



Thoughts on therapy strategy in the era of “after anti-HER2 TKI” in CSCO BC Guidelines 2022

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Contributions: (I) Conception and design: All authors; (II) Administrative support: Z Jiang; (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.

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Abstract: Treatment of breast cancer (BC) is becoming stratified on the basis of classified treatment. Different from trastuzumab emtansine (T-DM1) as 2nd-line anti-human epidermal growth factor receptor 2 (HER2) treatment is recommended by foreign guidelines and clinical practice, more patients in China are receiving anti-HER2 tyrosine kinase inhibitor (TKI) as 2nd-line anti-HER2 targeted therapy for metastatic BC, which raises the issue of subsequent targeted therapy after TKI failure, the preferred regimen and how to optimize it. Evidence from high-quality randomized controlled clinical trials is lacking up to now, but in clinical practice this stratified subgroup patients need to be treated. Failure to TKI treatment is first described in the Chinese Society of Clinical Oncology Breast Cancer (CSCO BC) Guidelines 2022, based on existing clinical trials data, real-world research data and expert opinions on HER2-positive metastatic BC, although there are no Level I recommendations and Level II options include anti-HER2 antibody-drug conjugate (ADC) (2A evidence), pertuzumab and trastuzumab plus other (non-taxane) chemotherapy (2A evidence), switching to another TKI plus chemotherapy (2A evidence) and entering strictly designed clinical trials. In the era of “after anti-HER2 TKI”, there will be more results of randomized controlled clinical trials and real-world researches as evidences to guide the therapy in the future, and clinicians must ensure accurate classification and precise stratification of patients to deliver optimized, precise subsequent therapy.

Keywords: Metastatic breast cancer (mBC); after anti-HER2 TKI; new therapy stratification; CSCO BC Guidelines 2022

Received: 10 July 2022; Accepted: 22 July 2022; Published: 30 July 2022.

doi: 10.21037/tbcr-22-32

View this article at: <https://dx.doi.org/10.21037/tbcr-22-32>

The treatment of breast cancer (BC) is moving towards stratification on the basis of classified treatment. Stratified treatment is planning for patients with the same molecular type of BC under different treatment backgrounds according to the overall disease evaluation, and making reasonable therapeutic decisions to maximize the treatment benefits for patients.

Anti-HER2 targeted therapies have improved the outcomes of HER2-positive metastatic breast cancer (mBC). For patients treated with trastuzumab and taxane as (neo)adjuvant therapy, if the interval from the end of

trastuzumab to recurrence and/or metastasis (disease-free interval) is >12 months, retreatment with trastuzumab and taxane potentially has good efficacy, so the regimen of trastuzumab + pertuzumab + taxane is recommended as 1st-line treatment in mBC. It was established in the CLEOPATRA trial, with mPFS of 18.7 months (1), but for the patients who have failure of trastuzumab, with recurrence and/or metastasis during adjuvant therapy or within 12 months after the end of trastuzumab therapy, as well as the increasing numbers of patients who have received pertuzumab therapy in the (neo)adjuvant setting,

the regimen of trastuzumab + pertuzumab + taxane is not suitable as 1st-line treatment. Taking into consideration drug accessibility and efficacy, the economic burden for the patient and the convenience of therapy, especially during the COVID-19 pandemic, most physicians chose the dual oral regimen of tyrosine kinase inhibitor (TKI) + capecitabine. Previously, lapatinib has been the main choice of TKI (2-4), but pyrotinib has proved to be significantly more effective than lapatinib (5-9) and was listed on medical insurance in China in 2019. Since 2020 the combination of pyrotinib and capecitabine has been recommended as Level I (category 1A evidence) in the Chinese Society of Clinical Oncology (CSCO) Breast Cancer Guidelines for patients who have failed trastuzumab (10) and is preferred in the Expert Consensus on Clinical Diagnosis and Treatment of Human Epidermal Growth Factor Receptor 2 Positive Breast Cancer [2021] (11).

Human epidermal growth factor receptor 2 (HER2)-TKI is the 2nd-line anti-HER2 treatment of mBC in China, which is different from foreign guidelines and clinical practice. The antibody-drug conjugate (ADC) trastuzumab emtansine (T-DM1) as 2nd-line anti-HER2 treatment is recommended by the recent NCCN (12), ASCO (13) and ABC6 (14) guidelines, but lack of access and the high cost of the drug not being covered by medical insurance has resulted in low use of T-DM1 as the 2nd-line anti-HER2 agent for patients in China (15). As increasing numbers of patients receive anti-HER2 TKI treatment, the problem arises of subsequent targeted therapy after TKI failure, the preferred regimen and how to optimize it. Evidence from high-quality randomized controlled clinical trials is lacking, but in clinical practice these patients need to be treated. Failure with TKI treatment in HER2-positive advanced BC is first described in the CSCO BC Guidelines 2022, based on existing clinical trials data, real-world research data and expert opinions on HER2-positive mBC. It is suggested that decision-making should be based on previous treatments. There is no Level I recommendation and Level II options include: (I) anti-HER2 ADC [e.g., trastuzumab deruxtecan (T-DXd), T-DM1] (2A evidence); (II) pertuzumab + trastuzumab plus other (non-taxane) chemotherapy (2A evidence); (III) switching to another TKI plus chemotherapy (2A evidence); and (IV) entering strictly designed clinical trials (16).

According to the available evidence, anti-HER2 ADC is the preferred treatment after TKI failure. Because of its superior efficacy, T-DXd is consistently recommended as the optimal ADC in the NCCN, ASCO and ABC6 guidelines in 2022.

T-DXd demonstrated robust activity in 3rd- or more lines of HER2-directed therapy in the metastatic setting in the phase II DESTINY-Breast 01 study (17). The median number of previous lines of therapy for metastatic disease was 6 (range, 2–27) and included HER2-targeting TKI (50.5%), T-DM1 (100%), trastuzumab (100%), and pertuzumab (65.8%). After a median follow-up of 20.5 months, the overall response rate (ORR) was 60.9% and disease control rate (DCR) was 97.3%, the median progression-free survival (mPFS) was 19.4 months and median overall survival (OS) was 24.6 months (18). T-DXd demonstrated a clear improvement of efficacy over other available therapies in a heavily pretreated population.

T-DXd *vs.* T-DM1 was evaluated in a head-to-head study in HER2-positive mBC patients previously treated with trastuzumab and taxane in the phase III DESTINY-Breast 03 trial and T-DXd significantly improved PFS and reduced the risk of disease progression or death compared to T-DM1. The mPFS evaluated by blinded independent central review (BICR) was not evaluable (NE) *vs.* 6.8 months, and the 12-month PFS rate was 75.8% *vs.* 34.1% [hazard ratio (HR) 0.28, $P=7.8 \times 10^{-22}$]. The mPFS evaluated by investigator was 25.1 *vs.* 7.2 (HR =0.27). The 12-month OS rate was 94.1% *vs.* 85.9% (HR =0.55, $P=0.007172$) and the ORR was 79.7% *vs.* 34.2% in the two groups (19).

In the Asian subgroup ($n=309$, 59%) of the DESTINY-breast 03 trial, T-DXd demonstrated meaningful PFS benefit compared to T-DM1, which was consistent with that in the overall population (20). A total of 22.8% of patients in the T-DXd group had received prior anti-HER2 TKI. The mPFS by BICR was NE *vs.* 5.6 months, and the 12-month PFS rate was 72.6% *vs.* 26.0% (HR =0.27). The mPFS by investigator was 25.1 *vs.* 7.0 (HR =0.26). The 12-month OS rate was 91.6% *vs.* 81.0% (HR =0.51).

T-DXd is the most powerful agent in 2nd- or more lines of anti-HER2 therapy, so the National Medical Products Administration of China has included it in the list of breakthrough treatment drugs, which almost synchronizes with Europe and America. It is believed that T-DXd treatment will change current clinical practice and bring benefits to patients with TKI failure. Although T-DXd is not yet available in China, patients are encouraged to actively participate in domestic or international clinical trials of anti-HER2 ADCs.

The efficacy data of T-DM1 are not excellent enough compared with the new generation anti-HER2 ADCs. Despite this, it has been approved that the efficacy of T-DM1 is superior to that of lapatinib + capecitabine based

on the results from the EMILIA trial with mPFS 9.6 *vs.* 6.4 months (21). In the phase III TH3RESA study, T-DM1 significantly improved PFS and OS compared with the regimen of physician's choice in patients with progression on ≥ 2 anti-HER2 targeted treatments (trastuzumab and lapatinib at least). The mPFS was prolonged by 2.9 months (6.2 *vs.* 3.3 months, $P < 0.0001$) and median OS was prolonged by 6.9 months (22.7 *vs.* 15.8 months, HR = 0.68, $P = 0.0007$) (22). Thus, T-DM1 is still the treatment option for patients with anti-HER2 TKI failure.

For patients who have not taken pertuzumab, if previous taxane failed, then the regimen of pertuzumab + trastuzumab combined with non-taxane chemotherapy can be considered for patients with anti-HER2 TKI failure, such as eribulin, vinorelbine and capecitabine.

The phase II JBCRG-M03 study evaluated eribulin in combination with pertuzumab + trastuzumab in patients with HER2-positive mBC who previously received adjuvant or 1st-line trastuzumab and a taxane. The mPFS was 9.2 months for all patients [95% confidence interval (CI): 7.0–11.4 months]. As the 2nd-line treatment, the mPFS was 10.2 months (95% CI: 7.5–12.8 months) in patients treated without prior pertuzumab (23). The PHEREXA study assessed the efficacy of capecitabine + pertuzumab + trastuzumab in patients who experienced disease progression during or after trastuzumab-based therapy and had received a prior taxane. The mPFS was 11.1 months and OS was 36.1 months (24). The results of the VELVET trial Cohort 1 showed that the combination of vinorelbine + pertuzumab + trastuzumab is active in the 1st-line setting and reasonably well tolerated. The investigator-assessed ORR was 74.2% (95% CI: 63.8–82.9%). The mPFS was 14.3 months (95% CI: 11.2–17.5 months) in the intent-to-treat population (25).

Thus it can be seen that the patients who experience disease progression on trastuzumab + taxane but were treated without prior pertuzumab can get a mPFS of ~10–15 months from the regimen of pertuzumab + trastuzumab combined with non-taxane chemotherapy. Certainly, the data on the application of this regimen for patients after TKI is insufficient, but based on the existing data, it is worth trying in this subgroup of patients.

Switching to another TKI plus chemotherapy can also be considered for patients in whom prior anti-HER2 TKI has failed. Because TKI-related phase III trials exclude patients who have previously used TKI and capecitabine treatment, the current data are mostly from real-world research and phase II trials.

The results of a real-world study suggested that patients with lapatinib failure can significantly benefit from pyrotinib treatment compared with T-DM1 (26). The mPFS was 6.0 months (95% CI: 4.7–7.3 months) with pyrotinib and 4.2 months (95% CI: 3.6–4.8 months) with T-DM1 ($P = 0.044$). ORR was 16.3% *vs.* 20.0% ($P = 0.629$) and CBR was 45.5% *vs.* 40.0% ($P = 0.573$) in the two cohorts. Subgroup analysis showed a mPFS of 8.1 months (95% CI: 4.8–11.4 months) *vs.* 4.4 months (95% CI: 3.8–5.0 months, $P = 0.013$) in patients who benefited from prior lapatinib treatment.

A phase II trial evaluated the combination of neratinib and vinorelbine in patients previously treated with lapatinib; CBR was 42% and mPFS was 22.7 weeks (95% CI: 12.0–41.0 weeks) by independent assessment (27). Another phase II trial investigating the combination of neratinib with capecitabine showed an ORR of 57% (95% CI: 18–90%), CBR of 71% (95% CI: 29–96%) and mPFS of 35.9 weeks (95% CI: 18.9–60.1 weeks) in patients with prior lapatinib exposure (28). The third phase II study evaluating the efficacy of neratinib plus paclitaxel reported the ORR for all evaluable patients was 73% (95% CI: 62.9–81.2%) and for patients with prior lapatinib treatment it was 77% (29).

Based on these data, mPFS of 5.7–9.0 months and ORR of 57–77% were achieved by using another TKI agent for patients with prior anti-HER2 TKI failure, so this therapy is certainly valuable in clinical practice.

Recommending patients to enter strictly designed clinical trials after prior TKI failure is emphasized in the CSCO BC Guidelines 2022, which is a therapy suggestion that is highly compliant with the rights and interests of patients. There are several clinical trials of anti-HER2 ADCs, such as ARX788, MRG002, A166 and so on, that are recruiting patients with prior TKI failure in China.

ARX788 is composed of an anti-HER2 monoclonal antibody (mAb), a non-cleavable linker and AS269 (a tubulin inhibitor). ARX788 was effective in T-DM1-resistant *in vitro* and *in vivo* models of HER2-positive BC (30). In the phase I ACE-Breast-01 trial, in the 1.5 mg/kg cohort of ARX788 (the recommended phase II dose), the median lines of previous treatments for metastasis were 4 (range, 2–12) and 79.3% of these patients had failed a prior TKI. The ORR was 65.5%, the DCR was 100% and the mPFS was 17.02 months (31). The novel ADC ARX788 demonstrated outstanding efficacy in the TKI failure population, and the phase Ib/II clinical trial of ARX788 in patients with prior TKI is ongoing.

MRG002 is composed of a humanized anti-HER2 mAb,

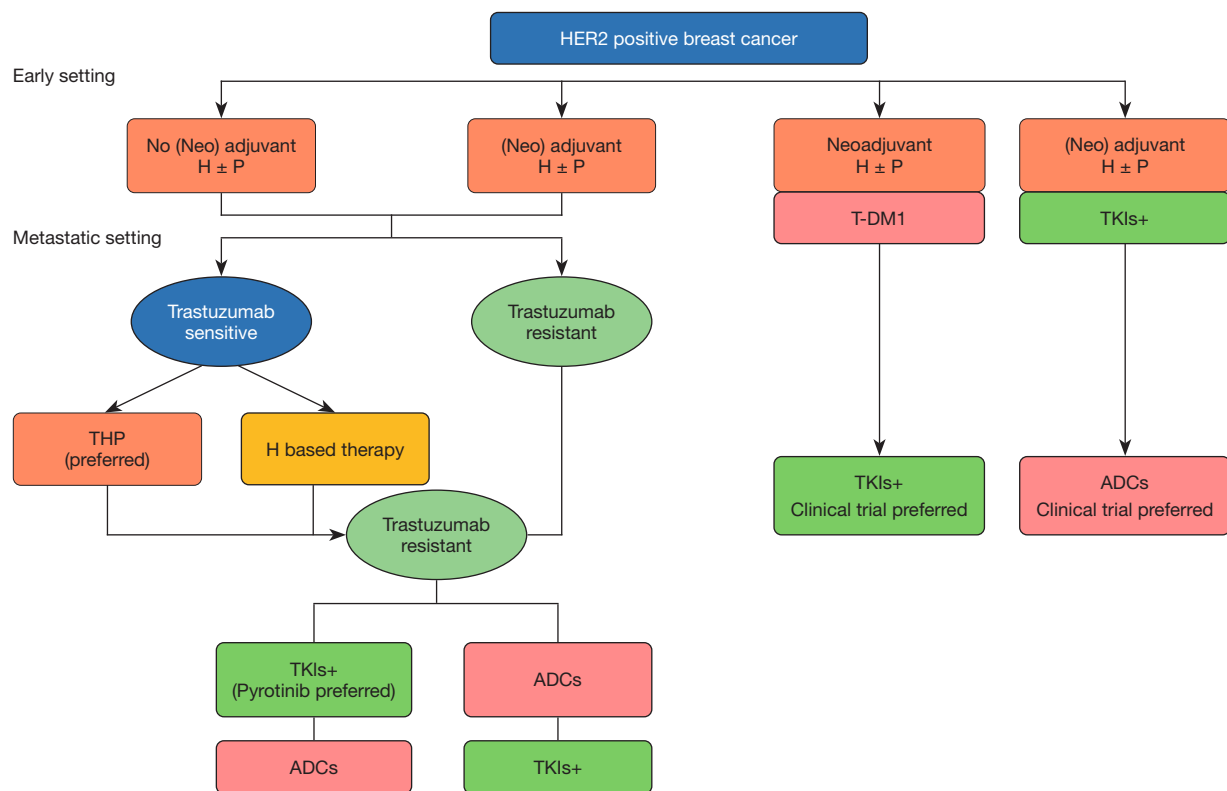


Figure 1 Algorithm for treatment of HER2-positive BC in the metastatic setting. HER2, human epidermal growth factor receptor 2; H, herceptin (trastuzumab); P, pertuzumab; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; THP, taxane+herceptin+pertuzumab; ADC, antibody-drug conjugate; BC, breast cancer.

a valine-citrulline linker and a microtubule disrupting monomethyl auristatin E (MMAE). In a preclinical study, MRG002 showed superior potency than trastuzumab and T-DM1 in mouse xenograft models (32). A phase I trial of MRG002 was performed in heavily pretreated patients with HER2-positive mBC. The median of previous treatments was 5 (range, 2–19) in a total of 55 patients, 84% of whom had prior TKI failure. The ORR was 55% in the total population and 74% in the cohort with liver metastasis. MRG002 displayed superior efficacy in the TKI failure subgroup; the phase II trial of MRG002 in patients with TKI pretreated HER2-positive mBC is currently recruiting.

A166 is composed of an anti-HER2 antibody conjugated with a monomethyl auristatin F (MMAF)-derived payload (duostatin-5) via a cleavable linker. In part 2 of the phase I trial investigating A166 in trastuzumab-pretreated patients, 94.8% of whom had prior TKI treatment, the ORR was 73.9% and mPFS was 12.3 months in the 4.8 mg/kg cohort. A166 showed excellent antitumor activity in heavily pretreated HER2-positive mBC patients and further clinical

trials are warranted.

As a typical subtype of the classification treatment strategy, HER-2-positive BC has entered the era of “accurate classification and precise stratification” (Figure 1) (33). Patients really need more optimized, precise subsequent therapy after failure to anti-HER2 TKI treatment. There will be more results of randomized controlled clinical trials and real-world research as evidence to guide therapy in the future, and bring more benefits to patients in this stratified subgroup.

Acknowledgments

Funding: This work was supported by The National Natural Science Foundation of China (No. 81602314).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tbcrcr.com>).

amegroups.com/article/view/10.21037/tbcr-22-32/coif). ZJ serves as the Editor-in-Chief of *Translational Breast Cancer Research*. 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.

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doi: 10.21037/tbcr-22-32

Cite this article as: Bian L, Li F, Jiang Z. Thoughts on therapy strategy in the era of “after anti-HER2 TKI” in CSCO BC Guidelines 2022. *Transl Breast Cancer Res* 2022;3:26.