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Original Article

Clinical outcome and tolerability of DS-8201 in patients with advanced HER2-positive breast cancer: a retrospective study

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Abstract: Objective: There are limited data about DS-8201 (trastuzumab deruxtecan) in Chinese patients with advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer previously treated with trastuzumab emtansine (T-DM1). This study aimed to evaluate the efficacy and safety of DS-8201 compared to the treatment of physician's choice (TPC) in this population. Methods: In this retrospective cohort study, 185 eligible patients treated between December 2022 and March 2025 were assigned to either the DS-8201 group (n=83) or the TPC group (n=102), which received regimens such as capecitabine combined with anti-HER2 therapy. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), quality of life (QoL), and safety were assessed. Results: The DS-8201 group demonstrated significantly superior 12- and 24-month PFS (62.65% vs. 42.16%; 50.60% vs. 23.53%) and OS (90.36% vs. 60.78%; 75.90% vs. 54.90%) compared to the TPC group (all P<0.05). ORR (72.29% vs. 45.10%), median DoR (20.00 vs. 9.00 months), and DCR (80.72% vs. 60.78%) were also significantly improved (all P<0.05). Patients receiving DS-8201 reported better QoL and delayed time to first hospitalization (all P<0.05). The overall incidence of treatment-emergent adverse events (TEAEs) was similar between groups (P>0.05). However, DS-8201 was associated with higher rates of nausea, alopecia, and drug-induced interstitial lung disease, while the TPC group had more diarrhea and palmar-plantar erythrodysesthesia (all P<0.05). Conclusion: DS-8201 showed significantly better efficacy and similar overall safety compared to TPC in patients with T-DM1-pretreated HER2-positive advanced breast cancer, supporting its use as a treatment option in this setting.

Keywords: Breast neoplasms, trastuzumab deruxtecan, immunoconjugates, real-world study, progression-free survival

Introduction

Globally, breast cancer is the second most common cancer among women and one of the leading causes of cancer-related death [1]. Currently, four women are diagnosed with breast cancer every minute worldwide, and one of them dies from it; this trend continues to worsen [2]. Molecular biology shows that breast cancer includes different molecular subtypes, making personalized treatment possible [3]. Human epidermal growth factor receptor 2 (HER2)-positive breast cancer accounts for approximately 30% of all breast cancers. This subtype is characterized by high invasiveness, rapid progression, a significant tendency for distant metastasis, and poor prognosis [4, 5].

HER2 gene amplification drives malignant phenotypes by continuously activating key signaling pathways such as PI3K/Akt and Ras/MAPK [6], making it an ideal model for targeted therapy. Since trastuzumab was innovatively applied in clinical practice in the late 1990s, the field of anti-HER2 therapy has developed particularly rapidly [7, 8]. During this development process, new antibody drugs such as pertuzumab have emerged, as well as small molecule tyrosine kinase inhibitors like lapatinib, nalatinib, and tocapatinib [9-11]. These drugs can block the HER2 signal through different mechanisms. By blocking the signal, the survival time of patients can be prolonged.

Her2-positive advanced breast cancer faces some challenges in treatment, mainly in terms

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of drug resistance and disease progression. Most advanced patients will eventually experience disease progression after receiving first-line and second-line anti-HER2 therapy. The emergence of antibody-drug conjugates (ADCs) provides a new solution to this challenge. ADCs use monoclonal antibodies to directly deliver cytotoxic drugs to tumor cells [12]. After binding to a specific antigen and being endocytosed, the stable conjugate is cleaved to release the payload, allowing precise cell killing [13]. This strategy can significantly increase the local tumor drug concentration while reducing systemic toxicity, thus overcoming the lack of selectivity of conventional chemotherapy.

Trastuzumab emtansine (T-DM1) is the first ADC for HER2-positive breast cancer, which combines trastuzumab and DM1. The success of T-DM1 has established the role of ADC in the treatment of HER2-positive breast cancer, especially as the second-line standard treatment after the failure of trastuzumab therapy, significantly improving the progression-free survival (PFS) and overall survival (OS) of patients [14]. However, like other targeted drugs, tumor cells may also develop resistance to T-DM1. The mechanisms include the down-regulation of HER2 expression, alterations in the internalization process, impaired lysosomal function leading to payload release failure, and mutations in the DM1 target tubulin [15]. Once resistance to T-DM1 occurs, subsequent treatment options become extremely limited, and their efficacy is often unsatisfactory, posing a serious risk to the patient's survival. In this case, traditional doctor-selective treatment (TPC) typically involves various chemotherapy drugs, sometimes in combination with previously used anti-HER2-targeted drugs. However, these schemes are often accompanied by significant toxic and side effects, seriously affecting the quality of life of patients. Therefore, there is an urgent need for new therapies to overcome T-DM1 resistance and provide survival benefit for patients.

DS-8201 is a new-generation HER2-targeted ADC, which was developed precisely to meet this urgent clinical need. DS-8201 integrates multiple key structural optimizations, making it possible to outperform earlier ADCs. Due to its remarkable efficacy and good safety, DS-8201 has gained wide recognition and approval worldwide, bringing new treatment hope to many cancer patients [16].

This study retrospectively analyzed and evaluated the clinical value of DS-8201 in Chinese patients with HER2-positive advanced breast cancer who failed T-DM1 treatment. It compared its efficacy and safety with those of the existing TPC.

Materials and methods

Subjects

This retrospective study included patients with HER2-positive metastatic breast cancer who experienced disease progression after T-DM1 treatment. Patients enrolled from December 2022 to March 2025 were divided into a DS-8201 group or a TPC group according to the subsequent treatment. Based on previous research data [17, 18], the 12-month PFS (P_1) in the TPC group was assumed to be 40%, while the DS-8201 group (P_2) was expected to increase to 60%. With a two-sided α of 0.05, statistical power (1-β) of 80%, and a 1:1 allocation ratio between the two groups, the minimum required sample size for each group was calculated to be 77 patients, with a total sample size of 154 patients. The final analysis of this study included 185 patients (83 in the DS-8201 group and 102 in the TPC group), exceeding the calculated minimum requirement. See **Figure 1**.

Inclusion criteria

(1) Female, age ≥18 years; (2) Diagnosed with HER2-positive metastatic breast cancer [19]; (3) Disease progression during or after T-DM1 treatment; (4) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; (5) First time receiving DS-8201 treatment; (6) If brain metastases are present, they must be clinically stable and previously treated; (7) Complete medical records, including blood routine and liver and kidney function tests during treatment.

Exclusion criteria

(1) Uncontrolled or clinically significant cardiovascular disease; (2) Current/suspected/past non-infectious interstitial lung disease (ILD) or pneumonitis requiring glucocorticoid therapy, or inability to exclude ILD on screening chest computed tomography (CT)/magnetic resonance imaging (MRI); (3) Clinically active brain metastases; (4) Presence of other malignan-

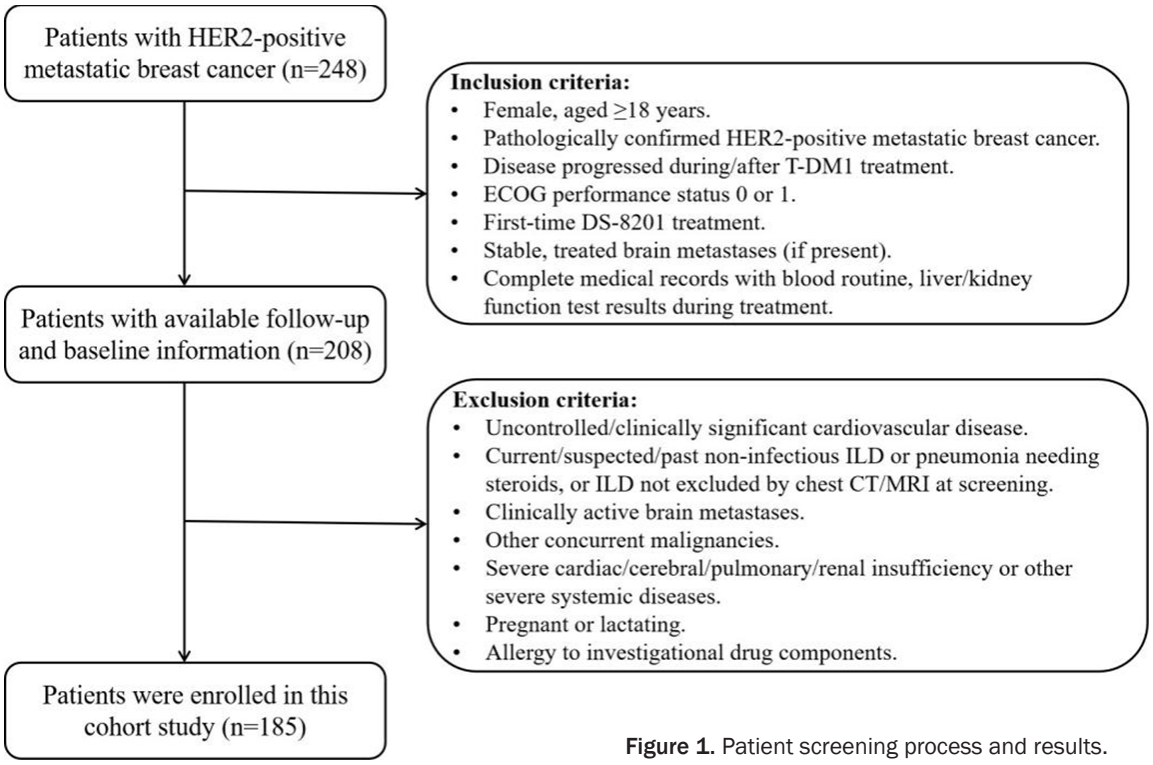

Figure 1. Patient screening process and results.

cies; (5) Severe cardiac, cerebral, pulmonary, renal dysfunction or other serious systemic diseases; (6) Pregnancy or breastfeeding; (7) Allergy to the study drug.

Treatment regimens [20, 21]

The DS-8201 group received 5.4 mg/kg intravenously once every 21 days. In the event of ≥ grade 3 adverse reactions, treatment was to be withheld until resolution to ≤ grade 1 or baseline, after which it could be resumed at the same or a reduced dose per investigator assessment. For drug-induced ILD, treatment was to be immediately interrupted, and corticosteroids initiated; the decision to rechallenge after recovery was based on the severity of ILD and multidisciplinary evaluation. The TPC group received one of two regimens: 1) Capecitabine (1250 mg/m^2 orally twice daily, days 1-14) with trastuzumab (8 mg/kg loading dose, then 6 mg/kg) and pertuzumab (840 mg loading dose, then 420 mg), both IV every 21 days; or 2) Capecitabine (1000 mg/m^2 orally twice daily, days 1-14) with lapatinib (1250 mg orally once daily). All treatments were given in 21-day cycles until progression, unacceptable toxicity, or withdrawal, with follow-up until death or study end. In this study, the median treatment cycles in both the DS-8201 group and the TPC group were 35.

Clinical outcome measures

Primary efficacy endpoint: Progression-free survival (PFS) [22]: Time from treatment initiation to disease progression (per modified response evaluation criteria in solid tumors (mRECIST) 1.1) [23] or death from any cause.

Secondary efficacy endpoints: (1) Overall survival (OS) [24]: Time from treatment initiation to death from any cause. (2) Objective response rate (ORR) [25]: Proportion of patients with a best overall response of complete response (CR) or partial response (PR), assessed per mRECIST v1.1 [23] with radiographic exams each cycle until disease progression. (3) Disease control rate (DCR) [26]: Proportion of patients achieving CR, PR, or stable disease (SD) lasting ≥6 months, assessed over the same observation period as ORR. (4) Duration of response (DoR) [27]: Defined as the time interval from the date of the first assessment at which CR or PR was achieved until the date of the first documented disease progression or death. (5) Quality of life (QoL): Assessed at baseline and the third cycle using the 36-item

Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire [28]. This reliable instrument measures five domains on a 5-point Likert scale. The total score is the sum of all items, with higher scores indicating better QoL. (6) Hospitalization-related indicators: Included the hospitalization rate during treatment, number of hospitalization days, time to first hospitalization, intensive care unit (ICU) admission rate, and ICU length of stay.

Safety endpoints

Treatment-Emergent Adverse Events (TEAEs) were recorded and graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 [29]. For DS-8201, special attention was paid to the occurrence, grading, and management of drug-related ILD. Laboratory data and vital signs were also monitored.

Statistical analysis

Statistical analyses were performed using SPSS 26.0. Normally distributed continuous variables (e.g., age, BMI) were presented as mean ± standard deviation (SD) (t-tests). Non-normal continuous variables (e.g., DoR, FACT-B) were expressed as M (Q_1, Q_3) (Mann-Whitney U test). Categorical variables (e.g., ORR, DCR, TEAEs) were summarized as n (%) (χ^2 test). Survival curves for PFS and OS were generated by the Kaplan-Meier method, with group comparisons made using the log-rank test. A two-sided P<0.05 defined statistical significance.

Results

Comparison of baseline characteristics

As presented in **Table 1**, the study groups were well-balanced with respect to all baseline demographic and clinical characteristics including age, BMI, marital status, place of residence, ethnicity, comorbidities, HER2 status, ECOG performance status, presence of brain metastases, and hormone receptor status (all P>0.05).

PFS comparison

As shown in **Table 2** and **Figure 2**, the PFS results based on Kaplan-Meier analysis demonstrated that the DS-8201 treatment group had significantly superior survival outcomes at both 12 and 24 months compared to the TPC group. The 12-month and 24-month PFS rates were 62.65% and 50.60% in the DS-8201 group, with corresponding mean PFS times of 10.012 months and 16.735 months, respectively. These were significantly higher than the 42.16%, 23.53%, 8.069 months, and 11.569 months observed in the TPC group (Log-rank test, 12-month: χ^2=10.709, P=0.001; 24-month: χ^2=17.927, P<0.001).

OS comparison

As shown in **Table 3** and **Figure 3**, the 12-month and 24-month OS rates in the DS-8201 group were 90.36% and 75.90%, respectively, with corresponding mean OS times of 11.783 months and 21.699 months. These were significantly higher than the rates of 60.78% and 54.90%, and mean OS times of 10.373 months and 17.245 months observed in the TPC group (Log-rank test, 12-month: χ^2=21.908, P<0.001; 24-month: χ^2=11.680, P<0.001).

ORR, DoR and DCR comparison

As shown in **Table 4**, the ORR in the DS-8201 group was 72.29%, significantly higher than 45.10% in the TPC group (χ^2=13.828, P<0.001). The median DoR was 20.00 months in the DS-8201 group, also significantly longer than the 9.00 months in the TPC group (Z=-9.566, P<0.001). Furthermore, the DCR reached 80.72% in the DS-8201 group, again significantly higher than the 60.78% in the TPC group (χ^2=8.619, P=0.003).

FACT-B comparison

Baseline FACT-B scores were equivalent between the groups, indicating no significant differences in any quality-of-life domain prior to intervention (all P>0.05). After 3 cycles of treatment, the DS-8201 group demonstrated significantly higher QoL scores than the TPC group across all domains (all P<0.001). See **Table 5**. This indicated a significant advantage for DS-8201 treatment in improving patients' QoL.

Comparison of inpatient related indicators

According to **Table 6**, the two groups were comparable in terms of the overall hospitalization rate, total hospitalization days, ICU admission rate, or ICU length of stay (all P>0.05). However,

Table 1. Comparison of baseline characteristics

Variable	DS-8201 group (n=83)	TPC group (n=102)	Statistic	P
Age (years), mean ± SD	54.12±8.65	55.81±7.44	t=-1.432	0.154
BMI (kg/m^2), mean ± SD	22.85±2.44	22.18±2.54	t=1.847	0.066
Marriage, n (%)			χ^2=0.235	0.889
Married	68 (81.93%)	81 (79.41%)		
Unmarried	7 (8.43%)	9 (8.82%)		
Divorced/Widowed	8 (9.64%)	12 (11.76%)		
Household Type, n (%)			χ^2=0.086	0.770
City	30 (36.14%)	39 (38.24%)		
Rural	53 (63.86%)	63 (61.76%)		
Ethnicity, n (%)			χ^2=0.000	0.990
Han ethnic group	74 (89.16%)	91 (89.22%)		
Other	9 (10.84%)	11 (10.78%)		
Underlying diseases, n (%)				
Hypertension	12 (14.46%)	9 (8.82%)	χ^2=1.444	0.230
Hyperlipidemia	18 (21.69%)	15 (14.71%)	χ^2=1.522	0.217
Diabetes Mellitus	12 (14.46%)	14 (13.73%)	χ^2=0.020	0.887
Coronary heart disease	8 (9.64%)	11 (10.78%)	χ^2=0.065	0.798
HER2 status (Immunohistochemistry), n (%)			χ^2=0.668	0.414
3+	72 (86.75%)	84 (82.35%)		
2+	11 (13.25%)	18 (17.65%)		
ECOG performance status, n (%)			χ^2=0.556	0.456
0	41 (49.40%)	56 (54.90%)		
1	42 (50.60%)	46 (45.10%)		
Brain metastases, n (%)	18 (21.69%)	26 (25.49%)	χ^2=0.365	0.546
Hormone-receptor status, n (%)				
Positive	38 (45.78%)	34 (33.33%)	χ^2=2.984	0.084
Negative	45 (54.22%)	68 (66.67%)		

Note: BMI: body mass index, HER2: human epidermal growth factor receptor 2, ECOG: Eastern Cooperative Oncology Group.

Table 2. PFS comparison

PFS	≥12 months	Median	Mean (95% CI)	Log-rank χ^2	P	HR (95% CI)
DS-8201 group	52 (62.65%)	12.0	10.012 (9.386-10.638)	10.709	0.001	0.506 (0.334-0.764)
TPC group	43 (42.16%)	8.0	8.069 (7.355-8.782)			1.978 (1.309-2.990)
PFS	≥24 months		Mean (95% CI)	Log-rank χ^2	P	HR (95% CI)
DS-8201 group	42 (50.60%)	21.5	16.735 (14.971-18.499)	17.927	<0.001	0.465 (0.325-0.667)
TPC group	24 (23.53%)	8.0	11.569 (9.997-13.140)			2.149 (1.500-3.081)

Note: PFS: progression-free survival, HR: hazard ratio, CI: confidence interval.

the time to first hospitalization was significantly longer in the DS-8201 group (132.54±40.47 days) compared to the TPC group (84.53± 26.46 days) (t=5.186, P<0.001), suggesting that treatment with DS-8201 may effectively delay the need for initial hospitalization.

Safety analysis

As shown in **Tables 7** and **8**, during the treatment process, there were no significant differences in the incidence of any-grade adverse events, ≥ grade 3 adverse events, or all treatment-emergent adverse events (TEAEs) (all P>0.05). However, the types of adverse events differed. Compared to the TPC group, the DS-8201 group had significantly higher incidences of nausea (74.70% vs. 38.24%), vomiting (40.96% vs. 14.71%), and alopecia (34.94% vs. 3.92%) (all P<0.001). Of particular importance, drug-induced ILD was observed exclusively in the DS-8201 group, with an incidence

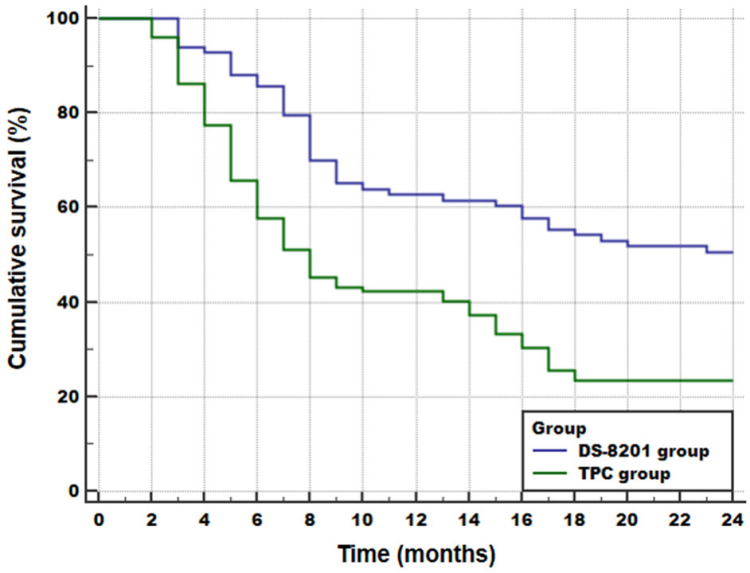

Figure 2. Kaplan-Meier curve of PFS.

of 14.46% (12/83). A detailed analysis revealed that all 12 ILD events were low-grade, with 10 cases classified as Grade 1 and 2 cases as Grade 2. Critically, none of the ILD events resulted in treatment interruption, dose reduction, or permanent discontinuation of DS-8201. All cases were managed successfully with corticosteroids, and no ILD-related deaths occurred. In contrast, diarrhea (54.90% vs. 26.51%) and palmar-plantar erythrodysesthesia syndrome (44.12% vs. 0.00%) were more common in the TPC group (all P<0.001).

Discussion

Disease progression after receiving second-line anti-HER2 therapy represents a critical turning point for patients with HER2-positive advanced breast cancer. After the failure of regimens such as T-DM1, subsequent treatment options are limited, leading to a poor prognosis for these patients [30]. Although treatment of physician's choice (TPC) is widely used in clinical practice, its objective response rate is low, survival benefits are limited, and it easily causes adverse reactions that affect quality of life, making it difficult to meet patients' dual needs of prolonged survival and maintained quality of life. DS-8201 is a new-generation HER2-targeted ADC and has demonstrated significant efficacy in multiple clinical trials worldwide. We conducted a retrospective analysis on 185 patients with HER2-positive advanced breast cancer who were resistant to T-DM1 to evaluate the clinical efficacy of DS-8201 versus TPC.

Our research results show that patients treated with DS-8201 demonstrated clinically significant survival improvement, with a PFS of 50.60%, while the PFS of the TPC group was 23.53% (HR=0.465), indicating that the risk of disease progression in patients was reduced by more than 50%. This result may be related to the multifaceted optimization design of DS-8201. Structurally, DS-8201 employs high-affinity trastuzumab as the targeting component, ensuring precise recognition and binding of HER2 tumor cells. In addition, DS-8201 has achieved significant breakthroughs in cytotoxic payload, drug-antibody ratio, and linker design [31]. The cytotoxic active ingredient of DS-8201 is DXd, which can effectively overcome T-DM1 resistance caused by tubulin mutations [32, 33].

Studies by Hurvitz et al. [34] and Cortés et al. [35] also indicate that in HER2-positive advanced breast cancer, DS-8201 demonstrates superior efficacy compared to T-DM1, significantly extending PFS and reducing the risk of death. DS-8201 can deliver more cytotoxic drugs to tumor cells, thereby significantly increasing the local drug concentration within the tumor [36, 37]. In addition, DXd has strong membrane permeability. After the initial target cells are lysed, the therapeutic agent can diffuse through the cell membrane to adjacent cells, thereby inducing the bystander effect. Even for tumor cells with low or uneven HER2 expression in tissues, DXd can effectively eliminate them [38]. Modi et al. [17] observed that even in patients with advanced breast cancer with low HER2, DS-8201 can significantly prolong PFS and OS. After a median follow-up of 32.0 months, median OS in the overall cohort was 22.9 months with DS-8201 versus 16.8 months with TPC (HR 0.69; 95% CI 0.55-0.86). In the hormone-receptor-positive subgroup, median OS was 23.9 months and 17.6 months, respectively (HR 0.69; 95% CI 0.55-0.87).

Table 3. OS comparison

OS	≥12 months	Median	Mean (95% CI)	Log-rank χ^2	P	HR (95% CI)
DS-8201 group	75 (90.36%)	12.0	11.783 (11.606-11.960)	21.908	<0.001	0.202 (0.114-0.356)
TPC group	62 (60.78%)	12.0	10.373 (9.900-10.846)			4.948 (2.810-8.712)
OS	≥24 months		Mean (95% CI)	Log-rank χ^2	P	HR (95% CI)
DS-8201 group	63 (75.90%)	24.0	21.699 (20.709-22.688)	11.680	<0.001	0.419 (0.258-0.678)
TPC group	56 (54.90%)	24.0	17.245 (15.718-18.772)			2.390 (1.475-3.872)

Note: OS: overall survival, HR: hazard ratio, CI: confidence interval.

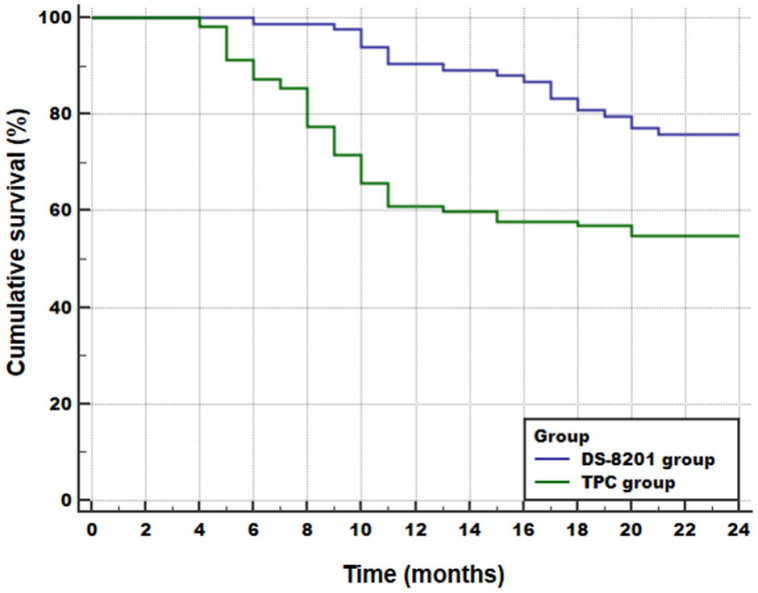

Figure 3. Kaplan-Meier curve of OS.

review showed a median progression-free survival of 17.8 months (95% CI 14.3-20.8) with DS-8201 versus 6.9 months (95% CI 5.5-8.4) with TPC (HR 0.36; 95% CI 0.28-0.45; P<0.001). The brain metastasis rates of the DS-8201 group and the TPC group were 21.69% and 25.49% respectively. The limited efficacy of traditional anti-HER2 drugs in this population is usually attributed to poor permeability of the blood-brain barrier. However, DS-8201 demonstrated potential efficacy in this challenging subgroup by taking advantage of the small molecular size and membrane permeability of its DXd payload [40, 41].

Exploratory analyses of median OS in the hormone-receptor-negative, ER-IHC 1-10% and ER-IHC >10% subgroups also favored DS-8201. This fully demonstrates the important value of the bystander effect in expanding the population that can benefit.

DS-8201 demonstrated superior efficacy compared to TPC in patients with advanced HER2 breast cancer. The confirmed ORR was 72.29% versus 45.10%, and the DCR was 80.72% versus 60.78%. Furthermore, the DoR of DS-8201 was more than twice that of the control group (20.00 months vs. 9.00 months). These results indicate that DS-8201 can achieve highly effective and durable tumor responses even in patients who have failed T-DM1 treatment. In contrast, Andre et al. [39] observed limited efficacy with the TPC regimen. After a median follow-up of 21.5 months (IQR 15.2-28.4) in the DS-8201 arm and 18.6 months (IQR 8.8-26.0) in the TPC arm, blinded independent central

The results showed that after three treatment cycles, the FACT-B score of the DS-8201 group was significantly higher than that of the TPC group. This indicates that DS-8201 can not only effectively control tumors, but also maintain and even improve the quality of life of patients. The improvement of the quality of life is closely related to the long-lasting efficacy and unique safety of DS-8201. On the one hand, the high ORR and prolonged DoR associated with DS-8201 can rapidly relieve tumor-related symptoms such as pain and fatigue, thereby reducing the effect of tumor burden on patients' physical function. On the other hand, although adverse events such as nausea and vomiting may occur in DS-8201, their severity is mostly grade 1-2 and can be effectively controlled through supportive treatment, thereby minimizing the disturbance to the patient's daily life to the greatest extent. In contrast, the TPC group had a higher incidence of diarrhea in the palms and soles of the palmar-plantar

Table 4. DoR and DCR comparison

Group	n	ORR, n (%)	DoR [d, M (Q_1, Q_3)]	DCR, n (%)
DS-8201 group	83	60 (72.29%)	20.00 (15.50, 23.00)	67 (80.72%)
TPC group	102	46 (45.10%)	9.00 (5.00, 13.00)	62 (60.78%)
Statistic		χ^2=13.828	Z=-9.566	χ^2=8.619
P		<0.001	<0.001	0.003

Note: ORR: objective response rate, DoR: duration of response, DCR: disease control rate.

Table 5. FACT-B comparison [M (Q_1, Q_3)]

FACT-B	Time	DS-8201 group (n=83)	TPC group (n=102)	Z	P
Physical	Baseline	5.00 (3.00, 6.00)	5.00 (3.00, 6.00)	-0.205	0.837
	Post-cycle 3	11.00 (9.00, 13.00)	9.00 (8.00, 10.750)	-5.705	<0.001
Social/Family	Baseline	15.00 (13.00, 22.00)	18.50 (14.00, 21.75)	-0.142	0.887
	Post-cycle 3	25.00 (21.50, 26.00)	20.00 (17.00, 22.00)	-7.585	<0.001
Emotional	Baseline	7.00 (4.00, 9.50)	7.00 (4.00, 8.00)	-1.086	0.278
	Post-cycle 3	12.00 (10.00, 16.00)	10.00 (9.00, 12.00)	-3.716	<0.001
Functional	Baseline	11.00 (9.00, 15.00)	11.00 (9.00, 13.00)	-0.739	0.460
	Post-cycle 3	18.00 (12.00, 22.50)	15.00 (12.00, 18.00)	-2.675	0.007
Additional Concerns	Baseline	10.00 (8.00, 13.00)	9.00 (8.00, 11.00)	-1.304	0.192
	Post-cycle 3	15.00 (12.00, 19.00)	12.00 (9.00, 15.00)	-4.384	<0.001

Note: FACT-B: functional assessment of cancer therapy-breast.

Table 6. Comparison of inpatient related indicators

Variable	DS-8201 group (n=83)	TPC group (n=102)	Statistic	P
Hospitalization rate, n (%)	24 (28.92%)	40 (39.22%)	χ^2=2.146	0.143
Length of hospital stay [d, mean ± SD]	11.79±3.11	11.20±3.63	t=0.665	0.509
Time to first hospitalization [d, mean ± SD]	132.54±40.47	84.53±26.46	t=5.186	<0.001
ICU admission rate, n (%)	5 (6.02%)	7 (6.86%)	χ^2=0.053	0.818
Length of ICU stay [d, median (Q_1, Q_3)]	5.00 (4.00, 5.00)	5.00 (5.00, 5.50)	Z=-0.696	0.486

Table 7. Comparison of overall incidence of TEAEs (n, %)

Group	n	TEAEs (Any Level)	TEAEs (Level ≥3)	Drug-related TEAEs (Any Level)	Drug-related TEAEs (Level ≥3)
DS-8201 group	83	83 (100.00%)	43 (51.81%)	82 (98.80%)	29 (34.94%)
TPC group	102	101 (99.02%)	45 (44.12%)	100 (98.04%)	32 (31.37%)
χ^2		-	1.085	0	0.263
P		1.000	0.298	1.000	0.608

erythrodysesthesia syndrome. These adverse events usually lead to symptoms such as difficulty in eating and skin pain, seriously affecting patients' daily activities and social functions, thereby reducing their quality of life. However, for patients with advanced cancer, quality of life is as important as survival time.

Most of the time, patients with advanced breast cancer who go to the hospital for treatment get disease progression or poor treatment outcome. Compared to the TPC group, DS-8201 significantly delayed the first hospitalization, which indicates that DS-8201 has strong antitumor activity and may slow the progression of cancer and reduce the risk of hospitalization. The probability of serious adverse events in both the DS-8201 group and the TPC group was relatively low, and the difference between them was not statistically significant. These

Table 8. Comparison of common TEAEs types and their incidence rates (n, %)

Group	n	Nausea	Vomiting	Alopecia	Fatigue	diarrhea	palmar-plantar erythrodysesthesia syndrome	ILD	ILD (Grade 1)	ILD (Grade 2)
DS-8201 group	83	62 (74.70%)	34 (40.96%)	29 (34.94%)	38 (45.78%)	22 (26.51%)	0 (0.00%)	12 (14.46%)	10 (12.05%)	2 (2.41%)
TPC group	102	39 (38.24%)	15 (14.71%)	4 (3.92%)	36 (35.29%)	56 (54.90%)	45 (44.12%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
χ^2		24.545	16.205	30.042	2.098	15.132	48.388	15.770	10.742	-
P		<0.001	<0.001	<0.001	0.148	<0.001	<0.001	<0.001	<0.001	1.000

Note: ILD: Interstitial Lung Disease.

adverse events can be effectively controlled by careful monitoring and providing supportive care, which can reduce the number of people requiring hospitalization due to toxicity caused by treatment. There was no significant difference in the overall hospitalization rate and total length of hospital stay between the two groups of patients. This may be related to the relatively short follow-up period. If the follow-up period had been extended, more significant differences may have been discovered.

There were significant differences in the types of adverse events between the DS-8201 group and the TPC group. This requires clinicians to tailor monitoring and management strategies based on the individual characteristics of patients. The incidences of nausea, vomiting and alopecia in the DS-8201 group were significantly higher than those in the TPC group. In addition, 14.46% of the patients developed ILD. In contrast, diarrhea and redness on the palms and soles were more common in the TPC group. Clinicians must pay special attention to ILD, which is specific to DS-8201. Although most cases are grade 1-2, a small number of patients may develop severe ILD, which can be life-threatening. Previous studies have shown that the occurrence of ILD is related to the dose of DS-8201, the number of treatment cycles, and the underlying lung diseases of patients. Regular chest CT monitoring, early identification of ILD-related symptoms, and timely initiation of corticosteroid treatment can effectively control the progression of ILD and reduce the risk of severe complications [42]. In addition, nausea and vomiting in the DS-8201 group were mostly grade 1-2 and could be effectively controlled by prophylactic antiemetic drugs. On the contrary, the treatment of diarrhea and redness and swelling of the palms and soles in the TPC group usually requires dose adjustment, local care and symptomatic treatment. When choosing a treatment plan, clinicians must take into account the patient's comorbidities, tolerance and lifestyle, and formulate a personalized adverse event management plan to improve compliance [43, 44].

This study on DS-8201 after the progression of T-DM1 was limited by a single-center, retrospective design, had a risk of selection bias, a relatively small sample size, and relied on complete medical records. Despite the implementation of strict inclusion and exclusion criteria, information bias may have existed. Prospective studies with standardized data collection procedures and regular follow-ups can mitigate the effect of this bias. Subsequent multi-center, large-sample prospective studies are necessary to further verify our research conclusions. Although our study population included patients with both HER2 IHC 3+ and 2+ expressions, the sample size was insufficient to conduct a meaningful subgroup analysis to compare the efficacy of DS-8201 across these different HER2 expression levels. Given that the 'bystander effect' of DS-8201 may confer a particular advantage in tumors with heterogeneous or lower HER2 expression, future studies with larger cohorts are warranted to explore this potential differential benefit. Similarly, we did not perform subgroup analyses based on metastatic sites or hormone receptor status due to the same sample size constraints. Clarifying the efficacy of DS-8201 in these specific subgroups, would be invaluable for refining patient selection in clinical practice. Subgroup analyses of previous clinical trials indicated that the expression level and metastasis site of HER2 might affect the efficacy of DS-8201. Therefore, in the future, subgroup analyses can be conducted to provide more precise treatment recommendations for patients with different characteristics.

In conclusion, for T-DM1-pretreated HER2+ advanced breast cancer, DS-8201 is a new treatment standard that has superior efficacy compared to conventional treatments, and has controllable safety.

Disclosure of conflict of interest

None.

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