Review Article

Strategies for the treatment of hormone receptor-positive HER2-low breast cancer based on clinical practice: a round table discussion

Xiang Huang[1#], Yijia Hua[1,2#], Chunxiao Sun[1], Yongmei Yin[1,2,3]

[1]Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [2]Gusu School, Suzhou Municipal Hospital, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou, China; [3]Jiangsu Key Lab of Cancer Biomarkers, Prevention and Treatment, Collaborative Innovation Center for Personalized Cancer Medicine, Nanjing Medical University, Nanjing, China

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

[#]These authors contributed equally to this work.

Correspondence to: Yongmei Yin, MD, PhD. Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, China; Gusu School, Suzhou Municipal Hospital, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou, China; Jiangsu Key Lab of Cancer Biomarkers, Prevention and Treatment, Collaborative Innovation Center for Personalized Cancer Medicine, Nanjing Medical University, Nanjing, China. Email: ymyin@njmu.edu.cn.

Abstract: Human epidermal growth factor receptor 2 (HER2)-low breast cancer is a newly identified targetable subset of breast tumors, and its clinical characteristics and treatment strategies are controversial. The emergence of novel anti-HER2 antibody-drug conjugate (ADC) has brought promising approaches for HER2-low breast cancer treatment. Several clinical trials have validated the efficacy and safety of trastuzumab deruxtecan (T-Dxd) in HER2-low breast cancer at different treatment settings. The treatment timing, candidate identification, long-term management, and overcoming drug resistance are crucial questions to improve breast cancer patient survival. Here we present a clinical case of hormone receptor-positive (HR$^+$) HER2-low breast cancer patient who experienced neoadjuvant chemotherapy, surgery, adjuvant, and first-line endocrine therapy with limited effectiveness. After the treatment failure of CDK4/6 inhibitors, the utilization of T-Dxd brought a long-term disease response and tolerable low toxicities. In this round table discussion, we summarized opinions and recommendations from breast cancer surgeons and oncologists on treatment strategies for this patient. The discussion mainly focused on the precise diagnosis of HER2-low breast cancer, treatment design at different disease status, regimens selection according to drug response, strategies consideration for overcoming drug resistance and the management of adverse events in long-term survival. These opinions would provide critical insights to improve HER2-low breast cancer treatment and offer valuable suggestions for clinical practice.

Keywords: Human epidermal growth factor receptor 2-low breast cancer (HER2-low breast cancer); trastuzumab deruxtecan (T-Dxd); metastatic breast cancer

Received: 23 July 2024; Accepted: 23 October 2024; Published online: 31 October 2024.

doi: 10.21037/tbcr-24-40

View this article at: https://dx.doi.org/10.21037/tbcr-24-40

Introduction

Breast cancer has been recognized as a disease with high heterogeneity (1,2). It could be divided into several subtypes according to the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (3,4). Based on current guidelines, HER2 positive expression is defined as HER2 immunohistochemistry (IHC) 3+ or IHC 2+ with in situ hybridization (ISH) amplification (5). Accounting for 60% in traditional HER2-negative breast cancers, a distinct subpopulation featuring HER2 IHC 1/2+ without ISH amplification has attracted much attention in recent years, which is named HER2-low breast cancer (6,7). Its unique biological and clinical characteristics have brought both opportunities and challenges in breast cancer treatment (8,9).

HER2-low breast cancers are composed of hormone receptor-positive (HR^+) and HR-negative (HR^-) breast cancers and were considered as HER2-negative breast cancer in clinical practice. For patients with HR^+/HER2-low breast cancer, endocrine therapies combined with targeted agents could improve progression-free survival (PFS) and overall survival (OS) in the metastatic setting (10,11). HR^-/HER2-low breast cancer patients were treated as triple-negative breast cancer (TNBC) and obtained benefits from chemotherapy or other targeted treatment, such as immune checkpoint inhibitor, PARP inhibition, and TROP-2 antibody-drug conjugate (ADC) (12,13). However, trastuzumab deruxtecan (T-Dxd; DS-8201), a novel anti-HER2 ADC, has shown promising efficacy in HER2-low breast cancer and reshaped the treatment landscape (14-16).

In DESTINY-Breast04 trial, compared with chemotherapy, T-Dxd significantly prolonged the survival of HER2-low metastatic breast cancer patients who had previously received at least one line of chemotherapy, irrespective of HR status (14). DESTINY-Breast06 further demonstrated the role of T-Dxd in patients with HER2-low or HER2-ultralow HR^+ metastatic breast cancer without any prior chemotherapies in the metastatic setting (17). These results revealed that HER2-low breast cancer patients might gain more benefits from anti-HER2 ADCs than conventional therapies, which would provide novel treatment options in clinical practice (13,18).

However, although T-Dxd illustrated remarkable efficacy, multiple questions regarding the management and treatment for HER2-low breast cancer remains obscure. How to incorporate the HER2-low concept in the rapidly evolving breast cancer treatment paradigm is a crucial topic for all researchers (19). The management of T-Dxd in different treatment timings and the selection after T-Dxd failure are also important questions to consider (20,21).

Here, by analyzing and reviewing a patient with HR^+/HER2-low metastatic breast cancer, we organized a round table discussion about treatment strategies for HER2-low breast cancer. Several breast cancer surgeons and oncologists shared their opinions on advantages and implications of T-Dxd utilization in clinical practice. The summary was recorded as this review.

Case presentation and discussion

Preoperative treatment

In October 2018, a 33-year-old female came to our hospital for complaining left breast mass. Ultrasound indicated that the left breast multifocal nodule was classified as Breast Imaging Reporting and Data System (BI-RADS) 5 and lymph nodes in the left axilla regions I, II, and III as 4C. Magnetic resonance imaging (MRI) confirmed left breast multiple lesions (multifocal; the largest lesion 2.4 cm × 2.3 cm × 1.9 cm) as BI-RADS 5 and multiple enlarged lymph nodes in the left axilla as 4C (*Figure 1A*).

She then received left breast mass biopsy and pathology tests confirmed left breast invasive carcinoma. IHC tests indicated invasive carcinoma with ER (90% 2+), PR (10% 1–2+), HER2 (2+) and FISH (–), Ki-67 (60%+). No metastases were observed on computed tomography (CT) and emission CT (ECT). No pathogenic *BRCA* mutations were detected.

(I) How to select the neoadjuvant therapy for HR^+/HER2-low early-stage breast cancer?

Expert opinion

In total, 70.7% of all experts recommended this patient to receive neoadjuvant chemotherapy, 29.3% recommended surgery while no experts recommended neoadjuvant endocrine therapy (*Figure 1B*).

The pathologic diagnosis of HER2-low breast cancer should refer to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) 2018 algorithm and HER2 IHC score (0, 1+, 2+, 3+) could help clinicians to better interpret HER2 status and determine clinical practices. The definition of HER2-low status could be based on either primary tumor or at any point during the metastatic settings. The pathological reassessment could be applied when necessary. However, the borderline

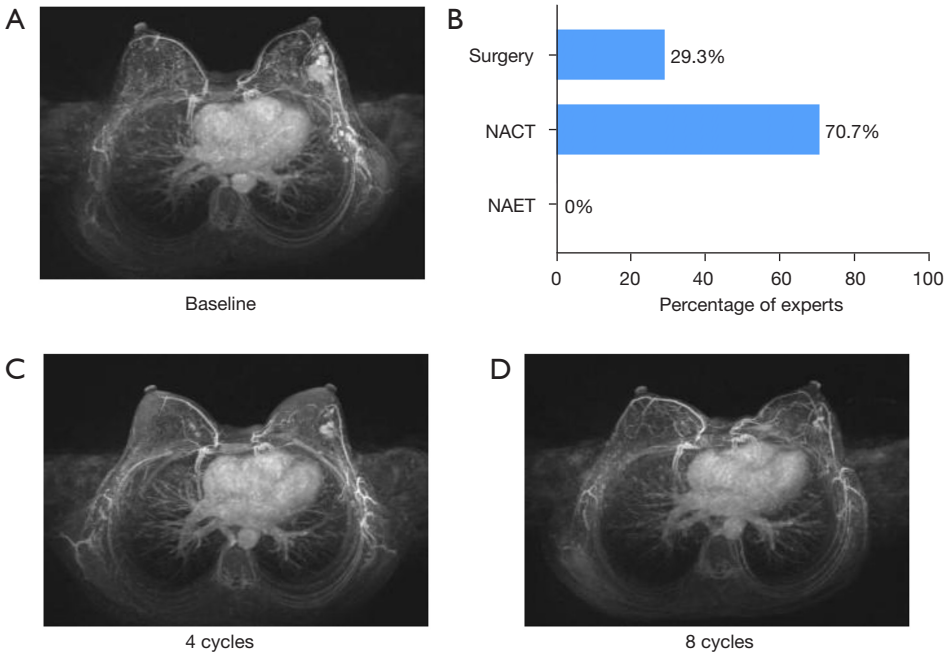

Figure 1 MRI scan during neoadjuvant treatment and expert opinions for therapy recommendation. (A) MRI scan of breast cancer and axillary lymph nodes in baseline detection. (B) Expert opinions for therapy selection. (C,D) MRI scan of breast cancer and axillary lymph nodes responses after 4 cycles (C) and 8 cycles (D) of neoadjuvant treatment. NACT, neoadjuvant chemotherapy; NAET, neoadjuvant endocrine therapy; MRI, magnetic resonance imaging.

to distinguish between HER2-zero and HER2-ultralow is still controversial. Improved higher-power techniques and a second review of other pathologists would be recommended (22).

Because of the special cancer biology, the effectiveness of neoadjuvant chemotherapy in ER$^+$/HER2-low breast cancer is still controversial. Several studies indicated that pathologic complete response (pCR) rates of ER$^+$/HER2-low breast cancer in the neoadjuvant settings were relatively lower than ER$^+$/HER2-zero breast cancer, with a longer disease-free survival (DFS) and OS (23,24). Yet some argued there was no significant difference in the survival between HER2-low and HER2-zero breast cancer, which opposed the independent classification of HER2-low breast cancer (25,26). The selection between neoadjuvant chemotherapy and surgery as an initial treatment should consider various issues, including tumor size, lymph nodes metastasis, tumor grade, and Ki-67 (27).

Neoadjuvant immunotherapy might become a potential strategy for ER$^+$/HER2-low breast cancer. KEYNOTE-756, CheckMate 7FL, and I-SPY2 trials showed the combination of immunotherapy and chemotherapy could increase pCR rates in ER$^+$/HER2$^-$ early breast cancer with tolerable toxicities (28-31). Patients featured tumor grade III or programmed cell death ligand 1 (PD-L1) positive expression might experience more benefits in neoadjuvant immunotherapy (28,29).

In addition, ER$^+$/HER2-low breast cancer might also benefit from neoadjuvant endocrine therapy. HR$^+$/HER2$^-$ breast cancer patients who experienced failure in neoadjuvant chemotherapy, or were eligible for neither neoadjuvant chemotherapy and surgery, could benefit from neoadjuvant endocrine therapy, including aromatase inhibitor (AI), fulvestrant, and CDK4/6 inhibitors (32-34). The efficacy of neoadjuvant endocrine therapy still needs more clinical trials to investigate.

Genetic testing, such as MammaPrint, could be utilized to better inform neoadjuvant treatment decisions in ER$^+$/HER2-low breast cancer between chemotherapy, endocrine therapy, and immunotherapy (35). This would evaluate genomic risks for recurrence and provide evidence for decision-making in adjuvant treatment settings.

Surgery and adjuvant treatment

This patient was diagnosed as HR$^+$/HER2$^-$ breast cancer with cT2(m)N+M0. She underwent neoadjuvant

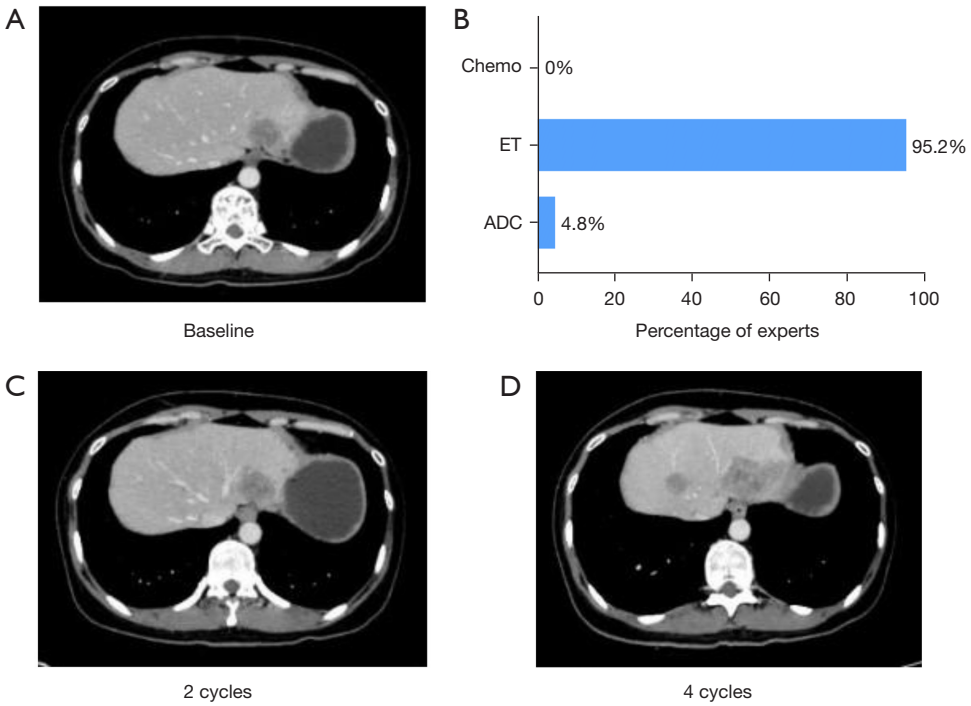

Figure 2 CT scan during the first-line treatment and expert opinions for therapy recommendation. (A) CT scan of liver metastases in baseline detection. (B) Expert opinions for therapy selection. (C,D) CT scan of liver metastases in the 2 cycle (C) and 4 cycle (D) of the first-line treatment. Chemo, chemotherapy; ET, endocrine therapy; ADC, antibody-drug conjugate; CT, computed tomography.

chemotherapy with ddEC-NabT and the best treatment response was partial response. After eight cycles, MRI showed that the tumor size decreased (the largest lesion approximately 0.7 cm), with reduced cell density (BI-RADS 6). Lymph nodes in the left axilla (BI-RADS 4A) have also decreased in size (*Figure 1C,1D*).

In March 2019, this patient received left breast modified radical mastectomy and pathology tests confirmed invasive ductal carcinoma (IDC) with grade II (1.5 cm × 1 cm × 1 cm). The pathological response to neoadjuvant treatment was grade 3 by Miller-Payne system. IHC tests showed that ER (90% 3+), PR (20% 2+), HER2 (2+) and FISH (–), Ki-67 (20%+). Lymph node metastases were detected (21/23). She was staged as ypT1cN3M0 (IIIC) and was treated with adjuvant radiotherapy, which focused on left chest wall, left supraclavicular region (upper and lower), and left internal mammary chain [total dose (DT) 50 Gy/25 f]. Adjuvant endocrine therapy included ovarian function suppression (OFS) and anastrozole. Frequent follow-up examinations were conducted timely.

Disease recurrence

In December 2020, CT indicated left liver mass as metastasis (*Figure 2A*). ECT and MRI showed abnormal signal intensity at the anterior superior margin of the right acetabulum. No brain metastasis was detected. The biopsy of liver mass confirmed poorly differentiated carcinoma with ER (>90%, 3+), PR (10%, 2+), HER2 (1+), Ki-67 (hotspot 25%+), CK7 (–), glypican-3 (–), hepatocyte-1 (–), GATA3 (++), GCDFP-15 (–), and mammaglobin (slightly +), consistent with metastatic adenocarcinoma of breast origin.

(II) How to optimize the first-line treatment for HR$^+$/HER2-low advanced breast cancer?

Expert opinion

In the first-line therapy, 95.2% of all experts recommended endocrine therapy, 4.8% recommended ADC and no experts recommended chemotherapy (*Figure 2B*).

The utilization of endocrine therapy in advanced breast cancer should consider several factors, including HR

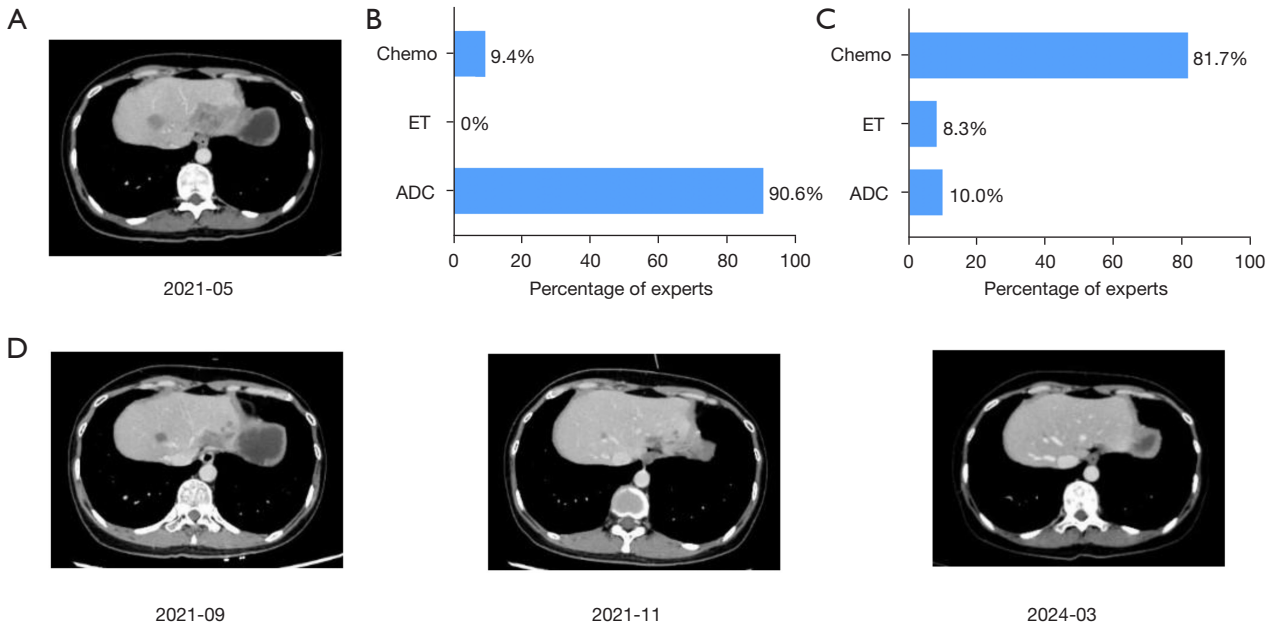

Figure 3 CT scan during the second-line treatment and expert opinions for therapy recommendation. (A) CT scan of liver metastases in baseline detection (2021-05). (B) Expert opinions for therapy selection if ADC was available. (C) Expert opinions for therapy selection if ADC was not available. (D) CT scan of liver metastases during the second-line treatment (2021-09, 2021-11, and 2024-03). Chemo, chemotherapy; ET, endocrine therapy; ADC, antibody-drug conjugate; CT, computed tomography.

expression status, menopausal status, tumor burden, and previous endocrine therapy response (36). In the first-line treatment for HR$^+$/HER2-low advanced breast cancer, physicians could approach suitable endocrine therapy according to previous adjuvant endocrine regimens and DFS. CDK4/6 inhibitors combined with AI would be recommended for patients failed in tamoxifen (37-39), and CDK4/6 inhibitors plus fulvestrant for AI failure (40-43). Recent advances also indicated that compared with chemotherapy, CDK4/6 inhibitors plus endocrine therapy provided better PFS and tolerability for patients with clinical aggressive disease (44).

Nowadays, there have been several kinds of CDK4/6 inhibitors available for Chinese breast cancer patients, and how to choose an appropriate CDK4/6 inhibitor has become an important issue. Previous studies confirmed the efficacy and safety of CDK4/6 inhibitors, and their recommendations levels should be equal, without any subjective preference. The selection of different CDK4/6 inhibitors should consider previous treatment response, tolerability of adverse events, and disease development.

First-line treatment

She next entered the clinical trial evaluating the efficacy, safety, and pharmacokinetic characteristics of FCN-437c in combination with fulvestrant ± goserelin in advanced ER$^+$/HER2$^-$ breast cancer and received FCN-437c (CDK4/6 inhibitor) plus fulvestrant and OFS (*Figure 2C,2D*).

In May 2021, CT showed multiple liver lesions increased in number and size, indicating disease progression (*Figure 3A*). The biopsy of liver mass confirmed metastatic adenocarcinoma with ER (95%, 3+), PR (–), HER2 (2+), Ki-67 (40%+), mammaglobin (slightly +), SOX11 (–), GCDFP-15 (–), AR (+), GATA3 (3+), CK7 (–), CK19 (+), CK20 (–), villin (–), Pax-8 (–), Napsin A (–), and TTF-1 (–), consistent with metastatic adenocarcinoma of breast origin.

(III) Which therapy would be recommended for HR$^+$/HER2-low advanced breast cancer after progression on CDK4/6 inhibitors?

Expert opinion

If ADC was available for this patient, 90.6% in all experts

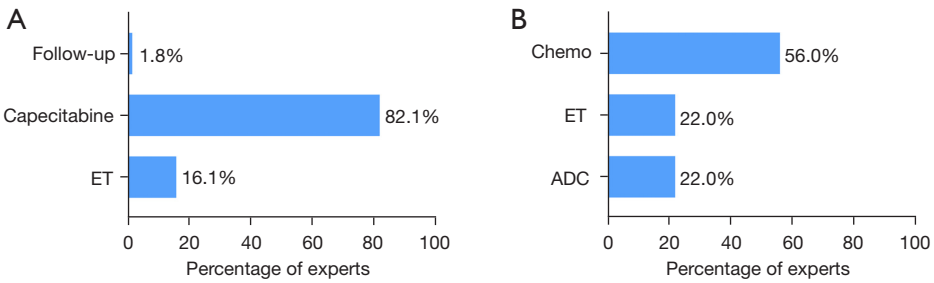

Figure 4 Expert opinions for the utilization of T-Dxd in advanced breast cancer. (A) Expert opinions for the maintenance therapy if ADC was not tolerable. (B) Expert opinions for therapy recommendation after T-Dxd failure. ET, endocrine therapy; chemo, chemotherapy; ADC, antibody-drug conjugate; T-Dxd, trastuzumab deruxtecan.

recommended ADC therapy, 9.4% recommended chemotherapy while no one recommended endocrine therapy (*Figure 3B*). Considering ADC was not available in China in 2021, 81.7% recommended this patient to receive chemotherapy, 8.3% recommended endocrine therapy and 10.0% suggested ADC utilization in clinical trials (*Figure 3C*).

The design of second-line therapy for HR$^+$/HER2-low advanced breast cancer needs to evaluate the sensitivity and response of adjuvant and first-line endocrine therapy, therefore overcoming drug resistance (45). In the real-world clinical practice, the next-generation sequencing (NGS) would be recommended after first-line treatment failure, which helps physicians to better understand the mechanisms of drug resistance and explore potential targets for further treatment (46,47).

For this patient, traditionally we would put priority on chemotherapy for second-line treatment, such as capecitabine, as the response of first-line CDK4/6 inhibitors was poor and only liver metastasis was detected in visceral settings. If the effectiveness of chemotherapy was limited, we would then consider other targets according to NGS results, such as PI3K or AKT inhibitors (48-50).

BYLieve study demonstrated that HR$^+$/HER2$^-$ breast cancer patients with PIK3CA mutation could benefit from the combination of alpelisib and fulvestrant after failure on CDK4/6 inhibitors and AIs (50). CAPItello-291 study also indicated that capivasertib plus fulvestrant could improve the survival HR$^+$/HER2$^-$ breast cancer patients with PIK3CA, AKT, or PTEN alterations after progression on AIs with or without CDK4/6 inhibitors (49). These results supported that the detection of PI3K/AKT/PTEN mutations could provide evidence for the design of treatment to overcome CDK4/6 inhibitors resistance.

However, recent advances on DESTINY-BREAST06 have reshaped the treatment landscape of HR$^+$/HER2-low advanced breast cancer. Compared with chemotherapy, T-Dxd significantly provided a better objective response rate (ORR; 57.3% *vs.* 31.2%) and PFS (13.2 *vs.* 8.1 months; hazard ratio, 0.63; P<0.0001) in HR$^+$/HER2-low and HER2-ultralow advanced breast cancer following ≥1 endocrine therapy. The efficacy of T-Dxd in HER2-low and HER2-ultralow was consistent and toxicities were tolerable. These results supported an earlier line treatment of T-Dxd in HR$^+$/HER2-low breast cancer (17). Therefore, this patient is also eligible to receive T-Dxd in the second-line treatment, but the selection of regimens should consider drug accessibilities, treatment tolerance, and patient preference.

Second-line treatment

This patient was then enrolled in DESTINY-Breast06 in June 2021 and received T-Dxd treatment. A partial response was observed after two cycles of treatment and this response was maintained at the latest follow-up in April 2024 (*Figure 3D*).

(IV) How to improve the clinical management of T-Dxd in HR$^+$/HER2-low advanced breast cancer?

Expert opinion

If this patient would not tolerate the utilization of T-Dxd, 82.1% of all experts recommended capecitabine, 16.1% recommended endocrine therapy and 1.8% suggested follow-up (*Figure 4A*).

Safety and tolerance are crucial issues throughout the whole treatment of T-Dxd. In DESTINY-BREAST06 trial, the most common treatment-emergent adverse event (TEAE) associated with discontinuation in T-Dxd was pneumonitis (5.3%) and the most common TEAE

associated with dose reduction in T-Dxd was nausea (4.4%) (17). Similar with previous DESTINY-Breast trials (14,51,52), interstitial lung disease (ILD) has remained as an important risk factor for T-Dxd.

In the real-world practice, physicians should monitor adverse effects (AEs) in the long-term use of T-Dxd and take relative measures in time according to patient-reported outcomes. Monitoring ILD and identifying patients who could be safely rechallenged with T-Dxd after ILD recovery would promote better implementation of T-Dxd. In addition, the financial toxicity should also be considered (53). Physicians need to pay attention to patients' tumor and living burden and help them select the most suitable regimens with guaranteed effectiveness and life quality.

For this patient, if the intolerance of T-Dxd occurs, chemotherapy or endocrine therapy could become an alternative option for maintenance treatment. NGS or circulating tumor DNA (ctDNA) tests are recommended to explore potential treatment targets. For example, if the ESR1 mutation is detected, which explains the rapid progression of fulvestrant (54,55), the oral selective ER degraders (SERDs) would be an optimal strategy (56). Capecitabine is also an appropriate choice for maintenance, as several studies have revealed its promising efficacy and safety.

(V) How to design treatment strategies for T-Dxd treatment failure?

Expert opinion

If this patient encountered disease progression after T-Dxd treatment, 56.0% of all experts recommended chemotherapy, 22.0% recommended endocrine therapy and 22.0% suggested another ADC (*Figure 4B*).

Although DESTINY-BREAST06 showed the earlier line treatment of T-Dxd could improve patient survival and might bring a prolonged response, we must understand that not every patient would be sensitive to T-Dxd utilization. How to better identify patients suitable for T-Dxd is an important clinical issue. For instance, it is urgent to improve HER2 testing assays to distinguish HER2-low, HER2-ultralow and HER2-zero, which would investigate the relationship between HER2 threshold and T-Dxd efficacy (6).

Moreover, the identification and validation of biomarkers related to T-Dxd treatment is another important topic. Previous studies showed that HER2 expression reduction, HER2 mutation and HER2 heterogeneity might play roles in resistance formation (57,58). We should contribute more efforts to the exploration of resistance mechanisms and conduct translational researches to overcome T-Dxd resistance.

If this patient encounters poor response or disease progression during the treatment of T-Dxd, it is recommended to personalize treatment strategies according to NGS tests. Physicians could choose relative measures to deal with different somatic mutations, such as using tyrosine kinase inhibitors (TKIs) for some somatic *HER2* mutations (59). This patient could also enter clinical trials to obtain more opportunities. Even though the utilization of chemotherapy could be a traditional standard option for late-line treatment, the emergence of numerous novel drugs provides more approaches and improves patient survival.

Conclusions

HER2-low breast cancer has attracted much attention and reshaped the current breast cancer treatment landscape. This round table discussion focused on the pathologic diagnosis, treatment sequencing, and toxicities management of HER2-low breast cancer and provided distinct value to optimize clinical practice and improve patient survival. The biological and clinical role of HER2-low breast cancer still needs further evidence, and we believe this round table discussion would provide support for future research.

Acknowledgments

Funding: None.

Footnote

Peer Review File: Available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-40/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-24-40/coif). Y.Y. serves as an unpaid editorial board member of *Translational Breast Cancer Research* from March 2024 to February 2026. The other authors have no conflicts of interest to declare.

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.

References

1. Nolan E, Lindeman GJ, Visvader JE. Deciphering breast cancer: from biology to the clinic. Cell 2023;186:1708-28.
2. Liang Y, Zhang H, Song X, et al. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. Semin Cancer Biol 2020;60:14-27.
3. Harbeck N, Gnant M. Breast cancer. Lancet 2017;389:1134-50.
4. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers 2019;5:66.
5. Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. J Clin Oncol 2023;41:3867-72.
6. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-Low Breast Cancer: Pathological and Clinical Landscape. J Clin Oncol 2020;38:1951-62.
7. Marchiò C, Annaratone L, Marques A, et al. Evolving concepts in HER2 evaluation in breast cancer: Heterogeneity, HER2-low carcinomas and beyond. Semin Cancer Biol 2021;72:123-35.
8. Dai LJ, Ma D, Xu YZ, et al. Molecular features and clinical implications of the heterogeneity in Chinese patients with HER2-low breast cancer. Nat Commun 2023;14:5112.
9. Schlam I, Tolaney SM, Tarantino P. How I treat HER2-low advanced breast cancer. Breast 2023;67:116-23.
10. Nicolò E, Boscolo Bielo L, Curigliano G, et al. The HER2-low revolution in breast oncology: steps forward and emerging challenges. Ther Adv Med Oncol 2023;15:17588359231152842.
11. Li H, Wu Y, Zou H, et al. Clinical efficacy of CDK4/6 inhibitor plus endocrine therapy in HR-positive/HER2-0 and HER2-low-positive metastatic breast cancer: a secondary analysis of PALOMA-2 and PALOMA-3 trials. EBioMedicine 2024;105:105186.
12. Li Y, Zhang H, Merkher Y, et al. Recent advances in therapeutic strategies for triple-negative breast cancer. J Hematol Oncol 2022;15:121.
13. Qu F, Lu R, Liu Q, et al. Antibody-drug conjugates transform the outcome of individuals with low-HER2-expression advanced breast cancer. Cancer 2024;130:1392-402.
14. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med 2022;387:9-20.
15. Mosele F, Deluche E, Lusque A, et al. Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial. Nat Med 2023;29:2110-20.
16. Martín M, Pandiella A, Vargas-Castrillón E, et al. Trastuzumab deruxtecan in breast cancer. Crit Rev Oncol Hematol 2024;198:104355.
17. Curigliano G, Hu X, Dent R A, et al. Trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): Primary results from DESTINY-Breast06 (DB-06). J Clin Oncol 2024;42:LBA1000.
18. von Arx C, De Placido P, Caltavituro A, et al. The evolving therapeutic landscape of trastuzumab-drug conjugates: Future perspectives beyond HER2-positive breast cancer. Cancer Treat Rev 2023;113:102500.
19. Yang C, Brezden-Masley C, Joy AA, et al. Targeting HER2-low in metastatic breast cancer: an evolving treatment paradigm. Ther Adv Med Oncol 2023;15:17588359231175440.
20. Li J, Jiang Z. Antibody drug conjugates in breast cancer in China: Highlights, challenges, and prospects. Cancer 2024;130:1371-7.
21. Antonarelli G, Corti C, Tarantino P, et al. Management of patients with HER2-positive metastatic breast cancer after trastuzumab deruxtecan failure. ESMO Open 2023;8:101608.
22. Tarantino P, Viale G, Press MF, et al. ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer. Ann Oncol 2023;34:645-59.
23. Denkert C, Seither F, Schneeweiss A, et al. Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. Lancet Oncol 2021;22:1151-61.
24. Li Y, Maimaitiaili A, Qu F, et al. Effect of HER2-low-positive status on neoadjuvant chemotherapy and survival outcome of breast cancer: a 10-year dual-center

retrospective study. Am J Cancer Res 2023;13:3571-81.
25. de Moura Leite L, Cesca MG, Tavares MC, et al. HER2-low status and response to neoadjuvant chemotherapy in HER2 negative early breast cancer. Breast Cancer Res Treat 2021;190:155-63.
26. Ilie SM, Briot N, Constantin G, et al. Pathologic complete response and survival in HER2-low and HER2-zero early breast cancer treated with neoadjuvant chemotherapy. Breast Cancer 2023;30:997-1007.
27. Jiang Z, Li J, Chen J, et al. Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines 2022. Transl Breast Cancer Res 2022;3:13.
28. Cardoso F, McArthur HL, Schmid P, et al. LBA21 KEYNOTE-756: Phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo)+ chemotherapy (chemo), followed by adjuvant pembro or pbo+ endocrine therapy (ET) for early-stage high-risk ER+/HER2–breast cancer. Ann Oncol 2023;34:S1260-1.
29. Loi S, Curigliano G, Salgado RF, et al. LBA20 A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET)±NIVO in patients (pts) with high-risk, ER+ HER2– primary breast cancer (BC). Ann Oncol 2023;34:S1259-60.
30. Pusztai L, Yau C, Wolf DM, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: Results from the adaptively randomized I-SPY2 trial. Cancer Cell 2021;39:989-998.e5.
31. Nanda R, Liu MC, Yau C, et al. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. JAMA Oncol 2020;6:676-84.
32. Jeong H, Kim SB. Neoadjuvant endocrine therapy in ER-positive breast cancer: evolution, indication, and tailored treatment strategy. Ther Adv Med Oncol 2023;15:17588359231200457.
33. Lerebours F, Cabel L, Pierga JY. Neoadjuvant Endocrine Therapy in Breast Cancer Management: State of the Art. Cancers (Basel) 2021;13:902.
34. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. J Clin Oncol 2021;39:1485-505.
35. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 2016;375:717-29.
36. Al Sukhun S, Temin S, Barrios CH, et al. Systemic Treatment of Patients With Metastatic Breast Cancer: ASCO Resource-Stratified Guideline. JCO Glob Oncol 2024;10:e2300285.
37. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016;375:1925-36.
38. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med 2016;375:1738-48.
39. Zhang P, Zhang Q, Tong Z, et al. Dalpiciclib plus letrozole or anastrozole versus placebo plus letrozole or anastrozole as first-line treatment in patients with hormone receptor-positive, HER2-negative advanced breast cancer (DAWNA-2): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2023;24:646-57.
40. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med 2018;379:1926-36.
41. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017;35:2875-84.
42. Xu B, Zhang Q, Zhang P, et al. Dalpiciclib or placebo plus fulvestrant in hormone receptor-positive and HER2-negative advanced breast cancer: a randomized, phase 3 trial. Nat Med 2021;27:1904-9.
43. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med 2020;382:514-24.
44. Lu YS, Mahidin EIBM, Azim H, et al. Final Results of RIGHT Choice: Ribociclib Plus Endocrine Therapy Versus Combination Chemotherapy in Premenopausal Women With Clinically Aggressive Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer. J Clin Oncol 2024;42:2812-21.
45. Huppert LA, Gumusay O, Idossa D, et al. Systemic therapy for hormone receptor-positive/human epidermal growth factor receptor 2-negative early stage and metastatic breast cancer. CA Cancer J Clin 2023;73:480-515.
46. Gibbs SN, Peneva D, Cuyun Carter G, et al. Comprehensive Review on the Clinical Impact of Next-Generation Sequencing Tests for the Management of Advanced Cancer. JCO Precis Oncol 2023;7:e2200715.
47. Colomer R, Mondejar R, Romero-Laorden N, et al. When should we order a next generation sequencing test in a

patient with cancer? EClinicalMedicine 2020;25:100487.
48. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2019;380:1929-40.
49. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2023;388:2058-70.
50. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. Lancet Oncol 2021;22:489-98.
51. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med 2022;386:1143-54.
52. André F, Hee Park Y, Kim SB, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. Lancet 2023;401:1773-85.
53. Lapen K, Dee ECC, Thom B, et al. Financial toxicity in patients with metastatic breast cancer on trastuzumab deruxtecan (T-DXd). J Clin Oncol 2024;42:1112.
54. Kingston B, Pearson A, Herrera-Abreu MT, et al. ESR1 F404 Mutations and Acquired Resistance to Fulvestrant in ESR1-Mutant Breast Cancer. Cancer Discov 2024;14:274-89.
55. Brett JO, Spring LM, Bardia A, et al. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res 2021;23:85.
56. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol 2022;40:3246-56. Erratum in: J Clin Oncol 2023;41:3962.
57. Chen YF, Xu YY, Shao ZM, et al. Resistance to antibody-drug conjugates in breast cancer: mechanisms and solutions. Cancer Commun (Lond) 2023;43:297-337.
58. Guidi L, Pellizzari G, Tarantino P, et al. Resistance to Antibody-Drug Conjugates Targeting HER2 in Breast Cancer: Molecular Landscape and Future Challenges. Cancers (Basel) 2023;15:1130.
59. Bon G, Di Lisa FS, Filomeno L, et al. HER2 mutation as an emerging target in advanced breast cancer. Cancer Sci 2024;115:2147-58.

doi: 10.21037/tbcr-24-40
Cite this article as: Huang X, Hua Y, Sun C, Yin Y. Strategies for the treatment of hormone receptor-positive HER2-low breast cancer based on clinical practice: a round table discussion. Transl Breast Cancer Res 2024;5:30.