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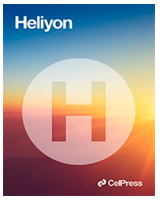

Review article

Impact of HER2-targeting antibody drug conjugates in treatment strategies for patients with breast cancer

Hanghang Ma [a,b], Jianbin Li [a,*]

[a] Senior Department of Oncology, Fifth Medical Center of PLA General Hospital, Beijing, China
[b] Outpatient Department of the 55th Retired Cadre Rest Center in Haidian District, Beijing, China

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ABSTRACT

Antibody drug conjugates (ADCs) are novel drugs that exert specific cytotoxicity against breast cancer. Although ADCs such as trastuzumab emtansine and trastuzumab deruxtecan have significantly improved survival for patients with breast cancer expressing HER2, there is still controversy over options after ADCs. The radiotherapy and ablation should also be used as an effective strategy for oligoprogressions. Herein, we conducted a review of ADCs, and then discussed several strategies to maximize the potential benefit to patients with HER2 expression breast cancer.

1. Background

Breast cancer has been the most common malignant tumor, in which human epidermal growth factor receptor 2 (HER2) is a very important biomarker. These patients have the characteristics of fast disease progression, high malignancy and poor prognosis [1]. Target therapy is the basic treatment for patients with HER2 positive breast cancer. Enhancing the ability to recognize specific tumor cells and improving tumor killing effects is a key research hotspot in the development of new targeted drugs. Connecting antibodies with small molecule chemical drugs to form antibody drug conjugates (ADCs) can exert targeted cell killing effects, which is a new choice for tumor treatment [2].

At present, there are two approved ADCs for breast cancer with HER2 expression, including trastuzumab emtansine (T-DM1), and trastuzumab deruxtecan (T-DXd),. Clinical practice has been changed as these ADCs included in guidelines. While the conundrum about therapies after anti-HER2 ADCs has been highlighted [3]. Therefore, we would like to discuss the hot issues of treatment sequencing for patients after ADCs.

2. Timing of using ADCs

The essence of ADC is to deliver chemotherapy drugs (payloads) to tumor tissue through targeted action, reducing the impact on normal tissue during transportation. Compared with traditional chemotherapy, ADC drugs can increase the local drug concentration of tumors and overcome the systemic toxicity caused by chemotherapy, thereby expanding the treatment window. Although ADC can exempt some patients from receiving chemotherapy, the KRISTINE study [4] shows that compared to chemotherapy, the T-DM1 combined with pertuzumab achieves a lower pathological complete response(pCR) rate, indicating that it is too early for ADC to

* Corresponding author. Fifth medical center of PLA general hospital, China.
E-mail address: lijianbin@csco.org.cn (J. Li).

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replace traditional chemotherapy.

Based on existing evidence, we have sorted out the timing of ADC use in different stages and populations. KATHERINE study [5] suggests patients received T-DM1 could achieve a longer survival than trastuzumab for those who did not achieve pCR in neoadjuvant setting. On this basis, T-DM1 is the only ADC approved in early breast cancer. However, there is still a lack of direct head-to-head studies on whether T-DM1 is superior to the dual target of HP in patients who have not achieved pCR after neoadjuvant therapy [6]. While in the KATHERINE study, the incidence of grade 3 or above adverse events in the T-DM1 treatment group has reached 25.7 %, significantly higher than that in the control group. The interruption rate of treatment due to adverse reactions was also as high as 18.0 % in T-DM1 group. Although the accessibility of T-DM1 and HP has been addressed in China, the high proportion of drug interruption rate will have negative impact on the clinical selection of T-DM1.

ADCs could also play an important role in the stage of recurrence and metastasis. DESTINY-Breast03 study [7] showed that compared to T-DM1, T-DXd can further improve progression free survival (PFS) in patients with HER2-positive metastatic breast cancer (HR = 0.28, 95 % CI, 0.22–0.3). On this basis, T-DXd has been included as the standard therapy regimen in the second line treatment of HER2 positive breast cancer. However, as a novel tyrosine kinase inhibitor (TKI), pyrotinib has shown significant efficacy in both trastuzumab sensitive and resistant populations. limited data [8] has shown that in patients who have previously failed treatment with lapatinib, pyrotinib is more effective than T-DM1. Compared to ADCs, pyrotinib has better accessibility and more controllable toxicity. Therefore, after the failure of trastuzumab treatment, pyrotinib has been one of the prioritized recommended regimens, than T-DM1 or T-DXd, in Chinese society of clinical oncology breast cancer guidelines [6].

For patients with HER2-low metastatic breast cancer, the DESTINY-breast 04 study [9] compared the efficacy of T-DXd with the chemotherapy regimen chosen by clinicians. The results showed that for patients who had previously received 1–2 lines treatment, T-DXd had significantly better efficacy than the chemotherapy chosen by clinicians, especially in the hormone receptor (HR) positive patients.

As an ADC drug targeting TROP-2, ASCENT study [10] explored the application of sacituzumab govitecan (SG) in triple negative breast cancer after second line treatment. The results showed that compared with the chemotherapy selected by clinicians, SG could significantly improve the PFS (HR = 0.43,95 % CI: 0.35–0.54) and overall survival (HR = 0.51,95 % CI: 0.41–0.62) of patients. In TROPICs-02 study [11], researches explored the treatment options for patients with HR positive, HER2 negative breast cancer treated after taxanes and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. The results also showed that SG can improve the PFS and OS of patients compared with chemotherapy, further indicating that SG can significantly prolong PFS in both HER2-low and HER2-0 populations.

At this moment, there are as many as 700 ADC drugs under research worldwide, including Dato-Dxd, MRG002, ARX788, SKB264 and other emerging ADCs [12]. These drugs are also playing an important role in anti-HER2 therapies, especially in addressing the poor cost-effectiveness of present ADCs [13]. A real-world study [14] showed in patients with HER2-positive previously treated with TKIs, both T-DXd and other novel anti-HER2 ADCs yielded statistically significant better PFS than T-DM1 did, with tolerable toxicities. The research and development of these drugs may change the clinical diagnosis and treatment practice of breast cancer in the near future [15].

Perspectives: 1. For patients with HER2 positive breast cancer who have not reached pCR after neoadjuvant therapy, multiple factors such as efficacy and adverse reactions during neoadjuvant therapy, postoperative pathology should be taken into account to decide the adjuvant target therapy. T-DM1 or trastuzumab-pertuzumab are optional; 2. In patients with HER2 positive failed to trastuzumab, T-DXd or pyrotinib could be considered based on the cost-effectiveness of these two drugs; 3. T-DXd or SG are both options for patients with HER2 low expression after standard treatment. T-DXd is preferred for hormone receptor positive patients.

3. What should we do after resistance to ADCs

Multiple factors may contribute to ADC resistance. For example, impaired Endo-II expression can delay HER2 internalization and ultimately result in T-DM1 resistance [16]. Tumor necrosis factor α (TNF α)induced upregulation of MUC4 can conceal the binding epitope of trastuzumab, leading to ADC resistance [17]. Overexpression of ROR1 can also lead to drug resistance in ADC through the Hippo/YAP pathway [18]. Heat shock protein 90 (HSP90) can maintain the stability of HER2 protein. So, inhibiting HSP90 can lead to ubiquitin dependent degradation of HER2, and antigen downregulation leads to the inability of ADC to bind to targeted receptors, resulting in new drug resistance. Meanwhile, the PI3K/AKT pathway is an important downstream pathway of HER2. Studies [19] have shown that upregulation of PTEN can block the continuously activated PI3K/Akt signaling pathway, thereby reversing ADC drug resistance and effectively inhibiting tumor development. In addition, decreased hydrolysis or acidification function of lysosomal proteins or loss of lysosomal transport protein function, inhibition of linker cleavage, etc. can also lead to drug resistance in ADCs [20].

To overcome ADC resistance, it is necessary to further optimize payload and linker to enhance stability of ADCs. Meanwhile, improve toxin utilization, and expand new toxin pathways is helpful to increase ADC efficacy [21]. Drug resistance can also be overcome in combination with other targeted therapies, such as immunotherapy, who offers a promising direction for enhancing outcomes in patients with HER2-positive breast cancer [22]. The KATE2 study [23] showed that in the subgroup of patients with PD-L1 positive breast cancer progressed with trastuzumab, T-DM1 combined with atezolizumab showed a trend towards improving patient survival compared to T-DM1 alone. In the DESTINY-Breast 07 study [24], T-DXd combined with pertuzumab could also achieve good objective response rates.

Perspectives: 1. With the promotion of hierarchical and classified treatment of breast cancer, dynamic monitoring technology, including circulating tumor cells, ctDNA, and second-generation sequencing technology, during the use of ADCs can be considered to predict drug resistance. 2. During the process of receiving ADC treatment, the occurrence of drug resistance can also be reduced

through combination therapy, target replacement, and other methods.

4. Options for patients with HER2 positive after ADCs

The clinical scenario of the first and second treatment lines is clearly defined, According to Destiny Breast-02 study [25], T-DXd is the preferred second-line therapy after progression on a taxane and trastuzumab. T-DM1 is a second-line treatment option after progression on a taxane and trastuzumab in cases where trastuzumab deruxtecan is not available. It is recommended to switch to third-generation ADCs after T-DM1, while there is lack of evidence for the target therapy after third generation of ADCs. There is no consensus on subsequent treatment lines, as there are no available clinical data of therapies beyond T-DXd progression [26]. Currently, multiple real-world studies and clinical studies are exploring the interactions between different ADCs and drug selection after ADC treatment. Before that, decision making must be supported by patient- and disease-related factors, including overall tolerability, clinical benefit to prior therapies, disease burden, and eventual central nervous system (CNS) involvement.

Building on previous experience with trastuzumab, maintenance of HER2 blockade beyond progression provides clinical benefit and prolongs survival, the sustained inhibition of the HER2 pathway is the basis for the long-term benefits of this kind of patients. In addition to ADCs, other anti HER2 drugs can also be chosen for treatment. In the DESTINY-Breast 03 study, it was found that after the progression of T-DXd treatment, 49 % (64/130) of patients chose T-DM1, and about 29 % (38/130) of patients chose the anti-HER2 TKI regimens. The results showed that the therapeutic effect of TKI was superior to T-DM1. HER2CLIMB study [27] explored the therapeutic regimens for patients who had received trastuzumab, pertuzumab and T-DM1, 48 % of which had central nervous system metastasis. The results suggest that combination of tucatinib can further prolong the PFS and OS, and also further reduce the risk of brain metastasis progression [28]. In the NALA study [29], 54 % of patients had previously received T-DM1 treatment, and the results showed that compared to the use of lapatinib, neratinib can further prolong the PFS (HR = 0.76, 95 % CI: 0.63–0.93) and delay the treatment time for central nervous system metastasis. As a modified drug of trastuzumab, SOPHIA study [30], 91 % of patients in which had previously received T-DM1 treatment, also proved that margetuximab can improve patient PFS. While OS was not prolonged by margetuximab, the CD16A genotype suggested an OS benefit of margetuximab in CD16A-158FF patients. In this context, preferred chemotherapeutic regimens with recognized activity in HER2-positive breast cancer are represented by anthracyclines, eribulin, and vinorelbine. Of note, several phase III clinical trials are conducted to find the survival benefit from novel ADCs like ARX788, SKB264 after progression of T-DXd, which may give us more evidence to tell us the optimal drugs after T-DXd.

Perspectives: 1. For patients with HER2 positive breast cancer, T-DXd are preferred after taxane and trastuzumab failure; 2. After the progression of T-DXd, continuous anti-HER2 treatment can bring benefits to patients. TKI such as tucatinib and pyrotinib, or other targeted drugs such as margetuximab, can be considered. participated in suitable clinical studies can also be an option; 3. Due to the lack of data on drug resistance, it is recommended to receive tumor re-biopsy after T-DXd in order to better guide subsequent treatment.

5. Options for patients with HER2 low expression after ADCs

HER2 low expression is a unique and clinically relevant population [31], which could benefit from the treatment of novel ADCs and promote the independence of this group of patients from the previously HER2 negative population. DAISY study [32] explored the benefits of T-DXd in breast cancer under different HER2 states, and the results showed that the ORR of T-DXd in tumor patients with HER2-0, HER2-low, and HER2-positive metastatic breast cancer was 30 %, 38 %, and 71 %, respectively. The expression level of HER2 will directly affect the degree of treatment benefit. In a translational analysis of the same trial, a greater uptake of T-Dxd in HER2-low cells than in HER2-nul cells was reported. Furthermore, it was also stressed that if the spatial distribution of HER2 clustered closer, the response was higher [33]. Therefore, it is necessary to adopt new and more sensitive methods to express the minimum threshold of HER2 expression. In the latest ASCO/CAP guidelines, the pathological report notes for HER2 have been supplemented and updated, highlighting the correlation between IHC 0 and 1+and treatment, as well as best practice recommendations on how to distinguish them [34].

Anyway, the emergence of T-DXd opens a new mode of breast cancer with HER2 low expression. Such patients are stratified based on hormone receptor status, and also show different treatment strategies and outcomes [35]。

5.1. HR positive/HER2 low expression

For patients with HER2 low expression, hormone receptor positive is more common. While it is unclear whether there is an interactive effect between HR and HER2 signaling pathways in this kind of patients [36]. According to the enrolment of patients in the DESTINY-breast 04 study, only those failed to taxane and CDK4/6 inhibitor are considered to receive ADC treatment. While in DESTINY-breast 06 study [37], trastuzumab deruxtecan could be recommended after resistance upon at least 2 lines of endocrine therapy or progression within first 6 months of endocrine therapy with CDK4/6 inhibitor for HER-low and -ultralow in metastatic breast cancer without any prior chemotherapy.

In the 2023 San Antonio Breast Cancer Conference, the real-world study from MD Anderson Cancer Center [38] analyzed use of ADCs in 274 patients with advanced breast cancer with low HER2 expression. Among them, 38 % had received $\geq$ 3-line treatment. The results showed that patients treated with T-DXd as the initial ADC had significantly longer PFS (7.6 vs 4.6 months, P = 0.005) and OS (22.9 vs 16.4 months, P = 0.049); However, in 33 patients receiving sequential ADC treatment, there was no significant difference in PFS (HR 1.02, P = 0.97) and OS (HR 0.78, P = 0.84) between SG sequential T-DXd and T-DXd sequential SG. From these real-world

data, it can be seen that T-DXd as the initial treatment for HER2 low expression has better survival, while no significant difference in survival benefits between T-DXd and SG in different sequential ways. Choosing ADCs with other targets and payloads may be a reasonable treatment strategy.

Choosing another ADC after one ADC needs to consider the issue of cross resistance. Returning to the path of endocrine therapy or chemotherapy might be more reasonable. The BYLIEVE study [39] confirmed that switching to the PI3K inhibitor can also improve PFS in patients after CDK4/6 inhibitor failure. CAPItello 291 study [40] also demonstrated that capivasertib resulted in significantly longer progression-free survival among patients with HR-positive breast cancer whose disease had progressed endocrine therapy with or without a CDK4/6 inhibitor for patients with AKT pathway-altered. The MANTAIN study is the first study to challenge the re-use of CDK4/6 inhibitor after progression, and the results showed that compared to endocrine monotherapy, switching to ribociclib after the progression of palbociclib can improve patient PFS to some extent. Besides, EMERALD study [41] and OlympiAD study [42] also demonstrated that patients with ESR1 or BRCA mutations, elacestrant or olaparib could be a better choice than standard therapy. Some real-world studies [43] have also proved the differences between switching to another CDK4/6 inhibitor and HDAC inhibitor after palbociclib. Unfortunately, these studies did not further distinguish HER2 expressions, which needs more data to explore these differences.

Perspectives: 1. For patients with HR positive and HER2-low or HER2 ultralow expression, endocrine therapy combined with CDK4/6 inhibitors is preferred. After that, T-DXd treatment can be considered; 2. After the failure of ADC, a reasonable selection of subsequent treatments should be made based on molecular characteristics, including some new targets such as HDAC inhibitors, AKT inhibitors, PIK3CA inhibitors, and other novel pathways.

5.2. HR negative/HER2 low or HER2-0

HR negative/HER2 low expression or no expression is a group of highly diversified and heterogeneous tumors, with a high risk of local and remote recurrence and poor patient survival. In this population, there is a more significant difference between low HER2 expression tumors and no expression [44]. Therefore, further classifying those patients into HER2 low expression and no expression can provide more effective personalized treatments.

For those patients, taxanes combined with PD-1 inhibitor showed a longer PFS than chemotherapy alone [45]. After that, ADC is recommended. For patients with HER2 no expression, SG is preferred. For patients with HER2 low expression, SG or T-DXd can be chosen. Several clinical studies have explored the feasibility of combining ADC with other treatments. In the BEGONIA study [46], cohort 7 explored the combination of Dato-Dxd and durvalumab. Results showed an objective response rate of up to 79 %, demonstrating controllable safety and high and persistent response rates. A phase 2 study [47] explored the effect of SKB264 on triple negative breast cancer patients. Among them, 89.8 % of patients received $\geq$3 lines of treatment for metastatic breast cancer before enrollment. The results suggest that the median PFS of SKB264 can reach 5.7 months, which has a good application prospect. After ADC treatment, including BRCA inhibitors, anti-angiogenic inhibitors can become an alternative for this kind of patients.

Perspectives: 1. Triple negative breast cancer should be further divided into HER2 low expression and non-expression, so as to provide multiple treatment strategies; 2. After ADCs, effective treatments should be selected based on BRCA or other mutations.

6. ADCs and local treatment in special organ

6.1. Brain metastases

As an effective systemic treatment, ADCs can also play an important role in treating some refractory lesions such as brain metastases. Previous studies on DESTINY-Breast 01 and DESTINY-Breast 03 have confirmed that T-DXd can also have sustained clinical activity in HER2 positive patients with brain metastases. However, both studies excluded patients with active brain metastases. DEBBRAH study [48] aims to explore the role of T-DXd in advanced breast cancer with different HER2 expression, including patients with multiple brain metastases such as stability, activity or meningeal metastasis. At present, some published cohort results show that T-DXd is effective in the treatment of HER2 positive breast cancer brain metastasis, and all untreated, stable or active patients show efficacy. In addition, the TUXEDO-1 study [49] suggests that for patients with active brain metastases on the median treatment line 3, the intracranial remission rate can reach 73.3 % (11/15), and the median PFS can reach 14 months. In DESTINY-Breast 12 study, T-DXd showed persistent overall and intracranial clinical activity in patients with HER2 positive, including a large cohort of stable/active brain metastasis, without any new safety signals. In HER2CLIMB study [50] and PERMATE study [51], the tyrosine kinase inhibitor, tucatinib or pyrotinib, also provided a clinically meaningful survival benefit for patients with HER2 positive metastatic breast cancer.

Although T-DXd can play an important role in brain metastases, especially in active brain metastases, the importance and necessity of local treatment like surgery and radiotherpay should not be ignored. A prospective study [52] suggests that pyrotinib combined with radiotherapy can reduce the risk of intracranial disease progression, resulting in a central nervous system symptom relief rate of up to 85 %. Therefore, for patients with indications for local treatment, active local treatment combined with targeted therapy should be carried out to avoid delaying.

Perspectives: For patients with active brain metastases, appropriate local treatment should be selected, combined with systemic anti-tumor drugs. T-DXd is preferred for patients with HER2 expression, while pyrotinib can also be considered for patients with HER2 positive.

6.2. Oligoprogression

The progression of the disease after ADC treatment is inevitable, while in clinical practice, it may be encountered that ADC treatment is effective, and during the maintenance treatment stage, one or a few lesions are found to have enlarged lesions due to drug resistance. Oligoprogression stems from clonal heterogeneity and tumor evolution, leading to the emergence of drug-resistant clone drivers in some lesions that do not exist in other areas [53]. There is still a lack of direct consensus on how to conduct tumor assessment for oligoprogression, especially in the era of ADC [54]. From the perspective of saving medical resources, it is more cautious to judge ADC resistance after oligoprogression occurs.

The most common occurrence of oligoprogression is in the liver, lungs, lymph nodes, and other areas. There is still controversy over whether to continue ADC or switch to other drug treatments after oligoprogression. Local treatment is the main treatment strategy for oligoprogression, including radiotherapy, thermal ablation, and surgery. The CURB study [55] showed that combining local therapy with systemic therapy, including local ablation, radiotherapy, and other methods, can bring survival benefits to patients. On the one hand, ablation can reduce drug-resistant tumor lesions, and on the other hand, the systemic immune response induced by ablation may also play an important role in systemic lesions [56].

Perspectives: 1. Attention should be paid to potential oligoprogression during targeted therapy, and caution should be exercised when evaluating the efficacy of ADC treatment failure; 2. When there is oligo-progression, local treatments such as ablation and radiation therapy can be considered to improve the therapeutic effect.

7. Conclusion

The introduction of ADC drugs has brought more opportunities to patients with breast cancer. While with the increase usage of ADCs, the number of drug resistance is also increasing. Fortunately, the acceleration of drug development target different pathways provide more options based on molecular diagnosis. The promotion of medical insurance further address the challenge of cost-effectiveness from novel target drugs [57]. A large number of studies are needed to explore treatment optimization after ADCs. Before that, the rational deployment of existing drugs will become an important issue for a long time.

CRediT authorship contribution statement

Jianbin Li: Writing – original draft, Validation, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation. **Hanghang Ma:** Revised the manuscript.

Data availability

Data extracted from https://pubmed.ncbi.nlm.nih.gov/with research terms “breast”, “antibody drug conjugate”, “HER2”. Data extracted on July 14, 2024. No new datasets have been generated or analyzed for this article.

Jianbin Li conceived and drafted the manuscript designed finalized article, and supervised the work. Hanghang Ma revised the manuscript. All the authors read and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Marra, S. Chandarlapaty, S. Modi, Management of patients with advanced-stage HER2-positive breast cancer: current evidence and future perspectives, Nat. Rev. Clin. Oncol. 21 (3) (2024) 185–202.
[2] J. Li, Z. Jiang, Antibody drug conjugates in breast cancer in China: highlights, challenges, and prospects, Cancer 130 (S8) (2023) 1371–1377.
[3] M. Di Maio, C. Bighin, F. Schettini, T. Ruelle, L. Marandino, A. Fabi, C. De Angelis, M. Giuliano, P. De Placido, M. De Laurentiis, et al., Evolving treatments and outcomes in HER2-Positive metastatic breast cancer: data from the GIM14/BIOMETA study, Breast 72 (2023) 103583.
[4] S.A. Hurvitz, M. Martin, K.H. Jung, C.S. Huang, N. Harbeck, V. Valero, D. Stroyakovskiy, H. Wildiers, M. Campone, J.F. Boileau, et al., Neoadjuvant trastuzumab emtansine and pertuzumab in human epidermal growth factor receptor 2-positive breast cancer: three-year outcomes from the phase III KRISTINE study, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 37 (25) (2019) 2206–2216.
[5] G. von Minckwitz, C.S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, et al., Trastuzumab emtansine for residual invasive HER2-positive breast cancer, N. Engl. J. Med. 380 (7) (2019) 617–628.
[6] J. Li, Z. Jiang, Chinese society of clinical oncology breast cancer (CSCO BC) guidelines in 2022: stratification and classification, Cancer biology & medicine 19 (6) (2022) 769–773.
[7] J. Cortés, S.B. Kim, W.P. Chung, S.A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.M. Tseng, V. Petry, C.F. Chung, et al., Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer, N. Engl. J. Med. 386 (12) (2022) 1143–1154.

[8] F. Li, F. Xu, J. Li, T. Wang, L. Bian, S. Zhang, Z. Jiang, Pyrotinib versus trastuzumab emtansine for HER2-positive metastatic breast cancer after previous trastuzumab and lapatinib treatment: a real-world study, Ann. Transl. Med. 9 (2) (2021) 103.
[9] S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, et al., Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer, N. Engl. J. Med. 387 (1) (2022) 9–20.
[10] A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, et al., Sacituzumab govitecan in metastatic triple-negative breast cancer, N. Engl. J. Med. 384 (16) (2021) 1529–1541.
[11] H.S. Rugo, A. Bardia, F. Marmé, J. Cortes, P. Schmid, D.T.O. Loirat, E. Ciruelos, F. Dalenc, P.G. Pardo, K.L. Jhaveri, R. Delaney, O. Fu, L. Lin, W. Verret, S. M. Tolaney, Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 40 (29) (2022) 3365–3376.
[12] G. Nader-Marta, C. Molinelli, V. Debien, D. Martins-Branco, P. Aftimos, E. de Azambuja, A. Awada, Antibody-drug conjugates: the evolving field of targeted chemotherapy for breast cancer treatment, Therapeutic advances in medical oncology 15 (2023) 17588359231183679.
[13] J. Yang, J. Han, N. Zeng, X. Yan, Cost-effectiveness of trastuzumab deruxtecan in previously treated human epidermal growth factor receptor 2-low metastatic breast cancer, Therapeutic advances in medical oncology 15 (2023) 17588359231169983.
[14] C. Ji, F. Li, Y. Yuan, H. Zhang, L. Bian, S. Zhang, T. Wang, J. Li, Z. Jiang, Novel anti-HER2 antibody-drug conjugates versus T-DM1 for HER2-positive metastatic breast cancer after tyrosine kinase inhibitors treatment, Oncol. 28 (10) (2023) e859–e866.
[15] H. Huang, D. Wu, H. Miao, Y. Tang, C. Liu, H. Fang, X. Meng, S. Wang, Q. Zhu, X. Wang, et al., Accelerating the integration of China into the global development of innovative anticancer drugs, Lancet Oncol. 23 (11) (2022) e515–e520.
[16] Y.F. Chen, Y.Y. Xu, Z.M. Shao, K.D. Yu, Resistance to antibody-drug conjugates in breast cancer: mechanisms and solutions, Cancer Commun. 43 (3) (2023) 297–337.
[17] S. Bruni, F.L. Mauro, C.J. Proietti, R.I. Cordo-Russo, M.A. Rivas, G. Inurrigarro, A. Dupont, D. Rocha, E.A. Fernández, E.G. Deza, et al., Blocking soluble TNFα sensitizes HER2-positive breast cancer to trastuzumab through MUC4 downregulation and subverts immunosuppression, Journal for immunotherapy of cancer 11 (3) (2023) e005325.
[18] S.S. Islam, M. Uddin, A.S.M. Noman, H. Akter, N.J. Dity, M. Basiruzzman, F. Uddin, J. Ahsan, S. Annoor, A.A. Alaiya, et al., Antibody-drug conjugate T-DM1 treatment for HER2+ breast cancer induces ROR1 and confers resistance through activation of Hippo transcriptional coactivator YAP1, EBioMedicine 43 (2019) 211–224.
[19] Z. Dong, Z. Huang, S. Li, Y. Wang, Y. Yao, X. Yang, X. Xu, Nanoparticles (NPs)-mediated systemic mRNA delivery to reverse trastuzumab resistance for effective breast cancer therapy, Acta Pharm. Sin. B 13 (3) (2023) 955–966.
[20] F.W. Hunter, H.R. Barker, B. Lipert, F. Rothé, G. Gebhart, M.J. Piccart-Gebhart, C. Sotiriou, S.M.F. Jamieson, Mechanisms of resistance to trastuzumab emtansine (T-DM1) in HER2-positive breast cancer, Br. J. Cancer 122 (5) (2020) 603–612.
[21] J.Z. Drago, S. Modi, S. Chandarlapaty, Unlocking the potential of antibody-drug conjugates for cancer therapy, Nat. Rev. Clin. Oncol. 18 (6) (2021) 327–344.
[22] E. Agostinetto, F. Montemurro, F. Puglisi, C. Criscitiello, G. Bianchini, L. Del Mastro, M. Introna, C. Tondini, A. Santoro, A. Zambelli, Immunotherapy for HER2-positive breast cancer: clinical evidence and future perspectives, Cancers 14 (9) (2022).
[23] L.A. Emens, F.J. Esteva, M. Beresford, C. Saura, M. De Laurentiis, S.B. Kim, S.A. Im, Y. Wang, R. Salgado, A. Mani, et al., Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial, Lancet Oncol. 21 (10) (2020) 1283–1295.
[24] F. Andre, E.P. Hamilton, S. Loi, C.K. Anders, P. Schmid, D. Stroyakovskiy, R. Villanueva, J.L. Pedrini, D.C. Doval, B. Zurawski, et al., DESTINY-Breast07: dose-expansion interim analysis of T-DXd monotherapy and T-DXd + pertuzumab in patients with previously untreated HER2+ mBC, J. Clin. Oncol. 42 (16_suppl) (2024), 1009-1009.
[25] F. André, Park Y. Hee, S.B. Kim, T. Takano, S.A. Im, G. Borges, J.P. Lima, S. Aksoy, J. Gavila Gregori, M. De Laurentiis, 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 (London, England) 401 (10390) (2023) 1773–1785.
[26] G. Antonarelli, C. Corti, P. Tarantino, B.T. Salimbeni, P. Zagami, A. Marra, D. Trapani, S. Tolaney, J. Cortes, G. Curigliano, Management of patients with HER2-positive metastatic breast cancer after trastuzumab deruxtecan failure, ESMO open 8 (4) (2023) 101608.
[27] N.U. Lin, R.K. Murthy, V. Abramson, C. Anders, T. Bachelot, P.L. Bedard, V. Borges, D. Cameron, L.A. Carey, A.J. Chien, et al., Tucatinib vs placebo, both in combination with trastuzumab and capecitabine, for previously treated ERBB2 (HER2)-Positive metastatic breast cancer in patients with brain metastases: updated exploratory analysis of the HER2CLIMB randomized clinical trial, JAMA Oncol. 9 (2) (2023) 197–205.
[28] C. Criscitiello, C. Corti, M. De Laurentiis, G. Bianchini, B. Pistilli, S. Cinieri, L. Castellan, G. Arpino, P. Conte, F. Di Meco, et al., Tucatinib's journey from clinical development to clinical practice: new horizons for HER2-positive metastatic disease and promising prospects for brain metastatic spread, Cancer Treat Rev. 120 (2023) 102618.
[29] C. Saura, M. Oliveira, Y.H. Feng, M.S. Dai, S.W. Chen, S.A. Hurvitz, S.B. Kim, B. Moy, S. Delaloge, W. Gradishar, et al., Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: phase III NALA trial, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 38 (27) (2020) 3138–3149.
[30] H.S. Rugo, S.A. Im, F. Cardoso, J. Cortés, G. Curigliano, A. Musolino, M.D. Pegram, G.S. Wright, C. Saura, S. Escrivá-de-Romaní, et al., Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial, JAMA Oncol. 7 (4) (2021) 573–584.
[31] P. Tarantino, G. Viale, M.F. Press, X. Hu, F. Penault-Llorca, A. Bardia, A. Batistatou, H.J. Burstein, L.A. Carey, J. Cortes, et al., ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer, Ann. Oncol. : official journal of the European Society for Medical Oncology / ESMO 34 (8) (2023) 645–659.
[32] F. Mosele, E. Deluche, A. Lusque, L. Le Bescond, T.P.Y. Filleron, A. Ducoulombier, B. Pistilli, T. Bachelot, F. Viret, C. Levy, N. Signolle, A. Alfaro, D.T.N. Tran, I. J. Garberis, H. Talbot, S. Christodoulidis, M. Vakalopoulou, N. Droin, A. Stourm, M. Kobayashi, T. Kakegawa, L. Lacroix, P. Saulnier, B. Job, M. Deloger, M. Jimenez, C. Mahier, V. Baris, P. Laplante, P. Kannouche, V. Marty, M. Lacroix-Triki, V. Diéras, F. André, Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial, Nat. Med. 29 (8) (2023) 2110–2120.
[33] C. von Arx, P. De Placido, A. Caltavituro, R. Di Rienzo, R. Buonaiuto, M. De Laurentiis, G. Arpino, F. Puglisi, M. Giuliano, L. Del Mastro, The evolving therapeutic landscape of trastuzumab-drug conjugates: future perspectives beyond HER2-positive breast cancer, Cancer Treat Rev. 113 (2023) 102500.
[34] A.C. Wolff, M.R. Somerfield, M. Dowsett, M.E.H. Hammond, D.F. Hayes, L.M. McShane, T.J. Saphner, P.A. Spears, KH. A: human epidermal growth factor receptor 2 testing in breast cancer: ASCO-college of American pathologists guideline update, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 41 (22) (2023) 3867–3872.
[35] P. Tarantino, E. Hamilton, S.M. Tolaney, J. Cortes, S. Morganti, E. Ferraro, A. Marra, G. Viale, D. Trapani, F. Cardoso, et al., HER2-Low breast cancer: pathological and clinical landscape, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 38 (17) (2020) 1951–1962.
[36] A. Prat, A. Bardia, G. Curigliano, M.E.H. Hammond, S. Loibl, S.M. Tolaney, G. Viale, An overview of clinical development of agents for metastatic or advanced breast cancer without ERBB2 amplification (HER2-Low), JAMA Oncol. (2022).
[37] A. Bardia, X. Hu, R. Dent, K. Yonemori, C.H. Barrios, J.A. O'Shaughnessy, H. Wildiers, J.Y. Pierga, Q. Zhang, C. Saura, et al., Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer, N. Engl. J. Med. (2024).
[38] A.S. Raghavendra, Z. Wang, R. Bassett, et al., Antibody-drug conjugates (ADCs) in breast cancer: real world analysis of outcomes, SABCS (2023). PS08-01.
[39] H.S. Rugo, F. Lerebours, E. Ciruelos, P. Drullinsky, M. Ruiz-Borrego, P. Neven, Y.H. Park, A. Prat, T. Bachelot, D. Juric, 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. 22 (4) (2021) 489–498.
[40] N.C. Turner, M. Oliveira, S.J. Howell, F. Dalenc, J. Cortes, H.L. Gomez Moreno, X. Hu, K. Jhaveri, P. Krivorotko, S. Loibl, et al., Capivasertib in hormone receptor-positive advanced breast cancer, N. Engl. J. Med. 388 (22) (2023) 2058–2070.

[41] F.C. Bidard, V.G. Kaklamani, P. Neven, G. Streich, A.J. Montero, F. Forget, M.A. Mouret-Reynier, J.H. Sohn, D. Taylor, K.K. Harnden, 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. : official journal of the American Society of Clinical Oncology 40 (28) (2022) 3246–3256.
[42] M. Robson, S.A. Im, E. Senkus, B. Xu, S.M. Domchek, N. Masuda, S. Delaloge, W. Li, N. Tung, A. Armstrong, et al., Olaparib for metastatic breast cancer in patients with a germline BRCA mutation, N. Engl. J. Med. 377 (6) (2017) 523–533.
[43] Y. Yuan, S. Zhang, T. Wang, B. Wang, S. Wang, J. Shi, T.Y.Y. Sun, Q. Ouyang, J. Li, Y. Wen, L. Zhang, Z. Jiang, Efficacy and safety of abemaciclib-based therapy versus tucidinostat-based therapy after progression on palbociclib in patients with HR+HER2− metastatic breast cancer, Transl Breast Cancer Res 4 (2023) 10.
[44] L.J. Dai, D. Ma, Y.Z. Xu, M. Li, Y.W.X.Y. Li, X. Jin, S.Y. Wu, Y.X. Zhao, H. Wang, W.T. Yang, Y.Z. Jiang, Z.M. Shao, Molecular features and clinical implications of the heterogeneity in Chinese patients with HER2-low breast cancer, Nat. Commun. 14 (1) (2023) 5112.
[45] Z. Jiang, Q. Ouyang, T. Sun, Q. Zhang, Y.C.J. Teng, H. Wang, Y. Yin, X. Wang, X. Zhou, Y. Wang, G. Sun, J. Wang, L. Zhang, J. Yang, J. Qian, M. Yan, X. Liu, T. Yi, Y. Cheng, M. Li, A. Zang, S. Wang, C. Wang, X. Wu, J. Cheng, H. Li, Y. Lin, C. Geng, K. Gu, C. Xie, H. Xiong, X. Wu, J. Yang, Q. Li, Y. Chen, F. Li, A. Zhang, Y. Zhang, Y. Wu, J. Nie, Q. Liu, K. Wang, X. Mo, L. Chen, Y. Pan, P. Fu, H. Zhang, D. Pang, Y. Sheng, Y. Han, H. Wang, S. Cang, X. Luo, W. Yu, R. Deng, C. Yang, P. Keegan, Toripalimab plus nab-paclitaxel in metastatic or recurrent triple-negative breast cancer: a randomized phase 3 trial, Nat. Med. 30 (1) (2024) 249–256.
[46] P. Schmid, P.J. Wysocki, C.X. Ma, et al., Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): updated results from BEGONIA, a phase Ib/II study, ESMO (2023). Abstract 379MO.
[47] Y. Yin, X. Mei, Q. Ouyang, M. Yan, Al Et, Updated efficacy and safety of SKB264 (MK-2870) for previously treated metastatic triple negative breast cancer (mTNBC) in Phase 2 study, SABCS (2023) PS08–8.
[48] J.M. Pérez-García, M. Vaz Batista, P. Cortez, M. Ruiz-Borrego, J.M. Cejalvo, J. de la Haba-Rodriguez, L. Garrigós, F. Racca, S. Servitja, S. Blanch, et al., Trastuzumab deruxtecan in patients with central nervous system involvement from HER2-positive breast cancer: the DEBBRAH trial, Neuro Oncol. 25 (1) (2023) 157–166.
[49] R. Bartsch, A.S. Berghoff, J. Furtner, M. Marhold, E.S. Bergen, S.S.A. Roider-Schur, H. Forstner, B. Rottenmanner, K. Dieckmann, Z. Bago-Horvath, H. Haslacher, G. Widhalm, A. Ilhan-Mutlu, C. Minichsdorfer, T. Fuereder, T. Szekeres, L. Oehler, B. Gruenberger, C.F. Singer, A. Weltermann, R. Puhr, M. Preusser, Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial, Nat. Med. 28 (9) (2022) 1840–1847.
[50] G. Curigliano, V. Mueller, V. Borges, E. Hamilton, S. Hurvitz, S. Loi, R. Murthy, A. Okines, E. Paplomata, D. Cameron, et al., Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis, Ann. Oncol. : official journal of the European Society for Medical Oncology / ESMO 33 (3) (2022) 321–329.
[51] Yan M., Ouyang Q., Sun T., Niu L., Yang J., Li L., Song Y., Hao C., Chen Z., Orlandi A., et al., Pyrotinib plus capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases (PERMEATE): a multicentre, single-arm, two-cohort, phase 2 trial, Lancet Oncol. 23(3) (2022)353-361.
[52] Z. Yang, J. Meng, X. Mei, M. Mo, Q. Xiao, X. Han, L. Zhang, W. Shi, X. Chen, J. Ma, et al., Brain radiotherapy with pyrotinib and capecitabine in patients with ERBB2-positive advanced breast cancer and brain metastases: a nonrandomized phase 2 trial, JAMA Oncol. (2024) e235791.
[53] M. Guckenberger, Y. Lievens, A.B. Bouma, L. Collette, A. Dekker, N.M. deSouza, A.C. Dingemans, B. Fournier, C. Hurkmans, F.E. Lecouvet, et al., Characterisation and classification of oligometastatic disease: a European society for radiotherapy and oncology and European organisation for research and treatment of cancer consensus recommendation, Lancet Oncol. 21 (1) (2020) e18–e28.
[54] S.M. Yoon, J.G. Bazan, Navigating breast cancer oligometastasis and oligoprogression: current landscape and future directions, Curr. Oncol. Rep. 26 (6) (2024) 647–664.
[55] C.J. Tsai, J.T. Yang, N. Shaverdian, J. Patel, A.F. Shepherd, J. Eng, D. Guttmann, R. Yeh, D.Y. Gelblum, A. Namakydoust, et al., Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study, Lancet (London, England) 403 (10422) (2024) 171–182.
[56] R. Olson, W. Jiang, M. Liu, A. Bergman, D. Schellenberg, B. Mou, A. Alexander, H. Carolan, F. Hsu, S. Miller, et al., Treatment with stereotactic ablative radiotherapy for up to 5 oligometastases in patients with cancer: primary toxic effect results of the nonrandomized phase 2 SABR-5 clinical trial, JAMA Oncol. 8 (11) (2022) 1644–1650.
[57] J. Li, J. Zhou, H. Wang, Z. Liu, Z. Fan, Y. Liu, C. Geng, Y. Xiao, Z. Jiang, Trends in disparities and transitions of treatment in patients with early breast cancer in China and the US, 2011 to 2021, JAMA Netw. Open 6 (6) (2023) e2321388.