Breast Cancer Research

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Trastuzumab deruxtecan in patients with active brain metastases from HER2-positive/low metastatic breast cancer: a retrospective multicenter real-world study

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Abstract

Background Brain metastases (BMs) are almost a norm and devastating complication of metastatic breast cancer (MBC), but patients with active BMs (untreated or progressing to prior local therapy) are usually excluded from participating in clinical trials. Trastuzumab deruxtecan (T-DXd) has shown remarkable intracranial activity in pretreated human epidermal growth factor receptor 2 (HER2)-positive MBC with active BMs in latest prospective trials, but real-world evidence about its efficacy and safety remains limited.

Methods This real-world study enrolled patients with active BMs from HER2-positive/low MBC receiving at least one cycle T-DXd (5.4 mg/kg, Q3W) in three hospitals in China between June 2022 to May 2024. The primary endpoint was the best intracranial overall response rate (iORR) following the response assessment in neuro-oncology brain metastases criteria. Secondary endpoints included the intracranial and overall progression-free survival (iPFS-PFS), overall survival (OS), and safety.

Results In total, 38 patients were enrolled, including 29 HER2-positive and 9 HER2-low MBC. Except for endocrine therapy, the median number of prior therapy lines was 2 (range 0–10). Among HER2-positive patients, one patient (11.1%) had a complete intracranial response and eighteen (62.1%) had a partial intracranial response as the best intracranial response, with an iORR of 65.5%. As for HER2-low patients, the iORR was 66.7%. During a median follow-up of 10.3 (range 1.53–24.4) months, the median iPFS and OS were not reached for both HER2-positive and HER2-low MBC, their 12-month iPFS rate stood at 79.8% (95% confidence interval (CI): 65.2–97.7%) and 51.9% (95% CI: 26.7–100.0%), respectively. In the HER2-positive cohort, the median PFS was 12.8 months (95% CI: 10.2-not reached) and the 12-month OS rate was 86.5% (95% CI: 69.4–100.0%). For HER2-low cohort, the median PFS and 12-month OS rate

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were 6.33 months (95% CI: 3.93-not reached) and 85.7% (95% CI: 63.3–100.0%), respectively. Most common adverse events were moderate and no new safety signals were observed.

Conclusions In this real-world population, T-DXd yielded encouraging intracranial activity in HER2-positive/low MBC patients with active BMs with acceptable tolerance, which was aligned with previous clinical trials data. These results support the concept of T-DXd as systemic therapy for MBC patients with active BMs irrespective of HER2-positive/low.

Keywords Trastuzumab Deruxtecan, HER2-positive/low breast cancer, Active brain metastases, Intracranial overall response rate, Real-world

Introduction

About half of human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) patients develop brain metastases (BMs) [1], and although the incidence of BMs in HER2-low MBC is not well described, BMs are commonly observed in metastatic triple-negative breast cancer patients and nearly 15% of estrogen receptor (ER)-positive/HER2-negative MBC during their respective course of disease [2, 3], leading MBC to the second most common cause of BMs after lung cancer [4]. Owing to improved detection and prolonged overall survival (OS) from therapeutic advances over the past two decades, BMs have become an increasingly prevalent complication [1, 5]. Local intervention, including whole-brain radiotherapy (WBRT), stereotactic radiotherapy (SRT), stereotactic radiosurgery (SRS) and neurosurgery has long been recommended for established BMs [6], but tumor-related death typically occurs within 2–16 months of therapy due to limited efficacy, along with high risk of radiation-associated neurocognitive decline and necrosis, surgical-associated infection and bleeding [7]. Thus, additional and effective systemic treatments are desperately required.

With breakthroughs in Antibody-drug conjugates (ADC), the therapeutic landscape of MBC has greatly changed. As the second-generation ADC, trastuzumab deruxtecan (T-DXd; formerly DS-8201a) is composed of a humanized monoclonal anti-HER2 antibody (MAAL-9001) with the same amino acid sequence as trastuzumab, a cleavable molecular linker stable in plasma and deruxtecan, a topoisomerase-I inhibitor with high inhibitory potency and high membrane permeability, with a high drug-to-antibody ratio of 8:1 [8, 9]. Hence, T-DXd theoretically could cross the blood-brain barrier and yield significant activity in BMs, which has been observed in several clinical trials [10–12]. Prescribed subgroup analysis of DESTINY-Breast01 trial reported a promising objective response rate (ORR) (14 of 24 patients (58.3%)) and long-lasting clinical activity of T-DXd in BMs from HER2-positive MBC [10]. DESTINY-Breast02 and 03 trials respectively showed the superiority of T-DXd to treatment of physician's choice (TPC) and trastuzumab emtansine (T-DM1) [11, 12] in patients with BMs, in which, T-DXd presented a superior median progression-free survival (PFS) with 13.9 months (95% confidence interval (CI): 11.1–18.0) to TPC with a median PFS of 5.6 months (95% CI: 3.3–8.1). Meanwhile, the DESTINY-Breast04 study demonstrated that T-DXd was also a superior therapeutic approach to TPC in HER2-low MBC [13]. While above mentioned studies only allowed patients with stable BMs (receiving prior therapy and radiographically stable) and intracranial response wasn't included in study endpoints. Owing to patients with active BMs (untreated or progressing to prior local therapy) usually being excluded from enrollment in clinical trials, understanding of its natural history and management in the real world are poorly elucidated [14, 15]. Recently, two prospective, single-arm, phase 2 trials, TUXEDO [16, 17] and DEBBRAH [18] have filled this gap, they evaluated the activity of T-DXd in population of HER2-positive breast cancer patients with active BMs and defined intracranial ORR (iORR) as the primary endpoint. Although high iORR of 73.3% and 44.4% were respectively reported in TUXEDO and DEBBRAH [16, 18], and long-term survival outcomes were observed in the former trial [17], they were limited to small sample size (number of 15 and 9) and unrandomized phase 2 design. Currently, the activity of T-DXd in MBC with active BMs remains lacking solid evidence, and real-world data for T-DXd would be particularly valuable due to weak prospective evidence.

Herein, we aimed to retrospectively evaluate the efficacy of intracranial lesions, survival, and safety of T-DXd in patients with active BMs from HER2-positive/low MBC in real-world treatment scenarios.

Methods

Patient selection

This is a multicenter, retrospective real-world study. From June 2022 to May 2024, HER2-positive/low MBC with active BMs receiving T-DXd at three hospitals in China were screened. We performed current study following the Declaration of Helsinki with the approvement from Sun Yat-sen University Cancer Center ethics committee (No. B2024-386-01), and given to its retrospective nature, written informed consent was waived.

Eligible patient had to fulfill following criteria: [1] age ≥ 18 years; [2] histologically conformed HER2-positve

(immunohistochemistry (IHC)3+, in situ hybridization (ISH) ratio ≥ 2.0, or average HER2 copy number ≥ 6.0 signals) or HER2-low (IHC2+/ISH-negative) MBC; [3] with active BMs (untreated or progressing to prior local therapy) at time of initiating T-DXd and no indication for immediate local therapy; [4] with measurable brain lesions according to neuro-oncology brain metastases (RANO-BM) criteria [19]; [5] Eastern Cooperative Oncology Group (ECOG) performance status < 2; [6] disease progressing on or after trastuzumab and a taxane in the advanced/metastatic setting or recurring within six months after neoadjuvant or adjuvant treatment involving trastuzumab and a taxane (if HER2-positive patients); [7] adequate hematological status, hepatic and kidney function at time of initiating T-DXd; [8]life expectancy of at least three months. Patients were excluded if they were lactation or pregnancy; had a history of malignancy other than squamous cell carcinoma, basal cell carcinoma of the skin or carcinoma in situ of the cervix within the last 3 years, including contralateral breast cancer; had leptomeningeal lesion; underwent uncontrolled seizures, central nervous system disorders or psychiatric disability; underwent clinically significant cardiac, hepatic/biliary or renal disease; underwent clinically severe or uncontrolled pulmonary disorder and active opportunistic infections.

Data collection and analysis

The following patients' clinicopathological data were collected, including age, ECOG, HER2 status, estrogen/progesterone receptor status, prior number of lines of HER2-directed therapy, prior local therapy for brain lesion, status of BMs, number of BMs, visceral metastases or not, time from last local therapy to T-DXd.

Study endpoints

The primary endpoint of current study was the rate of best intracranial responses (iORR) at any radiological assessment after administrating at least one cycle of T-DXd, defined as complete remission (CR) and partial remission (PR) by the RANO-BM criteria [19]. Second endpoints included the intracranial PFS (iPFS), defined as the time from initiating T-DXd until radiologically documented intracranial progression; PFS, defined as the time from the initiation of T-DXd until radiologically documented progression or death; OS, defined as the time from first dose of T-DXd to death from any cause, and safety.

Statistical analysis

Age was presented as its median and range, while categorical variables were listed as frequency counts with percentages. The Kaplan-Meier method was utilized to plot survival curves, and their Hazard ratio (HR) and 95% CI were estimated using the Cox multivariate regression model. All statistical analysis were performed though R software ("rms" package, version 4.0.1; Vanderbilt University, Nashville, TN).

Results

Patients

Between June 2022 to May 2024, a total of 38 patients with active BMs receiving T-DXd were screened for eligibility in current study (Fig. 1). Table 1 summary the baseline characteristics of all selected patients. The median age was 48.0 years (range 31.0–84.0). ECOG performance status was 0 in 32 patients (84.2%) and 30 patients (78.9%) had hormone-receptor-negative. A total of 29 patients (76.3%) had conformed HER2-positive by IHC and another 9 patients (23.7%) were diagnosed as HER2-low. 8 patients (21.1%) were heavily pretreated with the number of prior lines of therapy ≥ 5, 28 patients (73.7%) had a history of HER2-directed treatment with trastuzumab, and 12 patients (31.6%) had a history of T-DM1, while 23 of 38 (60.5%) patients underwent a previous HER2 tyrosine kinase inhibitor (lapatinib or pyrotinib). Newly diagnosed and untreated BMs occupied in 20 patients (52.6%), and 18 patients (47.4%) had BMs progressing after previous local therapy. A total of 24 patients underwent visceral metastasis, including 19 patients (65.5%) in the HER2-positive cohort and 5 patients (55.6%) in the HER2-low cohort. As for the BMs, 9 of 38 (23.7%) patients had single metastasis, and 29 of 38 (76.3%) patients had multiple metastases. 2 of 38 (5.3%) patients had received previous WBRT and 11 patients (28.9%) previously underwent SRS/SRT. The median time from the last local treatment to receiving T-DXd in patients with previous local intervention was 3.87months (range 0.03–17.7).

Intracranial efficacy

At data off (22 July, 2024), 21 patients (55.3%) still continued the T-DXd treatment. Among HER2-positive MBC patients with active BMs, the iORR assessed by RANO-BM reached to 65.5% (19/29), including 1 patient in CR and 18 patients in PR, while for HER2-low MBC with active BMs, the iORR was 66.7% (6/9), among which, there was 1 CR and 5 PR (Table 2). The best response and tumor changes in intracranial target lesions during follow-up was presented as the waterfall in Fig. 2A. And the intracranial activity of the T-DXd in HER2-positive MBC with active BMs could be exemplified in Fig. 2B, where after four treatment cycles for patient 1 and patient 2, nine cycles for patient 3, their intracranial targets significantly reduced in size. Similarly, Fig. 2C showed that after nine cycles T-DXd for patient 1 and two cycles T-DXd for patient 2 with active BMs from HER2-low MBC, intracranial targets also significantly reduced in size.

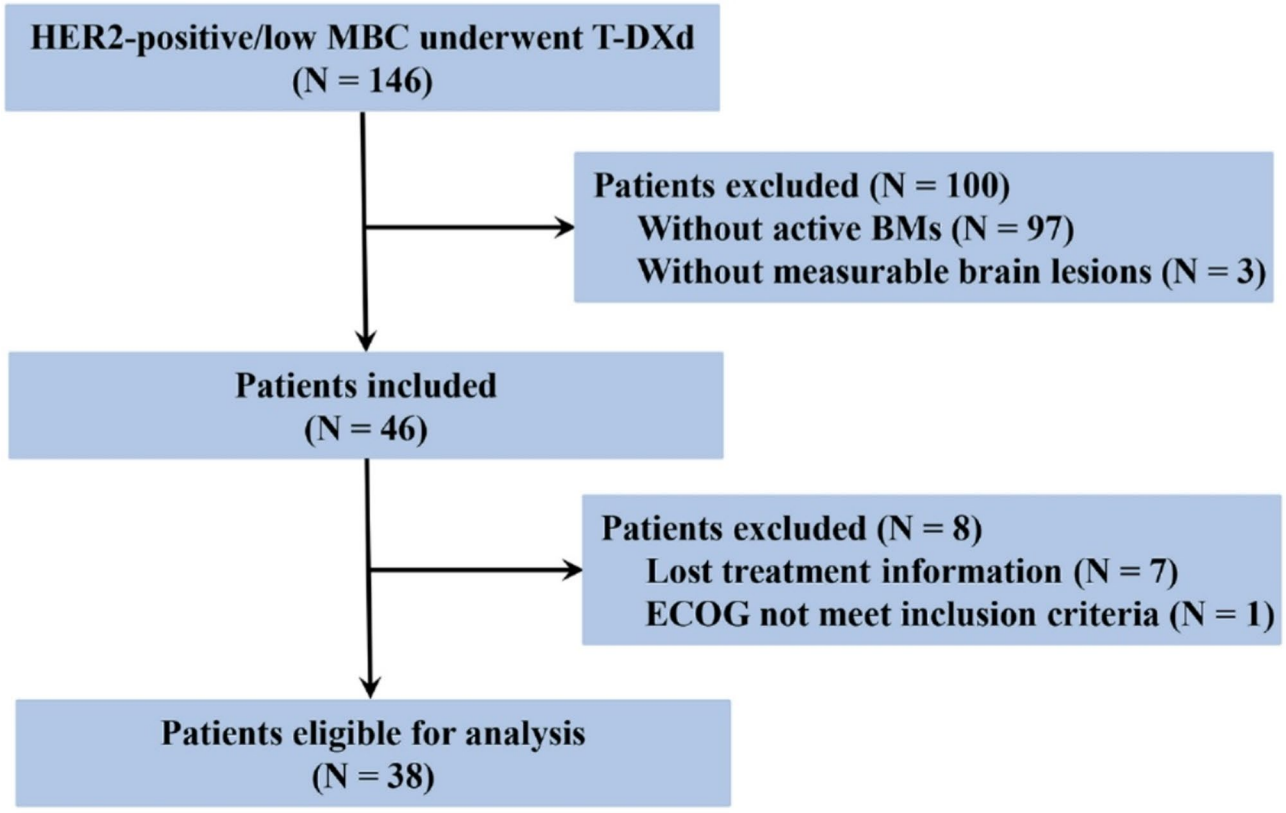

Fig. 1 Flow chart of patient selection in this study

When considering the treatment line, among the HER2-positive cohort, there were 2 PR in first line, 7 PR in second line, 5 PR in third line, 1 CR and 3 PR in fourth line, 1 PR in fifth or later lines. As for the HER2-low cohort, there were 4 PR in first line, 1 PR in third line, 1 CR in fifth or later lines (Table 3). Additionally, Table 4 summarized the data regarding intracranial activity according to BMs status, which showed higher iORR in untreated BMs than that in BMs progressing after prior local intervention regardless of HER2 status.

Safety

Treatment-emergent adverse events (AEs) in current study were listed in Table 5. Most AEs were mild and moderate. Overall, the most common AEs was fatigue, with 23 patients (60.5%) experiencing grade 1–2 and 2 patients (5.3%) facing grade 3. Nausea was also common, occurring in 11 patients (28.9%), including 8 HER2-positive patients (27.6%) and 3 HER2-low patients (33.3%), and all of them underwent grade 1–2. The main grade 1–2 hematological toxicities were anemia (9/38, 23.7%) and neutropenia (6/38, 15.8%), all of which occurred in HER2-positive MBC patients. Grade 3 AEs incorporated anemia, neutropenia, depression, interstitial lung disease (ILD) and fatigue, and 1 HER2-positive patients underwent Grade 4 ILD, all of them were reported as recovered/resolved. No treatment-related deaths occurred.

Survival analysis

The median follow-up period from initiating T-DXd was 10.3 (range 1.53–24.4) months. Time to intracranial progression (time from beginning T-DXd until documented progression in brain lesions) and OS data were immature at the time of analysis, so the median iPFS and OS were not calculated for HER2-positive and HER2-low patients, their 12-month iPFS rate stood at 79.8% (95% CI: 65.2–97.7%) (Fig. 3A) and 51.9% (95% CI: 26.7–100.0%) (Fig. 3D), respectively. In the cohort of active BMs from HER2-positive MBC, the median PFS since initiating T-DXd was 12.8 months (95% CI: 10.2-not reached) (Fig. 3B), and the 12-month OS rate was 86.5% (95% CI: 69.4–100.0%) (Fig. 3C). For HER2-low patients, the median PFS and 12-month OS rate were 6.33 months (95% CI: 3.93-not reached) (Fig. 3E) and 85.7% (95% CI: 63.3–100.0%) (Fig. 3F), respectively.

Discussion

This was a study of 38 HER2-positive/low MBC patients with active BMs receiving T-DXd in a real-world clinical setting, to provide an authentic understanding of T-DXd outcomes for treating this challenging population.

Table 1 Patient demographics and baseline characteristics

Characteristic	Total cohort	HER2-positive	HER2-low
		N = 29	*N* = 9
Age, years			
Median	48.0	49.0	47.0
Range	31.0–84.0	31.0–84.0	34.0–64.0
ECOG performance status [a]: n (%)			
0	32 (84.2)	23 (79.3)	9 (100)
1	6 (15.8)	6 (20.7)	0
HER2 status [b]: n (%)			
IHC 3+	22 (57.9)	22 (75.9)	0
IHC 2+/ISH amplified	7 (18.4)	7 (24.1)	0
ICH 1 + or IHC 2+/ISH negative	9 (23.7)	0	9 (100)
Hormone receptor status: n (%)			
ER- and/or PgR-positive	30 (78.9)	21 (72.4)	9 (100%)
ER- and PgR-negative	8 (21.1)	8 (27.6)	0
Visceral metastases: n (%)			
Yes	24 (63.2)	19 (65.5)	5 (55.6)
No	14 (36.8)	10 (34.5)	4 (44.4)
Prior lines of therapy for MBC [c]: n (%)			
0	7 (18.4)	3 (10.3)	4 (44.4)
1	7 (18.4)	7 (24.1)	0
2	7 (18.4)	5 (17.2)	2 (22.2)
3	7 (18.4)	7 (24.1)	0
4	2 (5.3)	2 (6.9)	0
≥ 5	8 (21.1)	5 (17.2)	3 (33.3)
Median (range)	2 (0–10)	2 (0–10)	2 (0–10)
Prior therapy of CDK4/6 inhibitors: n (%)	8 (21.1)	3 (10.3)	5 (55.6)
Prior HER2-directed therapy: n (%)			
Trastuzumab	28 (73.7)	28 (96.6)	0
Pertuzumab	19 (50.0)	19 (65.5)	0
T-DM1	12 (31.6)	12 (41.4)	0
Lapatinib	4 (10.5)	4 (13.8)	0
Pyrotinib	19 (50.0)	19 (65.5)	0
RC-48	2 (5.3)	1 (3.4)	1 (11.1)
Other	8 (21.1)	8 (27.6)	0
Best response to prior therapy [d]: n (%):			
CR or PR	24 (63.2)	19 (65.5)	5 (55.6)
SD ≥ 24 weeks	3 (7.9)	3 (10.3)	0
SD < 24 weeks	3 (7.9)	3 (10.3)	0
PD	2 (5.3)	2 (6.9)	0
Not evaluable	6 (15.8)	2 (6.9)	4 (44.4)
Status of BMs: n (%)			
Untreated	20 (52.6)	14 (48.3)	6 (66.7)
Progressing after previous local therapy	18 (47.4)	15 (51.7)	3 (33.3)
Number of BMs			
Single	9 (23.7)	7 (24.1)	2 (22.2)
Multiple	29 (76.3)	22 (75.9)	7 (77.8)
Prior local therapy for BMs: n (%)			
WBRT	2 (5.3)	2 (6.9)	0
SRS/SRT	11 (28.9)	9 (31.0)	2 (22.2)
WBR + SRS/SRT and/or neurosurgery	5 (13.2)	4 (13.8)	1 (11.1)
Best response to prior local therapy [e]: n (%)			
CR or PR	8 (21.1)	5 (17.2)	3 (33.3)
SD ≥ 24 weeks	2 (5.3)	2 (6.9)	0

Table 1 (continued)

Characteristic	Total cohort	HER2-positive	HER2-low
		N = 29	*N* = 9
SD < 24 weeks	5 (13.2)	5 (17.2)	0
PD	1 (2.6)	1 (3.4)	0
Not evaluable	2 (5.3)	2 (6.9)	0
Time from last prior local therapy to inclusion (months): median (range)	3.87 (0.03–17.7)	2.93 (0.03–17.7)	8.07 (1.2–11.6)

Abbreviations: MBC, metastatic breast cancer; HER2, human epidermal growth factor receptor 2; BMs, brain metastases; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PgR, progesterone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DM1, Trastuzumab emtansine; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; WBRT, whole-brain radiotherapy; SRS/SRT, stereotactic radiosurgery/ stereotactic radiotherapy. All values are No. (%) unless otherwise specified

[a] ECOG performance status scores range from 0 to 5, with higher score indicating greater disability. [b] HER2 status was evaluated locally. HER2-positive status was defined as IHC 3+, ISH ratio ≥ 2.0, or average HER2 copy number ≥ 6.0 signals

[c] Prior therapies for ABC do not include hormone therapy

[d] Overall response to prior therapy assessed according to the RECIST 1.1 criteria

[e] Intracranial response to prior local therapy assessed according to the RANO-BM criteria

Table 2 The best intracranial response of T-DXd in patients

	HER2-positive	HER2-low
	N = 29	*N* = 9
Best intracranial response to T-DXd [a]: n (%)		
CR	1 (3.4)	1 (11.1)
PR	18 (62.1)	5 (55.6)
SD	7 (24.1)	1 (11.1)
PD	3 (10.3)	1 (22.2)
iORR: (CR + PR) %	65.5	66.7

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; HER2, human epidermal growth factor receptor 2; iORR, intracranial objective response rate

[a] Intracranial response to prior local therapy assessed according to the RANO-BM criteria

Because we mainly focused on the intracranial efficacy of T-DXd, iORR was selected as the primary endpoint of current analysis, which demonstrated an encouraging iORR of 65.5% in HER2-positive and 66.7% in HER2-low patients, respectively. This real-world evidence further solidified T-DXd as a potent therapeutic option for patients with active brain involvement from HER2-positive and HER2-low MBC.

Current, small-molecule HER2-targeting tyrosine kinase inhibitors (TKIs) as upfront systemic care of breast cancer BMs have been well established [20–23]. The single-arm phase 2 LANDSCAPE trial reported that lapatinib combining capecitabine yielded an intracranial response rate of 65.9% by RECIST 1.1 in HER2-positive MBC with BMs untreated with WBRT [22, 24]. The TBCRC-022 trial showed that the iORR in lapatinib-naïve ($n = 37$) or lapatinib-treated patients ($n = 12$) with progressive BMs receiving neratinib and capecitabine was 49% and 33%, respectively [21]. In the double-blind HER2CLIMB study, adding tucatinib to trastuzumab and capecitabine confirmed an iORR of 47.3% in heavily pretreated HER2-positive MBC with active BMs (median 3.0 previous therapy regimens in the metastatic setting), this triple combination significantly prolonged median iPFS by RECIST 1.1 from 4.0 to 9.6 months and median OS from 11.8 to 21.4 months [23, 25]. These data firmly established the status of TKIs in treating breast cancer BMs, the most current version of European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO)-Society for Neuro-Oncology (SNO)-American Society for Radiation Oncology (ASTRO) guidelines therefore recommend tucatinib plus trastuzumab and capecitabine as the preferred treatment in active BMs from HER2-positive MBC [6, 26].

Given the aggressive nature and poor prognosis of BMs [3, 7], additional options for this challenging patient population are urgent, especially for late lines of treatment. Increasing studies documented that molecules larger than TKIs could pass blood-brain barrier and penetrate the brain parenchyma [27]. In the subgroup of HER2-positive MBC with untreated BMs in the phase 3b KAMILLA trial ($n = 67$), T-DM1 presented an iORR of 49.3% [28], comparing favorably with that reported in the HER2CLIMB trial, and suggested the intracranial efficacy of ADCs in principle. Subsequently, the randomized, phase 3 DESTINY-Breast03 established T-DXd as the second-line standard in HER2-positive MBC [12], an exploratory analysis of which further revealed that T-DXd yielded an iORR of 65.7% (23/35) superior to that (34.3%, 12/35) in T-DM1 for patients with baseline BMs [29]. Considering these favorable data, study on clinical activity of T-DXd in MBC with BMs catch more and more attention. Emerging clinical trials and real-world evidence suggested that T-DXd might offer comparable or superior intracranial efficacy in later treatment lines, and the recent consensus highlighted its growing role in this setting, particularly for HER2-positive MBC patients refractory to tucatinib or those requiring alternative sequencing strategies [30].

The promising efficacy of T-DXd in BMs from MBC was initially observed in DESTINY-Breast series trials (DESTINY-Breast01, 02, 03 and 04) [10–13], but they only recruited few patients with treated/stable BMs. In

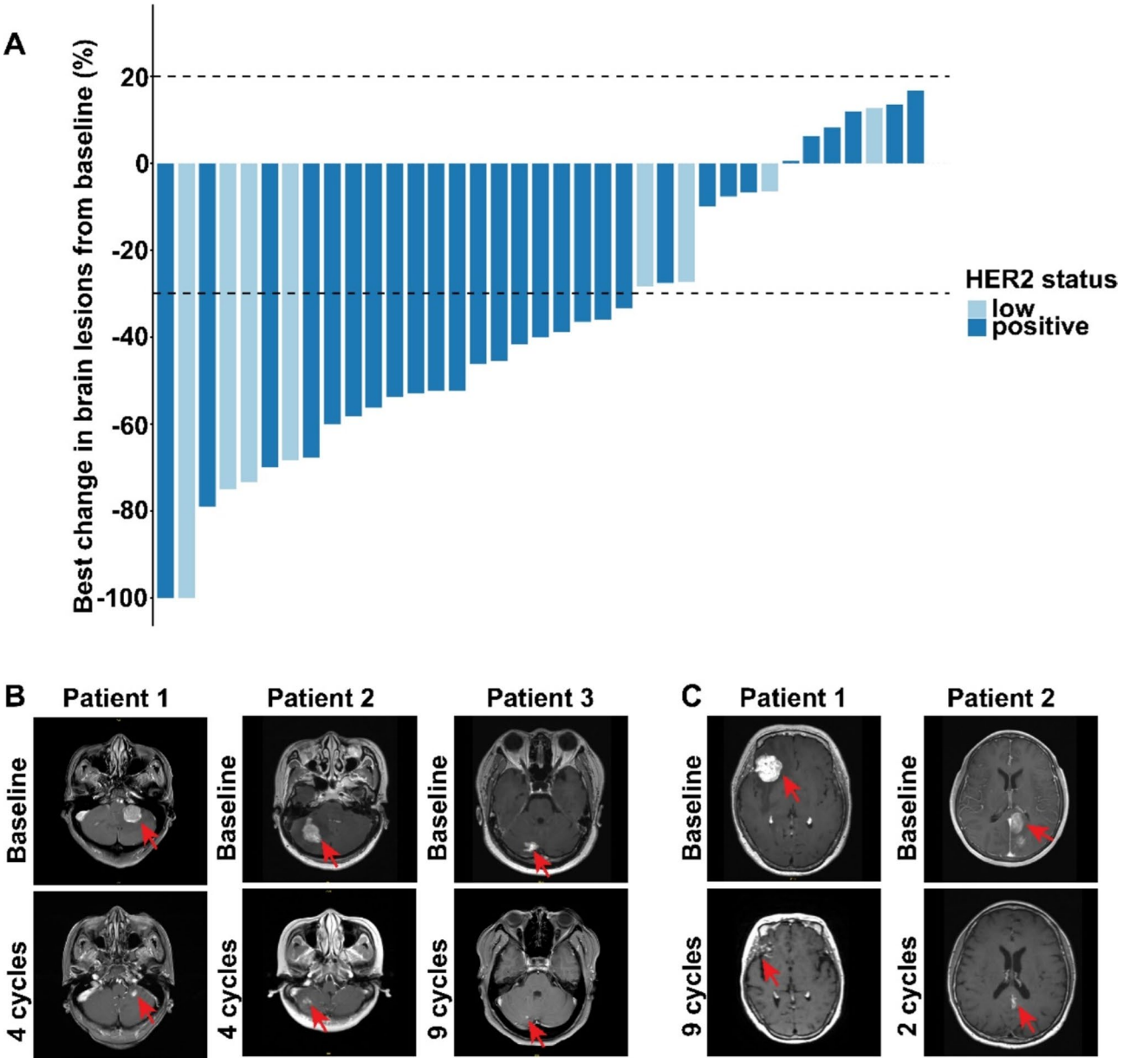

Fig. 2 The best response and tumor change in brain to T-DXd during follow-up. **(A)** Waterfall plot of tumor best changes in intracranial target lesion size. **(B)** Contrast-enhanced brain MRIs scans of tumor metastases in brain during four/four/nine cycles of treatment for HER2-positive patients. **(C)** Contrast-enhanced brain MRIs scans of tumor metastases in brain during nine/two cycles of treatment for HER2-low patients

view of the fact that quite a few MBC patients undergo active BMs or require systemic intervention except for local treatment, questions remain regarding the intracranial activity of T-DXd in MBC with active BMs. Encouraging intracranial efficacy for T-DXd despite its large molecular size has been previously suggested in published retrospective or small prospective cohorts. An exploratory pooled analysis of DESTINY-Breast01, 02 and 03 presented an iORR of 45.5% of T-DXd in HER2-positive MBC with untreated asymptomatic (i.e., active) BMs ($n = 44$) [31], which was lower than that observed in our real-world evidence, perhaps because the more heavily pretreated cohort analyzed in the pooled analysis (median 3.0 prior therapy regimens in metastatic setting versus 2.0 for our study). Because intracranial endpoints in DESTINY-Breast01, 02 and 03 were not prespecified in protocols and exploratory, as well as the small patient numbers in each BM subgroup, potential introduced bias and limitations of cross-trial comparisons should be noted. The retrospective ROSET-BM study also showed sustained intracranial efficacy in the population with analytical active BMs ($n = 37$), with an iORR of 62.7% comparable to our study [32]. As for prespecified prospective trials, DEBBRAH ($n = 13$) evaluated the

Table 3 The best intracranial efficacy of T-DXd based on treatment line

	Treatment line	Best intracranial response to T-DXd [a]				iORR: (CR + PR) %
		CR	PR	SD	PD	
HER2-positive (*N* = 29)	I line (*N* = 3)		2	1		2 (66.7)
	II line (*N* = 7)		7			7 (100.0)
	III line (*N* = 5)		5			5(100.0)
	IV line (*N* = 7)	1	3	1	2	4 (57.1)
	≥V line (*N* = 7)		1	5	1	1 (14.3)
HER2-low (*N* = 9)	I line (*N* = 4)		4			4 (100.0)
	II line					
	III line (*N* = 2)		1		1	1 (50.0)
	IV line					
	≥V line (*N* = 3)	1		1	1	1 (33.3)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; HER2, human epidermal growth factor receptor 2; iORR, intracranial objective response rate

[a] Intracranial response to prior local therapy assessed according to the RANO-BM criteria

Table 4 The best intracranial efficacy of T-DXd based on status of BMs

	Treatment line	Best intracranial response to T-DXd [a]				iORR: (CR + PR) %
		CR	PR	SD	PD	
HER2-positive (*N* = 29)	Untreated (*N* = 14)	1	10	3		11 (78.6)
	A history of local therapy (*N* = 15)		8	4	3	8 (53.3)
HER2-low (*N* = 9)	Untreated (*N* = 6)		5		1	5 (83.3)
	A history of local therapy (*N* = 3)	1		1	1	1 (33.3)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; HER2, human epidermal growth factor receptor 2; iORR, intracranial objective response rate

[a] Intracranial response to prior local therapy assessed according to the RANO-BM criteria

activity of T-DXd in HER2-positive/low MBC with BMs and/or leptomeningeal carcinomatosis, and reported an iORR of 46.2% in active BMs cohort [18]. The largest so far prospective, phase 3b/4 DESTINY-Breast12 trial indicated that the iORR of T-DXd in active BMs from HER2-positive MBC ($n = 106$) reached to 62.3% [33], in line with our result in the HER2-positive patients. The TUXEDO-1 study ($n = 15$) showed an impressive high iORR of 73.7% of T-DXd in HER2-positive patients with active BMs [16], this could be explained that a significant number of HER2-postive MBC (5/29, 17.2%) in our study had heavily pretreated disease and received T-DXd in a treatment line ≥ 5, but patients in TUXEDO-1 received T-DXd within a treatment line of 5. Interestingly, there were differences in iORR of T-DXd among different treatment lines in our study, and compared to the Italian real-world analysis [34], we registered higher iORR in I line (66.7% vs. 50.0%), II line (100% vs. 91.7%), III line (100% vs. 75.0%) and IV line (57.1% vs. 91.7%), but a lower iORR in ≥ V line (14.3% vs. 22.2%). These differences might be explained by the unselected cohort and racial differentiation, rather than in a true difference in drug activity for the different cohorts. In addition, significant difference in iORR was found for patients that did or did not receive local intervention for BMs both in HER2-positive (78.6% vs. 53.3%) and HER2-low MBC (83.3% vs. 33.3%). This probably highlighted the significance of utilizing T-DXd in the upfront line for MBC patients with active BMs.

Despite a relatively short follow-up of 10.3 months of current study, T-DXd also showed encouraging intracranial duration of response and substantial survival benefits in patients with active BMs. The median iPFS in HER2-positive patients was not reached and its 12-month iPFS rate stood at 79.8% (95% CI: 65.2–97.7%), which was apparent longer than that in the pooled analysis of DESTINY-Breast01, 02 and 03 trials (median iPFS 18.5 months (95% CI: 13.6–23.3)) [31]. The median PFS of HER2-positive MBC in our study was 12.8 months (95% CI: 10.2-not reached), which was numerally lower than that (21 months, 95% CI: 13.3-not reached) in the TUXEDO-1 study [35], this PFS gap might be caused due to the imbalance of follow-up time, patients' numbers and treatment lines of T-DXd between two studies. The 12-month OS rate for HER2-positive MBC in our study reached 86.5% (95% CI: 69.4–100.0%), similar to that observed in patients with active BMs in the DESTINY-Breast12 study (86.1% (95% CI: 77.6–91.5%)) [33]. These data indicated that T-DXd not only offered potent intracranial activity but also contributed to long-term survival, which was a key consideration in the treatment of patients with active BMs from HER2-positive MBC.

Interestingly, our HER2-low MBC patients also demonstrated an encouraging iORR of 66.7%, aligning with

Table 5 Treatment-related adverse events

	Total cohort (*N* = 38)				HER2-positive (*N* = 29)				HER2-low (*N* = 9)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders												
Anemia	9 (23.7)	2 (5.3)			9 (31.0)	2 (6.9)						
Neutropenia	6 (15.8)	2 (5.3)			6 (20.7)	2 (6.9)						
Thrombopenia	5 (13.2)				5 (17.2)							
Gastrointestinal disorders												
Nausea	11 (28.9)				8 (27.6)				3 (33.3)			
Diarrhea	3 (7.9)				3 (10.3)							
Vomiting	5 (13.2)				4 (13.8)				1 (11.1)			
Constipation	4 (10.5)				3 (10.3)				1 (11.1)			
Metabolism and nutritional disorders												
Loss of appetite	2 (5.3)				2 (6.9)							
Musculoskeletal and connective tissue disorders												
Bone pain	4 (10.5)				3 (10.3)				1 (11.1)			
Headache	2 (5.3)				2 (6.9)							
Muscle cramp	1 (2.6)				1 (3.4)							
Psychiatric disorders												
Insomnia	6 (15.8)				4 (13.8)				2 (22.2)			
Depression	3 (7.9)	2 (5.3)			2 (6.9)	2 (6.9)			1 (11.1)			
Anxiety	3 (7.9)				2 (6.9)				1 (11.1)			
ALT increased	2 (5.3)				2 (6.9)							
ILD	1 (2.6)	1 (2.6)	1 (2.6)		1 (3.4)	1 (3.4)	1 (3.4)					
Fatigue	23 (60.5)	2 (5.3)			17 (58.6)	2 (6.9)			6 (66.7)			

Abbreviations: ALT, alanine aminotransferase; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease. All values are No. (%) unless otherwise specified

Medical Dictionary for Regulatory Activities version 20.1 was used for coding of system organ class. Analysis was performed on the safety analysis population that included all patients who received ≥ 1 dose of T-DXd

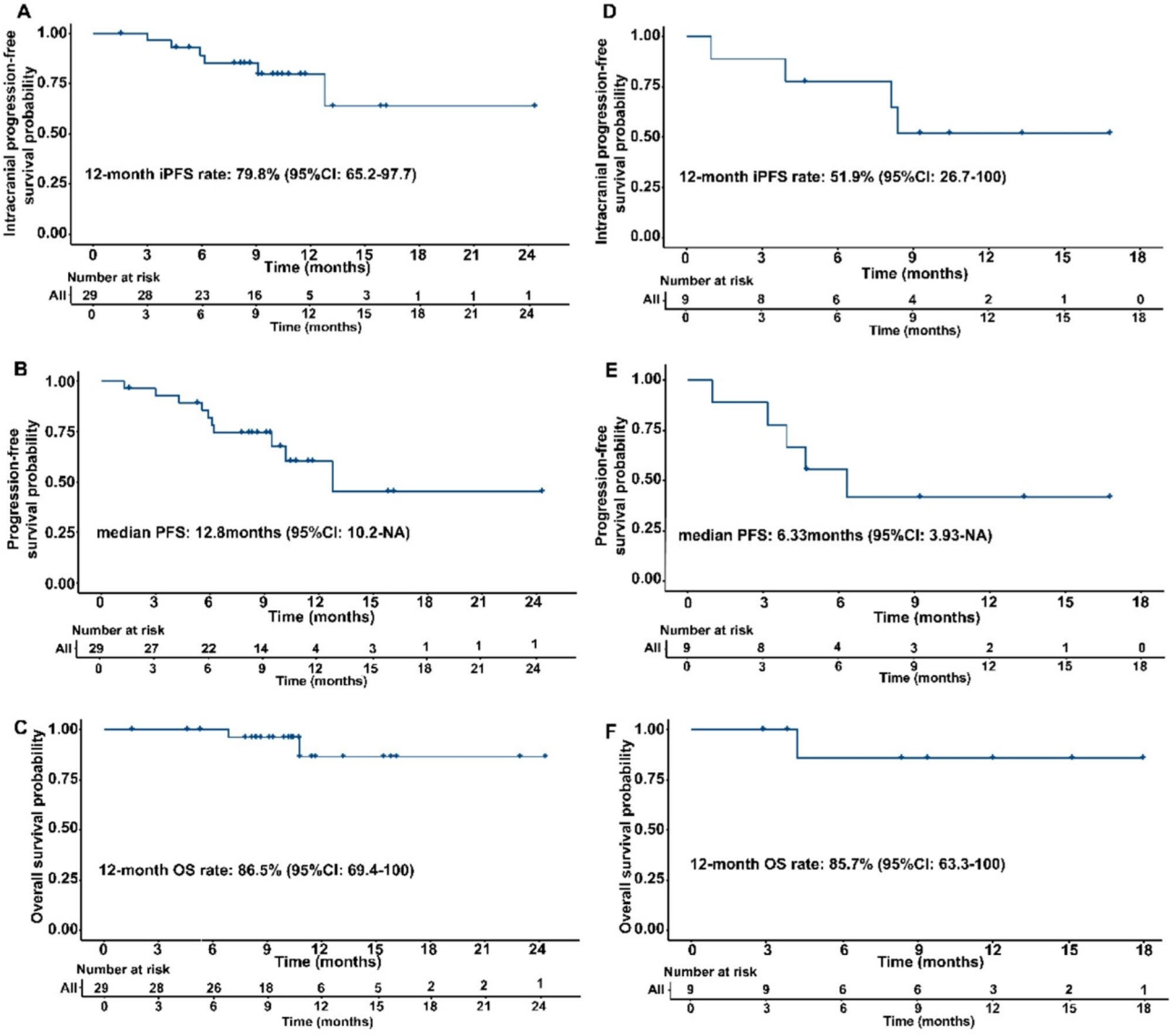

Fig. 3 Kaplan-Meier estimates of survival. **(A)** The intracranial progressive-free survival for HER2-positive patients. **(B)** The progressive-free survival for HER2-positive patients. **(C)** The overall survival for HER2-positive patients. **(D)** The intracranial progressive-free survival for HER2-low patients. **(E)** The progressive-free survival for HER2- low patients. **(F)** The overall survival for HER2-low patients

that in HER2-positive MBC. HER2-low MBC has historically been considered less responsive to HER2-targeted therapies, our real-world data underscore the potential of T-DXd in overcoming the biological barriers associated with HER2-low tumors, and its potential as a viable option for HER2-low active BMs, a population historically lacking targeted strategies. The randomized, phase 3 DESTINY-Breast04 trial [13] reported that T-DXd generated superior survival benefits in previously heavily treated HER2-low MBC to TPC regardless of hormone receptor status. And its subgroup analysis indicated once again that T-DXd provided clinically meaningful survival benefits versus TPC in HER2-low MBC ($n = 213$) from Asian countries and regions [36]. Similarly, in current real-world analysis, stable and durable survival benefits of T-DXd in active BMs from HER2-low MBC also were observed, with a 12-month iPFS of 51.9%, a median PFS of 6.33 months and a 12-month OS rate of 85.7%. These promising findings indicated the potential value of T-DXd in improving the treatment outcome for HER2-low MBC patients with active BMs and broadened its therapeutic spectrum. Currently, an ongoing international, multicenter, single-arm, phase II TUXEDO-4 trial specifically evaluates the intracranial efficacy of T-DXd in HER2-low MBC patients presented with active BMs [37], we are looking forward to its outcomes, which might provide prospective validation for our real-world HER2-low findings.

Overall, no new treatment-related toxicity was observed and the safety profile of T-DXd in active BMs from MBC was consistent with published trials [16, 18, 30, 32]. The majority of AEs were mild to moderate, among which, fatigue was the most common, experienced by 60.5% of patients, followed by nausea in 28.9%. The most frequent hematological toxicities were anemia and neutropenia, and both were predominantly grade 1–2. Notably, no treatment-related deaths were reported, and the incidence of severe toxicities (grade ≥ 3) was relatively low, including only a few cases of anemia, neutropenia, depression, ILD and fatigue. Usually, patients with active BMs are often frail and more susceptible to treatment-related toxicity, our data suggested T-DXd to be a safe and efficacious therapeutic option for this difficult-to-treat population.

Despite our important insights into the real-world efficacy of T-DXd in patients with active BMs, several limitations should be noted. First, as a retrospective design, it was inherently subject to selection and information bias, such as treatment preferences in three hospitals, collected data being originally not designed to collect data for research, and the heterogeneity in previous treatment line and local interventions might confound results, in view of our retrospective design limiting data granularity, we did not perform multivariate analysis to adjust for these variables. And due to lacking randomization, comparisons with other treatments (e.g., TKIs, TPC) were indirect and based on historical data, limiting the ability to attribute efficacy solely to T-DXd. Therefore, the results should be interpreted with caution and validated in larger, prospective studies with controlled designs to strengthen our conclusion. While the retrospective design limited causal inferences, our study added meaningful real-world evidence to the growing literature on T-DXd for active BMs from MBC. Second, the sample size was relatively small, and the follow-up period was limited, particularly for those yet reaching the 12-month survival milestone, the long-term benefits and risks of T-DXd might not fully be captured. Future longer follow-up with larger cohort is crucial and needed in confirming its activity and safety in this patient population. Third, all HER2-low MBC included here were hormone receptor-positive, extension of our results needs careful and proper evaluation in patients with active BMs from hormone receptor-negative/HER2-low MBC. And patients with leptomeningeal disease were exclusionary, so our findings might not be generalizable to the entire spectrum of MBC patients with BMs, further detailed research is warranted to assess the intracranial efficacy of T-DXd in these subgroups.

Conclusion

In conclusion, T-DXd yields clinically intracranial activity in previously treated patients with HER2-positive/low MBC with active BMs and allows for promising survival outcomes with acceptable tolerability. These results highlight T-DXd as a potential treatment for this challenging patient population. Further long-term monitoring and larger cohort are necessary to confirm and expand upon these findings.

Abbreviations

HER2	human epidermal growth factor receptor 2
MBC	metastatic breast cancer
BMs	brain metastases
ER	estrogen receptor
OS	overall survival
WBRT	whole-brain radiotherapy
SRT	stereotactic radiotherapy
SRS	stereotactic radiosurgery
ADC	antibody-drug conjugates
ORR	objective response rate
TPC	treatment of physician's choice
T-DM1	trastuzumab emtansine
ECOG	Eastern Cooperative Oncology Group
IHC	immunohistochemistry
ISH	in situ hybridization
RANO-BM	neuro-oncology brain metastases
CR	complete remission
PR	partial remission
PFS	progressive-free survival
HR	hazard ratio
CI	confidence interval
TKIs	tyrosine kinase inhibitors
ILD	interstitial lung disease
ESMO	European Society for Medical Oncology
ASCO	American Society of Clinical Oncology
SNO	Society for Neuro-Oncology
ASTRO	American Society for Radiation Oncology

Acknowledgements

We extend our sincere gratitude to all patients and clinicians who participated in this study.

Author contributions

FFD conceived of the study question and designed the study. FFD, XH and WL contributed to the statistical analysis, validation of analysis, interpretation of findings, draft-writing and editing. XXG, JDX, XDW and YYM conducted data curation and writing-editing. WYZ and WX conducted study administration, data collection and validation, funding acquisition, draft-editing, administrative and technical support. All authors read and approved the final manuscript.

Funding

This work was funded by the Natural Science Foundation of China (No.82173293).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the ethics and research committee of Sun Yat-Sen University Cancer Center (No. B2024-386-01), and we conducted it following the Declaration of Helsinki. Patients' individual consent was waived for its retrospective nature.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 17 January 2025 / Accepted: 14 July 2025
Published online: 21 July 2025

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