Review Article

A round table discussion: clinical landscape of trastuzumab deruxtecan in breast cancer: a retrospective and prospective view

Xu Liang, Ying Yan, Guohong Song

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Breast Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Contributions: (I) Conception and design: X Liang; (II) Administrative support: X Liang, G Song; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Guohong Song; Xu Liang. Department of Breast Oncology, Peking University Cancer Hospital & Institute, 52 Fucheng Road, Haidian District, Beijing 100142, China. Email: songguohong918@hotmail.com; liang_xu7788@163.com.

Abstract: The treatment landscape of breast cancer has been greatly changed by the innovative targeting therapies. Antibody-drug conjugates (ADCs) with a representative of trastuzumab deruxtecan (T-DXd) are the most successful ones. The revolutionary next-generation design of ADC transformed to the unprecedented clinical data. The DESTINY-BREAST01 and DESTINY-BREAST03 trials have changed the standard of care for HER2-positve metastatic breast cancer (MBC). At the same time the clinical data of T-DXd in HER2-postive patients with brain metastasis (BM) is numerously gaining and challenging the current treatment concept for central nerve system (CNS) involved disease. The DESTINY-BREAST series trials have quickly expanded to first-line (1L) and early setting of breast cancer. The newly reported positive result of DESTINY-BREAST04 trial has also opening the door of human epidermal growth factor receptor 2 (HER2)-low era. The breast cancer experts are facing a world of massive data and rapidly changing. Therefore, round table discussion meeting is a great way to share the information and options of among oncologists. This time, the breast cancer experts in China gathered to discuss the important clinical advances of T-DXd and its impact to clinical practice. The meeting minutes were recorded and organized as the review article. This would provide insights to better understanding of the current data and shape the further research directions of breast cancer.

Keywords: HER2-postive; breast cancer; HER2-low; trastuzumab deruxtecan (T-DXd); brain metastasis (BM)

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Experts participating in the discussion (sorted by surname):
Chunfang Hao (Tumor Hospital of Tianjin Medical University); Zefei Jiang (Fifth Medical Center of Chinese PLA General Hospital); Qiang Liu (Sun Yat-sen Memorial Hospital of Sun Yat-sen University); Tao Sun (Liaoning Cancer Hospital); Shusen Wang (Sun Yat-sen University Cancer Center); Tao Wang (Fifth Medical Center of PLA General Hospital); Xiaojia Wang (Cancer Hospital Affiliated to Chinese Academy of Sciences); Min Yan (The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital); Ying Yan (Peking University Cancer Hospital & Institute); Yongmei Yin (the First Affiliation Hospital with Nanjing Medical University); Peng Yuan (Cancer Hospital of Chinese Academy of Medical Sciences); Yueping Liu (The Fourth Hospital of Hebei Medical University); Kun Wang (Guangdong Provincial People's Hospital); Jiayi Chen (Ruijin Hospital, Shanghai Jiaotong University School of Medicine); Qingyuan Zhang (Harbin Medical University Cancer Hospital); Xu Liang (Peking University Cancer Hospital & Institute).

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Introduction

In recent decades, innovative targeted drugs have greatly advanced the treatment of breast cancer (1). A new class of targeted therapies called antibody-drug conjugates (ADCs) have begun to be explored and greatly impact the clinical landscape of cancer treatment (2), with trastuzumab deruxtecan (T-DXd, DS-8201) being one of the most successful ADC. T-DXd is a revolutionary next-generation innovative anti-HER2 drug with multifaceted properties that enhance its antitumor effect and maintain a manageable safety profile. Its humanized anti-HER2 IgG1 monoclonal antibody was developed as trastuzumab biosimilar, and each monoclonal antibody contains about 8 novel topoisomerase I inhibitor payload molecules, called DXd via stable tumor-specific cleavage tetra-peptide linker (3) (*Figure 1*). This design seems give the agent some advantages over previous ADCs. Firstly, the killing range was higher in HER2-expressing tumors. In preclinical trials, T-DXd can kill HER2 immunohistochemical (IHC) 1+, 2+ and 3+ cells, whereas trastuzumab emtansine (T-DM1) can only act on HER2 3+ cells (4). Secondly, the potent bystander killing effect of T-DXd is due to the characteristics of the cleavage linker and membrane permeable payload. This can kill HER2-negative tumor cells surrounding to HER2-expressing tumor cells, which will be able to act on HER2 heterogeneity (5). Third, the stable conjugation technology conferred by the hydrophobic linker, the tumor-specific lysosome-degrading linker, increases the highly selective targeting. The payload has a short half-life of 1.37 hours (6), ensuring no toxicity builds up after the payload is released. The design of the T-DXd sets a new standard for current ADC product development. There have been five publications on New England Journal of Medicine and 4 approved indications reported regarding T-DXd.

DESTINY-BREAST trial series of T-DXd have sparked a great deal of interest and attractions among experts recently (*Figure 2*). The DESTINY-BREAST01 is the first impressive trial with an unprecedented 19.4-month median progression-free survival (mPFS) of T-DXd for the 3rd or later line therapy of HER2-positive metastatic breast cancer (MBC) (7,8). Not long later, the DESTINY-BREAST03 made a new record for T-DXd in HER2-positve MBC, with a 25.1-month mPFS by investigator assessment (9). T-DXd has not only significantly changed the treatment of HER2-postive MBC, but will also re-define the paradigm of HER2-low breast cancer. Recently, the DESTINY-BREAST04 trial has been reported to meet its co-primary end points of progression-free survival (PFS) and overall survival (OS), regardless of hormonal receptor (HR) expression status (10,11).

The clinical data is appealing, but the clinical practice is complicated. Whether the level II recommendation of T-DXd as treatment for patients failed to trastuzumab therapy, prior to approval in China is reasonable? And what's the optimized sequent therapy for patients had failed to anti-HER2 TKIs and ADC? What's the implications of T-DXd in patients with brain metastasis (BM)? What's the expectation of T-DXd in further landscape as first-line therapy, neoadjuvant or adjuvant therapy with the ongoing trials of DESTINY-BREAST09, DESTINY-BREAST11 and DESTINY-BREAST05? For HER2-low, HR-positive patients, what's the ideal time-window for endocrine therapy (ET) and chemotherapy (CT) switching? What's the best indicator to evaluate the efficacy of later line therapy for HR-positive MBC patients, such as objective response (ORR), duration of response (DOR), PFS or OS? What's will be treatment strategy for patients with HER2-low MBC? These questions are yet to be answered clearly. So, in a round table discussion, numerous breast cancer oncologists and surgeons came together to discuss the exciting advances of T-DXd and its implications in real world clinical practice. The highly summary is recorded as this review article.

T-DXd current status in clinical practice based on the success of DESTINY-BREAST03

DESTINY-BREAST03 was a phase 3 trial aim for the comparison of T-DXd with T-DM1 for the treatment of HER2-positive MBC, and was reported to meet the primary endpoint of PFS (9). The trial enrolled 524 patients with prior trastuzumab therapy; among them, 60% of the patients were also treated with pertuzumab (P). T-DXd showed significant improvement in mPFS (not reached *vs.* 6.8 months; hazard ratio, 0.28) and ORR (79.7% *vs.* 34.2%). The immature OS date also showed improvement trend (12-month survival rate, 94.1% *vs.* 85.9%; hazard ratio, 0.56). Interstitial lung disease (ILD) was the most concerned adverse event (AE) leading to discontinuation of T-DXd, with incidence as 10.5% in the T-DXd arm *vs.* 1.9% in the T-DM1. No grade 4 and 5 ILD events were reported in this trial. This indicates population with less pre-treatment or high awareness of ILD management may attributes to reduced fatal outcomes of ILD during T-DXd

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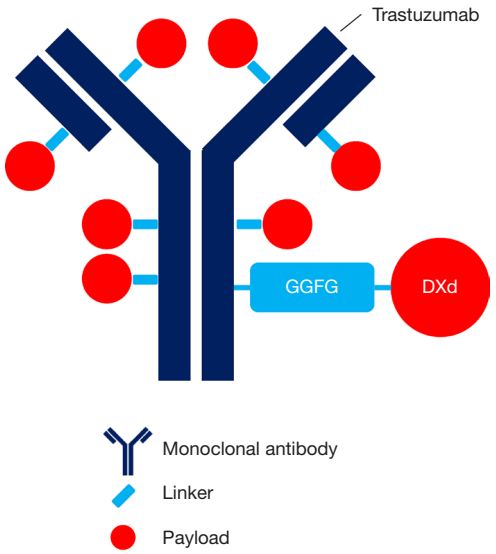

T-DXd has three key components:

- Monoclonal antibody with same sequence as trastuzumab (dyeing with dark blue),
- Novel topoisomerase I inhibitor payload, deruxtecan (or DXd, dyeing with red) with drug-antibody ratio as high as 8:1. And the free DXd has high membrane permeability and short half-life,
- Stable maleimide GGFG tetra-peptide linker (dyeing with light blue), which is tumor-specific enzymatically cleavable and highly hydrophilic.

T-DXd actives through the following mechanism:

- High stable in circulatory system, while released free DXd can fast eliminate, that makes high tumor specified targeting and reduced toxicity of T-DXd.
- Stronger bystander tumor kill effect and direct inhibition of HER2 low-moderate expression tumor cell.

Figure 1 Features of trastuzumab deruxtecan as next-generation anti-HER2 antibody-drug conjugate. GGFG, glycine-glycine-phenylalanine-glycine; DXd, deruxtecan; T-DXd, trastuzumab deruxtecan.

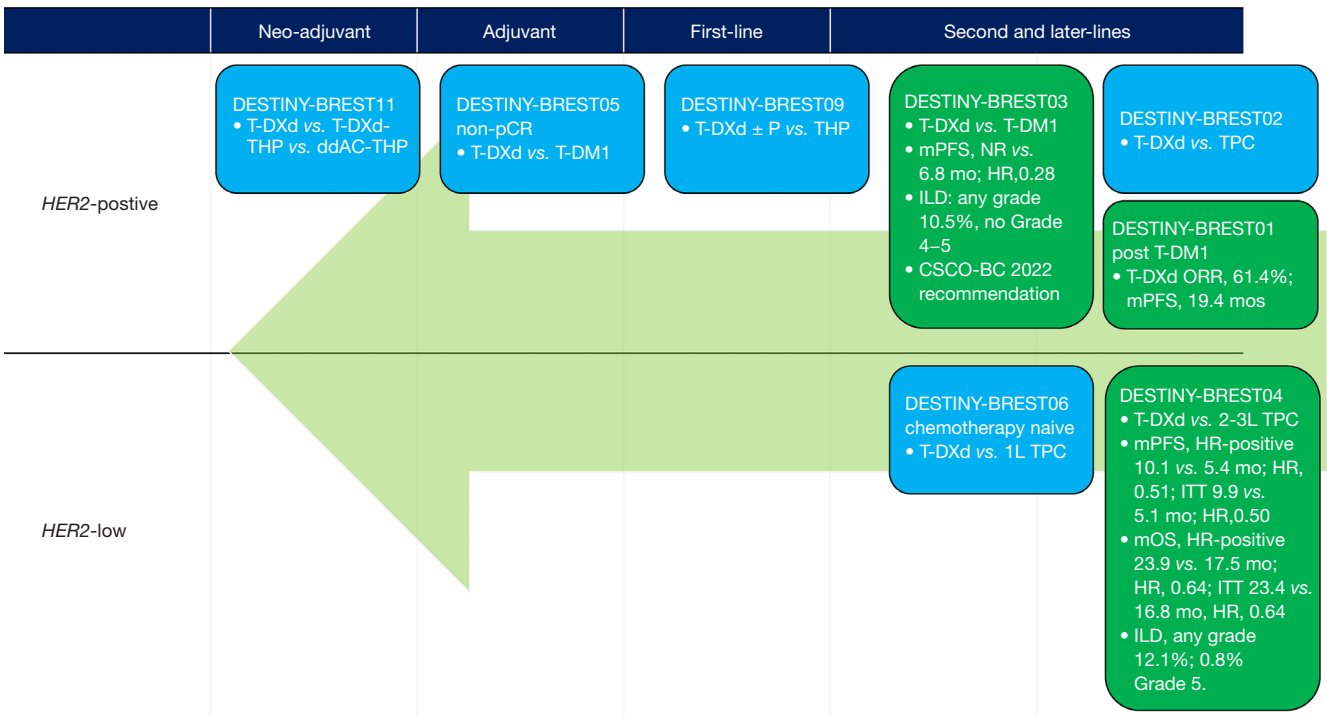

Figure 2 Summary of key clinical trials of trastuzumab deruxtecan in breast cancer. T-DXd, trastuzumab deruxtecan; T, taxane; H, trastuzumab; P, pertuzumab; dd, dose-density; A, doxorubicin; C, cyclophosphamide; pCR, pathological complete response; T-DM1, trastuzumab emtansine; mPFS, median progression-free survival; NR, not reached; mo, month; HR, hazard ratio; ILD, interstitial lung disease; CSCO-BC 2022, Chinese Society of Clinical Oncology Breast Cancer Guidelines 2022; TPC, treatment of physician's choice; ORR, objective response rate; L, line of therapy; HR-positive, hormonal receptor positive; mOS, median overall survival; ITT, intention-to-treatment population.

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therapy. Notably, the strictly management strategy of ILD was taken in the DESTINY-BREAST-03 trial. T-DXd should be interrupted for any grade of suspected ILD and permanently discontinued for Grade 2 or higher level. Steroids were proactively recommended in the management of ILD, even for Grade 1 (9).

Based on these compelling results, the latest version of Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guideline [2022] (12) recommends T-DXd as the new standard of care (SOC) for patients failed from trastuzumab therapy (level of recommendation II and level of evidence 1A). T-DXd is also recommended as an optional treatment for patients who have failed anti-HER2 tyrosine kinase inhibitors (TKI) therapy (level of recommendation II and level of evidence 2A). Since pyrotinib was well used as a second line treatment for metastatic HER2-positive breast cancer, T-DXd probably will be the preferred therapy in TKI-resistant patients as soon as it is available in China.

Expert opinion

All experts agreed that DESTINY-BREAST03's data is strong enough to suggest us T-DXd as a 2L SOC in HER2-positive MBC. Notably, mPFS and ORR were even comparable to the regimen of trastuzumab, pertuzumab and taxane in the first treatment in the CLEOPATRA trial (13). In an updated safety analysis from ASCO 2022 (14), the general safety profile of T-DXd was consistent and tolerant. T-DXd had longer therapy duration, but exposure-adjusted incidence rates (EAIRs) of T-DXd were lower than T-DXd. The incidence of ILD/pneumonitis was not increased for patient treated with T-DXd, compared with trials. This safety update with longer duration of follow-up again showed good benefit-risk profile of T-DXd in clinical usage. However, the mechanism of resistance to T-DXd is unclear. There are no data to demonstrate the optimal sequential therapy for progression on T-DXd. An interesting ideal proposed by experts is worth exploring, namely that strategies can be determined based on mechanism of resistance to T-DXd. (I) For resistance caused by HER2 degradation or loss, anti-HER2 TKIs acting inside the cell membrane may be a better choice; (II) for payload-induced resistance, switching to another ADC may be effective; (III) for cancers with altered PI3K signaling, the efficacy of TKIs is compromised, but not T-DM1, T-DM1 is a better choice given the evidence from the biomarker analysis of the EMILIA trial (15). Therefore, new ADC may be the effective therapy if the PI3K/AKT/mTOR pathway alteration can be found.

T-DXd for brain metastatic (BM) breast cancer (BCBM): stable or active BM (*Figure 3*)

The updated results of DESTINY-BREAST03 in SABCS2021 also sparked discussions on the clinical application of T-DXd for treatment of HER2-positive MBC with central nerve system (CNS) metastasis (16). Total 36 cases were with measurable brain disease in both groups. In the T-DXd arm, 10 cases showed complete remission (CR) in BM; 17 cases' CNS lesion had radiological reduction >30%. These data indicated that T-DXd had significant effect for the treatment of HER2-positive BM. Recently there are some clinical trials with small sample size revealed the efficacy of T-DXd in patients with active BM. Initial data from TUXEDO-1 trial showed an intracranial response rate of 73.3% (5/6), mPFS of 14 months (17). The ongoing DEBBRAH study is investigating the efficacy of T-DXd in patient who had HER2-positive or HER2-low advanced breast cancer with CNS metastasis. In breast cancer patients with active BM, the intracranial ORR for T-DXd was 44.4% (4/9) (18). Another retrospective study (19) showed that T-DXd achieved 70% CNS-ORR in 10 previously treated patients with progressive BM. More intriguingly, T-DXd also showed promising efficacy in a Duke & Dana Farber study (20) in patients with refractory leptomeningeal metastases (LM) HER2-positive breast cancer, 5/6 patients CNS-ORR was achieved. Based on those very compelling results of T-DXd efficacy for BM. The DESTINY-BREAST12 trial (NCT04739761) enrolled women with newly diagnosed or advanced BM HER2-positive MBC (21). So far, tucatinib in HER2CLIMB trial showed a promising result for active BM (22,23), and in HER2CLIMB-04 trial (NCT04539938), the combination of T-DXd and tucatinib is under testing to improve the treatment outcome of HER2-positive BCBM (24). Results from these trials will further clarify the efficacy of T-DXd in breast cancer patients with BM, especially in active BM.

Expert opinion

The efficacy of T-DXd in pretreated stable BM is very promising. However, the definition of stable or active BM is ambiguous. Experts believe that active BM is defined as symptomatic and progressive, while stable BM is considered

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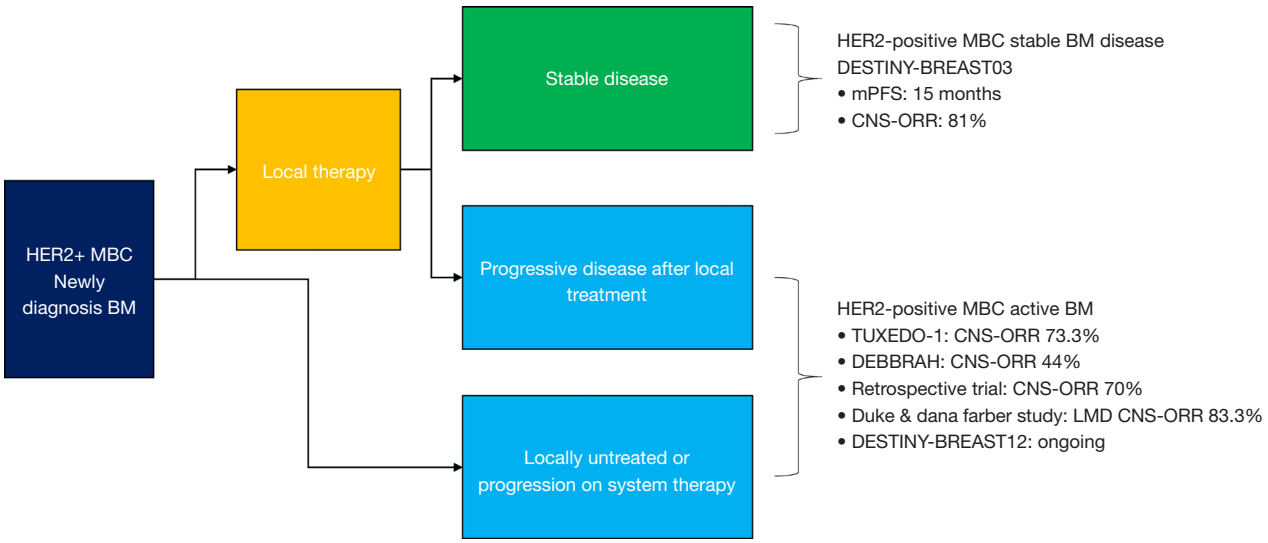

Figure 3 Clinical data of trastuzumab deruxtecan in HER2-positive brain metastasis. MBC, metastasis breast cancer; BM, brain metastasis; mPFS, median progression-free survival; CNS-ORR, central nerve system objective response rate; LMD, leptomeningeal disease.

asymptomatic or non-progressive. Clinical trials have shown that in asymptomatic patients with BM, anti-HER2 therapy without local management can have excellent outcomes (23,25). Therefore, the clinical data of T-DXd in these BM trials may be referred in clinical practice. Several trials have also explored the combination between anti-HER2 ADC & TKIs (26,27).

LM have poor prognosis. Treatment recommendations for LM are practically based on expert opinions. There has been no effective treatment option for breast cancer patients with LM (28). LM may develop with or without parenchymal disease in breast cancer patients; meanwhile, assessment of progression is based on developing new brain or meninges lesions (29,30). There has been no strong evidence regarding the treatment of anti-HER2 agents in patients with LM, either isolated or synchronous with BM. One case report had showed efficacy of anti-HER2 TKI in management of breast cancer with LM (31). At the same time, the efficacy in brain parenchyma and meninges were not assessed separately. Despite T-DXd data in HER2-positive MBC with LM from a small population, the data of CNS-ORR is promising (20). Consider the limitation of sample size, it is better to design a nationwide multicenter clinical trial to investigate this special metastatic subtype. Meanwhile, real-world studies may help us to understand the current treatment of breast cancer patients with brain and leptomeningeal disease. T-DXd as a good option is also worth exploring in larger sample sizes.

Prospect of T-DXd in HER2-positive breast cancer: ongoing studies in first line and early breast cancer (EBC)

The therapeutic landscape for HER2-positive BC in first-line, neoadjuvant and adjuvant settings has been changing rapidly (32). With the power of T-DXd, it has great confidence to step into these front lines.

DESTINY-BREAST09 (NCT04784715) is the first global trial of T-DXd in first-line MBC setting, T-DXd is being administered with or without pertuzumab comparison with the current standard of care for women with HER2-positive MBC. Results from this head-to-head phase III trial will provide answers as to whether T-DXd alone or as part of a combination regimen could provide more effective first-line HER2-directed therapy for women with HER2-positive MBC.

DESTINY-BREAST05 (NCT04622319) is a phase III, randomized, open-label study evaluating T-DXd versus T-DM1 as adjuvant therapy for high risk HER2-positive breast cancer who have not achieved pathological complete response (pCR). The primary endpoint of the trial was invasive disease-free survival (iDFS).

DESTINY-BREAST11 (NCT05113251) is a trial to assess the efficacy of T-DXd as pre-operative system therapy for patients with high-risk HER2-positive EBC. Approximately 624 patients will be randomized 1:1:1 to receive T-DXd as monotherapy or T-DXd followed by dual

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blockage with trastuzumab and pertuzumab plus paclitaxel (THP), or the standard regimen with dose-density doxorubicin (A) and cyclophosphamide (C) followed by trastuzumab, pertuzumab and paclitaxel (ddAC-THP). The primary endpoints will be pCR.

Another exploratory trial, DESTINY-BREAST07 (NCT04538742), is underway to explore the safety and efficacy of combination therapy of T-DXd with other anticancer drugs in HER2-positive MBC patients.

Expert opinion

Considering the big success of DESTINY-BREAST03 in second-line settings, future results of DESTINY-BREAST09 is worth looking forward to. However, most experts believe that choice of first-line therapy should be referred to activity, tolerance, and safety. The benefit of OS is associated with tolerance and patients' compliance, longer OS comes from scenario of all lines of anti-HER2 therapy. Current data and clinical guidelines suggest that regimen with dual antibodies is still the SOC for who are sensitive to trastuzumab in first-line anti-HER2 therapy, it might not be changed until the long-term follow-up to prove that T-DXd can have great efficacy as well as good quality of life.

Currently, the combination of trastuzumab, pertuzumab and CT can achieve nearly 60% pCR in the neoadjuvant setting (33-35). The attempt with DESTINY-BREAST11 in a neoadjuvant environment is challenging. But some patients may not respond to PH therapy in the first two neoadjuvant cycles, switching to T-DXd may be an interesting endeavor worth exploring.

A new era of HER2-low breast cancer

HER2-low is an emerging breast cancer treatment concept that will be truly defined by the data released by anti-HER2 ADC (36). HER2-low accounts for 45–55% of the entire breast cancer population (37). But there are no approved anti-HER2 treatments in these patients, and those with low HER2 are considered HER2-negative. There have been several unsuccessful attempts to explore the efficacy of previous anti-HER2 drugs in HER2-low patients (38-41). T-DXd brings some breaking through data in this new era, we summarized the clinical data of T-DXd in HER2-low breast cancer in *Table 1*.

J101, a phase Ib study evaluating the safety and efficacy of T-DXd in HER2-low MBC, demonstrated an ORR of 37.0% for T-DXd. The DOR was 10.4 months in heavily pretreated patients. Currently, the HER2-low population was explored in two phase III trials (42).

The DESTINY-BREAST04 trial (10) investigated the efficacy and safety of T-DXd compared with CT by physician's choice (TPC) for the treatment of advanced breast cancer with HER2-low expression. Four hundred and eighty HR-positive and 60 HR-negative HER2-low (HER2 IHC 1+ or HER2 IHC 2+/ISH–) were registered. Patients should receive one or two lines of CT, at least one line of ET, and be assessed by the investigator as not benefiting from ET if HR-positive. As reported, both PFS and OS in T-DXd arm were statistically significant and clinically meaningful improved compared with TPC arm. The efficacy was consistent in either HR-positive or HR-negative or whole population. The mPFS in HR-positive and all patients were 10.1 months in T-DXd arm versus 5.4 months in TPC arm, respectively (HR, 0.51; P<0.001) and 9.9 months versus 5.1 months in each arm respectively (HR, 0.50; P<0.001). The median OS in HR-positive and all patients were 23.9 months in T-DXd arm and 17.5 months in TPC arm, respectively (HR, 0.64; P=0.003) and 23.4 months versus 16.8 months in each arm, respectively (HR, 0.64; P=0.001).

Interestingly, a report from an exploratory DAISY trial presents a new concept of HER2 ultra-low (43). One hundred and seventy-nine pre-treated patients were recruited into the trial, all of whom were assigned to one of three cohorts based on HER2 expression. HER2 overexpression (n=68), defined as HER2 immunohistochemically (IHC) score of 3+ or IHC 2+ and positive *in situ* hybridization; HER2-low (n=73), defined as HER2 IHC 2+ and negative ISH result or IHC 1+; or HER2-negative (n=38), defined as HER2 IHC 0. T-DXd treatment achieved ORR rate of 71.0% in the HER2-overexpressing cohort, 37.5% in the HER2-low cohort, and 30.0% in the HER2-negative cohort. This is the first trial to show that T-DXd may be active in patients with ultra-low HER2 expression.

Concurrently, the DESTINYBreast06 (NCT04494425) trial is evaluating the comparison between T-DXd versus physician-chosen CT in patients with HER2-low, HR-positive breast cancer with at least two lines of previous ET, or fast progression on CDK4/6 inhibitors in the metastatic setting within 6 months. Patients should not receive CT in the metastatic setting. The trial plans to enroll approximately 700 HER2-low (IHC1+ or IHC2+/ISH–) and 150 HER2 ultra-low (HER2 IHC >0 and <1+) patients. The results of this study may provide evidence to support T-DXd to be a new option for patients with advanced HER2-low breast cancer who are refractory to ET. And

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Table 1 Summary of key clinical updates of trastuzumab deruxtecan in HER2-low breast cancer

Trial	Patient	Intervention	Outcomes
J101	HER2-low MBC, N=54	T-DXd (5.4 or 6.4 mg/kg)[a]	ORR, 37%; mPFS, 10.4 mo
DESTINY-BREST04	HER2-low MBC HR-positive (N=494) or HR-negative (N=63) PD on ET and CT	T-DXd *vs.* TPC[b]	mPFS, 10.1 *vs.* 5.4 mo in HR-positive, hazard ratio 0.51, P<0.001; 9.9 *vs.* 5.1 mo in ITT, hazard ratio 0.50, P<0.001 mOS, 23.9 *vs.* 17.5 mo in HR-positive, hazard ratio 0.64, P=0.003; 23.4 *vs.* 16.8 mo in ITT, hazard ratio 0.64, P=0.001
DESTINY-BREST08 (module 4 and 5)	HER2-low HR-positive MBC Module 4, N=6; module 5, N=6	T-DXd + anastrozole (module 4) T-DXd + fulvestrant (module 5)	RP2D
DAISY	MBC Cohort 2: HER2-low, N=44 Cohort 3: HER2 IHC 0, N=44	T-DXd	Cohort 2: ORR, 37.5%; mPFS, 6.7 mo Cohort 3: ORR, 29.7%; mPFS, 4.2 mo
DS8201-A-U105	HER2-low MBC, N=16	T-DXd + nivolumab	ORR, 50%, mPFS,7.0 mo, OS, 19.5 mo
BEGONIA arm 6	HER2-low mTNBC, no pre-CT, N=21	T-DXd + durvalumab (arm 6)	ORR, 66.7%
DESTINY-BREST06	HER2-low[c] HR-positive MBC PD on ET and no pre-CT, N=850	T-DXd *vs.* TPC[d]	PFS and OS, not reported
TALENT	HER2-low HR-positive EBC, N=58	T-DXd ± anastrozole as neoadjuvant	pCR, not reported

[a], T-DXd is administrated at dosage of 5.4 mg/kg q3w, else other specified; [b], treatment of physician' choice in DB04 includes capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel; [c], HER2 IHC >0 and <1+ is included; [d], treatment of physician' s choice in DB06 includes capecitabine, paclitaxel, or nab-paclitaxel. MBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; ORR, objective response rate; mPFS, median progression-free survival; mo, month; HR, hormonal receptor; PD, progression disease; ET, endocrine therapy; CT, chemotherapy; TPC, treatment of physician's choice; mOS, median overall survival; ITT, intention-to-treatment population; RP2D, recommended dose of phase two trial; IHC, immunohistochemical; OS, overall survival; mTNBC, metastatic triple-negative breast cancer; EBC, early breast cancer, pCR, pathological complete response.

could address the benefit of T-DXd in patients with ultra-low HER2 as well.

An exploratory trial, DESTINY-BREAST08 (NCT04556773), is also underway to investigate the safety and efficacy of combination therapy with T-DXd and other agents in MBC with HER2-low expression.

With the data shown above, the T-DXd-targeted population will go beyond the limits of HER2 positivity, ushering in a new era of HER2-low.

Expert opinion

The testing of HER2-low is a big challenge, and it is difficult to differentiate between 0 and 1+ HER2 ICH scores (44). While new approaches to address these issues are being explored, including AI imaging (45), HER2 mRNA (46), and more. HER2 heterogeneous is another issue for precise HER2-low identification. For an example, HER2 re-testing for 2 formalin-fixed paraffin-embedded blocks in a patients may be read as different scores. It's worth exploration that HER2-low diagnostic rate may increase if scoring 2 blocks in a HER2 testing, and then this may make more patients benefit from treatment with T-DXd. More evidence is needed on whether HER2 ultra-low can benefit from T-DXd, considering available HER2 monoclonal antibodies currently used to test for HER2 antigen are less sensitive. While IHC detection is a semi-quantitative method, a true quantitative method may provide more evidence. More real-world data on treatment patterns and efficacy are needed to elucidate the position of T-DXd after its approval in HER2-low breast cancer. Combination of T-DXd with other anti-cancer therapy in HER2-low was another interest topic discussed. In the HR-positive and HER2-low expression breast cancer, combination of T-DXd and ET may be effective. The DESTINY-BREAST08 study (47) reported on ASCO annual meeting 2022 showed that no dose-limited toxicity (DLT) was reported for T-DXd (5.4 mg/kg q3w) combination with anastrozole (1 mg daily) or fulvestrant

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[500 mg every 4 weeks (loading dose: 500 mg cycle 1 days 1 and 15)], but no efficacy data was reported this time and the study is under further follow-up. As DAISY trial (48) has proved that the efficacy of T-DXd is associated with level of HER2 expression. HER2-low patients who may have less PFS or ORR compared to that in HER2-positive patients, may have additional benefit from T-DXd combinations. More radically T-DXd as neoadjuvant in HER2-low EBC is also could be considered, since the pCR rate in HR-positive EBC is relatively lower. A trial has been reported to explore for T-DXd with or without anastrozole as neoadjuvant treatment (49).

The clinical positioning of T-DXd in HER2-low HR-positive MBC has be more clarified with the data from DESTINY-BREAST04. The HER2-low HR-positive metastatic patients have been treated as HER2-negative patients and normally will start CDK4/6 inhibitor as first or second-line therapy and then receive PI3K or mTOR inhibitors plus ET. When the patients are refractory to ET, one or two lines of CT will also be administrated, which include platinum-based regimen, or taxane or capecitabine mono therapy. After that T-DXd may be administrated. There will also be another ADC, sacituzumab govitecan has been on the scientific meetings this year in HR-positive MBC (50). So, the sequencing between these two ADC is also very interesting to be discussed.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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