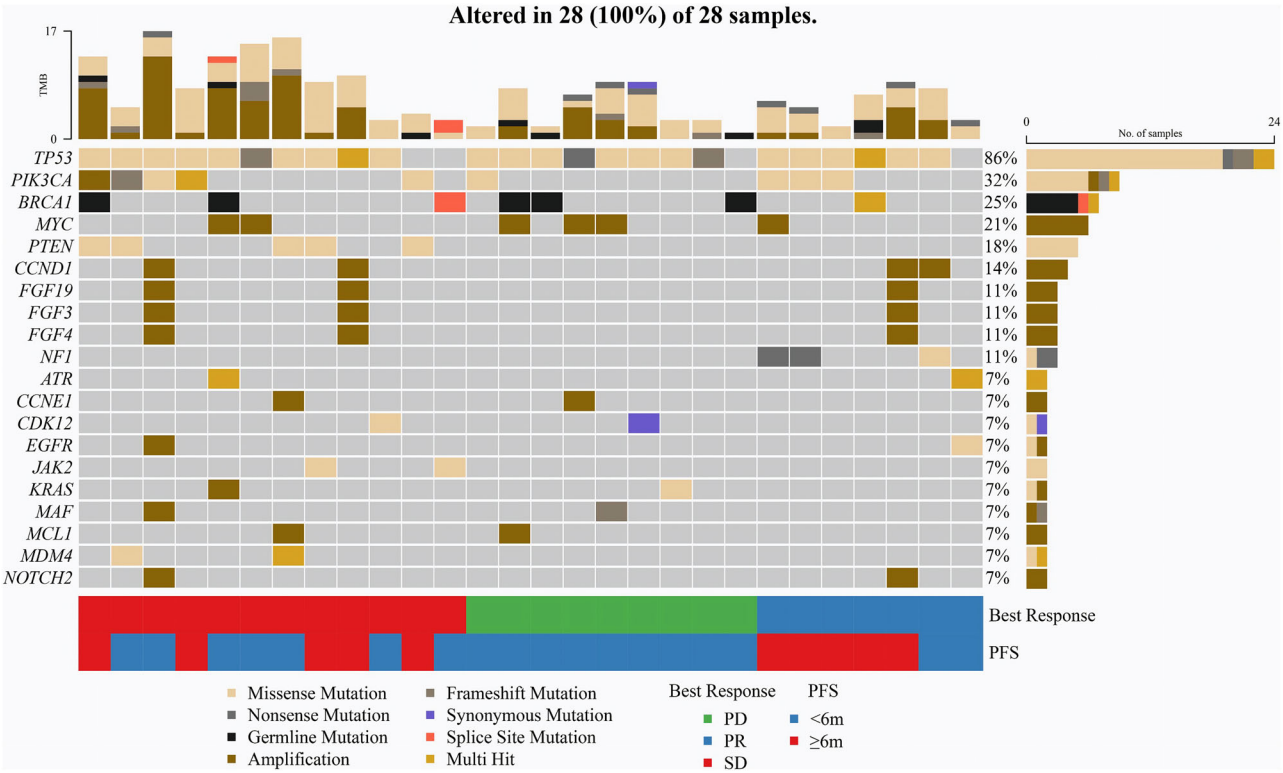


Fig. 4 | The landscape of high frequency altered genes in patients. Each column represents an individual patient. PFS, progression-free survival.

and corresponding treatment response was shown in Fig. 4. The most frequently mutated genes were *TP53* (86%), *PIK3CA* (32%), *MYC* (21%) and *PTEN* (18%), respectively. *BRCA1* mutations were detected in 7 (25%) patients, including 5 germline mutations and 2 somatic mutations. The ORRs were comparable between patients with and without TP53 and PI3K/AKT/mTOR (PAM) pathway mutations. Meanwhile, compared with patients without these alterations, those with *MYC* amplifications or *BRCA1* mutations showed numerically lower, but statistically insignificant, with ORRs of 16.7% and 14.3%, respectively (Supplementary Fig. 4).

Table 3 | Summary of the adverse events

Adverse event	All grades, no. (%)	Grade 3/4, no. (%)
Any AE	60 (93.8)	9 (14.1)
Nausea	46 (71.9)	2 (3.1)
Fatigue	25 (39.1)	0 (0.0)
Anorexia	20 (31.3)	2 (3.1)
Neutropenia	20 (31.3)	6 (9.4)
Anemia	19 (29.7)	2 (3.1)
Vomiting	17 (26.6)	2 (3.1)
Thrombocytopenia	11 (17.2)	5 (7.8)
Diarrhea	8 (12.5)	0 (0.0)
Constipation	8 (12.5)	0 (0.0)
Increased amino transaminases	6 (9.4)	0 (0.0)
Headache	4 (6.3)	0 (0.0)
Drug-induced interstitial lung disease	3 (4.7)	1 (1.6)
Myalgia	2 (3.1)	0 (0.0)
Febrile neutropenia	1 (1.6)	1 (1.6)
Skin pruritus and/or rash	1 (1.6)	0 (0.0)

AE adverse event.

Safety

Treatment-related AEs were summarized in Table 3. Among the 64 patients, 93.8% experienced at least one AE, and grade 3/4 AEs occurred in 14.1%. The most common AEs of any grade were nausea (71.9%), fatigue (39.1%), anorexia (31.3%), neutropenia (31.3%), anemia (29.7%), vomiting (26.6%), and thrombocytopenia (17.2%). The most common grade 3/4 AEs were neutropenia (9.4%), thrombocytopenia (7.8%), nausea (3.1%), anorexia (3.1%), anemia (3.1%), vomiting (3.1%). Drug-related interstitial lung disease (ILD) occurred in three patients (4.7%), including one case of grade 3 ILD that required hospitalization for steroid treatment. Dose reduction was required in 5 (10.9%) patients due to thrombocytopenia ($n = 3$), vomiting ($n = 1$), and neutropenia ($n = 1$). Dose delay occurred in 10 (15.6%) patients (Supplementary Table 1).

Discussion

This study provides the first real-world evidence specifically evaluating the efficacy and safety of T-DXd in patients with HR-negative, HER2-low mBC. Compared to HR-negative subgroup in the DB-04 trial, our cohort included a higher proportion of heavily pretreated patients (over two-thirds receiving third-line or later therapy), more cases with BM, and individuals with prior exposure to ADCs. Despite these less favorable baseline characteristics, T-DXd monotherapy demonstrated clinically meaningful outcomes, with an ORR of 35.9%, a median rwPFS of 5.0 months, and a median OS of 14.9 months. Although these results are somewhat lower than those reported in the DB-04 trial (ORR of 50%, median PFS of 8.5 months, and median OS of 18.2 months in HR-negative subgroup)5, they remain encouraging given the more challenging clinical profile of our real-world population.

In contrast to DB-04 and DAISY trials, which reported comparable efficacy between HER2 2+ and 1+ subgroups[5,8], our analysis showed significantly improved outcomes in patients with HER2 2+ expression, including higher ORR and longer rwPFS. This observation is supported by another real-world study, which also indicated superior T-DXd efficacy in HER2 2+/FISH-negative patients compared to those with HER2 1+ disease[9]. A similar trend has also been observed with the anti-HER2 ADC RC48, which demonstrated enhanced activity in HER2 2+ tumors relative to HER2 1+ cases[10]. Several biological mechanisms may explain this differential response. First, HER2 2+ tumors express 10–50 times more surface HER2 receptors than HER2 1+ tumors[11,12], which may facilitate more efficient internalization of ADC and delivery of the cytotoxic payload. Second, HER2 1+ tumors often exhibit greater spatial heterogeneity[13–15], which may compromise uniform drug distribution and target engagement. Third, current HER2 IHC assessment is subject to interobserver variability, with reported concordance rates as low as 18–26% in distinguishing between HER2 zero from HER2 1+[16,17]. The adoption of quantitative HER2 scoring methods may improve patient stratification and predictive accuracy for ADC efficacy in the future.

Additional clinical factors associated with poorer T-DXd outcomes included the presence of BM and prior ADC treatment. Among the 10 patients pretreated with SG, none achieved an objective response, and this subgroup exhibited significantly shorter median rwPFS and OS compared with ADC-naïve patients, consistent with prior reports[18,19]. Given the structural similarities in the payloads of SG and T-DXd, potential cross-resistance mechanism may involve altered intracellular trafficking, enhanced lysosomal degradation, upregulation of drug efflux pumps, or activation of alternative survival and DNA repair pathway[20,21]. In addition, patients with BM also experienced significantly inferior rwPFS and OS compared to those without BM, aligning with previous clinical observations[22,23].

NGS analysis performed in 28 patients showed comparable ORR between those with and without alterations in the PAM pathway, consistent with biomarker findings from the DB-06 trial presented at American Society of Clinical Oncology (ASCO) 2025[24]. Although numerical trends suggesting lower ORRs in patients with BRCA1 mutations or MYC amplifications, these differences were not statistically significant, likely due to the limited sample size, and should therefore be interpreted with caution.

The safety profile of T-DXd in this cohort was consistent with previous studies, with no new safety signals observed[5,25,26]. The most common AEs were gastrointestinal, particularly nausea, which affected over 70% of patients. This occurred despite the majority of patients receiving triple-agent antiemetic prophylaxis (typically comprising a 5-HT3 antagonist, an NK-1 antagonist, and dexamethasone). The recently published landmark ERICA study demonstrated that adding olanzapine to a standard triple regimen achieved a nearly 20% reduction in the incidence of nausea[27]. Therefore, adopting this enhanced prophylactic strategy could be key to optimizing treatment continuity and patient compliance with T-DXd. Other toxicities were manageable: hematological events necessitated supportive care and occasional dose modifications, while the incidence of ILD was favorably low[28], with the single grade 3 event responding to steroids.

Several limitations of this study should be acknowledged. Its retrospective design introduces potential biases in data collection and patient selection. The sample size was limited, particularly in key subgroups such as those with prior ADC exposure or presence of BM, which may affect the generalizability and statistical power of the findings. The lack of centralized pathology review for HER2 and HR status may also contribute to assessment variability. Moreover, the inclusion of only Chinese patients may limit the extrapolation of results to other ethnic populations. Heterogeneity in treatment patterns across participating centers could have additionally influenced outcomes. Future prospective, multicenter studies with larger cohorts, longer follow-up, and centralized biomarker validation are warranted to confirm these findings.

In summary, this real-world analysis supports T-DXd as an effective treatment option for patients with HR-negative HER2-low mBC, extending evidence from pivotal trials to a more heterogeneous clinical setting. Larger prospective studies incorporating comprehensive biomarker evaluation are needed to validate these results across diverse populations, identify reliable predictive biomarkers and optimize treatment sequencing strategies for this distinct molecular subtype.

Methods

Patient selection and enrollment criteria

We conducted a multicenter, retrospective cohort study of patients with HR-negative, HER2-low mBC who were treated with T-DXd across four

participating institutions: Sun Yat-sen University Cancer Center (SYSUCC), the Cancer Hospital, Affiliated Hospital of Guangdong Medical University, Macau Kiang Wu Hospital, and Foshan First People's Hospital. The study period spanned from May 2022 to May 2025. Inclusion criteria were (1) histologically confirmed mBC; (2) received at least one cycle of T-DXd treatment; (3) confirmation of HR-negative and HER2-low status on the most recent tumor biopsy prior to T-DXd initiation (HR-negative defined as estrogen receptor and progesterone receptor were <1% by IHC, and HER2-low expression defined as HER2 IHC 1+ or 2+/ISH-negative); and (4) presence of measurable metastatic disease with available response assessments. Clinical data were systematically extracted from electronic medical records within each hospital's information system. Collected variables included demographic information, tumor clinicopathological characteristics, treatment history, laboratory results, and radiographic assessment reports. The study was approved by the ethical committee of the Sun Yat-sen University Cancer Center (B2025-180-01) and the requirement for informed consent was waived due to the retrospective design. The study adhered to the ethical principles of the Declaration of Helsinki.

Treatment and response assessment

T-DXd was administered intravenously on day 1 of 21-day cycle. Treatment continued until disease progression, intolerable toxicity, or any other reasons necessitating discontinuation. Treatment response was evaluated by investigators based on radiographic assessments conducted in real-world clinical practice. All patients underwent computed tomography (CT) scan, and Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria were applied retrospectively as a study purpose to evaluate the response of treatment. ORR was defined as the proportion of evaluable patients achieving a complete response (CR) or partial response (PR) as their best objective tumor response. DCR included patients with CR, PR, or stable disease (SD). Real-world PFS (rwPFS) was measured from the start of T-DXd treatment to the first documented disease progression (clinical or radiographic) or death from any cause. OS was defined as the time from T-DXd initiation to death from any cause or the last follow-up. Adverse events (AEs) were graded according to the National Cancer Institute-Common Terminology Criteria (NCI-CTCAE) version 5.0.

Next-generation sequencing

Genomic profiling data were obtained from clinical notes and molecular sequencing reports. Hybrid capture-based targeted next-generation sequencing (NGS) was performed using OncoScreen Plus panel (OncoScreenPlus™, Burning Rock, Guangzhou, China) which covers the whole exons of 312 genes and hotspot mutations of 208 genes[29]. Genomic DNA was extracted and sheared from archival formalin-fixed paraffin-embedded (FFPE) tumor samples along with matched normal tissues. Cell-free DNA (cfDNA) from plasma was analyzed alongside matched germline DNA from whole blood to identify somatic alterations. Libraries were constructed with a median coverage depth >500×. Somatic variant analysis included single-nucleotide variants, small insertions and deletions, copy number alterations, and gene fusions/rearrangements. Tumor mutational burden (TMB) was calculated as the number of nonsynonymous somatic mutations (including SNVs and Indels) per megabase (Mb) of the sequenced coding region.

Statistics analysis

All statistical analyses were performed using Prism 5.01 (GraphPad Software Inc, San Diego, CA, USA) and R version 4.2.2 (The R Project for Statistical Computing, www.r-project.org). Baseline characteristics, effectiveness and safety data were summarized using descriptive statistics. Categorical variables were compared using Fisher's exact test. Time-to-event endpoints (rwPFS and OS) were estimated using Kaplan–Meier method, with median values and corresponding 95% confidence intervals (CIs) reported. Hazard ratios (HRs) were calculated from Cox regression models. Univariate and multivariate Cox regression analyses were used to evaluate prognostic factors. A two-sided P value < 0.05 was considered statistically significant.

Data availability

The datasets generated during the current study are not publicly available to protect patient privacy but are available from the corresponding author on reasonable request.

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M.N. and D.W.: Writing—original draft, data curation, formal analysis, visualization. S.D. and Q.Z.: Conceptualization, resources. W.X., R.H., and Y.S.: Methodology, data curation. Z.Y. and J.H.: Resources. F.X., L.L., Y.C., and D.P.: Data curation, validation. X.A. and S.W.: Conceptualization, investigation, supervision, writing—reviewing and editing. All authors read and approved this manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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