Cancer Biol Med 2025. doi: 10.20892/j.issn.2095-3941.2024.0486

PERSPECTIVE

Antibody-drug conjugates in breast cancer: advances and prospects

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The "Global Cancer Statistics Report 2022" estimates that there were approximately 20 million new cancer cases worldwide, including 9.7 million in females, of which 2.31 million were breast cancer cases[1]. Breast cancer is the most common malignant tumor in women and one of the leading causes of cancer-related deaths. Breast cancer treatment primarily involves surgery, often in combination with chemotherapy, radiotherapy, endocrine therapy, and targeted therapies. Despite continuous advances in these treatments, significant limitations remain. Traditional chemotherapy and radiotherapy are effective but lack specificity. While endocrine and human epidermal growth factor receptor 2 (HER2) targeted therapies are highly effective in some breast cancer subtypes, targeted therapies offer limited benefit to patients with triple-negative breast cancer (TNBC). However, antibody-drug conjugates (ADCs) have shown great promise in overcoming these challenges.

ADCs are a class of immunoconjugates consisting of a monoclonal antibody linked to a cytotoxic payload *via* a specialized connector. The monoclonal antibody and the cytotoxic payload are the key components driving the anti-tumor effect, while the characteristics of the connector can significantly influence the efficacy of the ADC. The development of ADCs has progressed through several phases[2,3], as detailed in **Table 1**. The rationale and mechanisms underlying third-generation ADCs are detailed in **Figure 1**. This article reviews current clinical evidence and recent research progress in the development of ADCs for breast cancer treatment.

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Received November 1, 2024; accepted January 17, 2025;
published online February 17, 2025.
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Advances in ADC therapy

Despite significant advances in treatment, advanced breast cancer remains incurable. The primary breast cancer treatment goals focus on prolonging survival, alleviating symptoms, and enhancing the quality of life to achieve long-term disease management. Although early-stage breast cancer has a relatively high cure rate, there remains a considerable risk of recurrence and metastasis, underscoring the need for new therapeutic strategies to further improve patient outcomes.

Advanced breast cancer

T-DM1 was the first ADC approved for breast cancer based on reported superiority over lapatinib plus capecitabine in the EMILIA study[4]. T-DM1 has been globally recognized as the standard second-line treatment for HER2-positive breast cancer since 2013. However, data from the recent DESTINY-Breast03 study have demonstrated remarkable results with T-DXd. Specifically, the median overall survival (OS) was 52.6 months for the T-DXd group compared to 42.7 months for the T-DM1 group[5]. Furthermore, the median progression-free survival (PFS) was 29.0 months for T-DXd and 7.2 months for T-DM1. Given the superior performance in the DESTINY-Breast03 study, T-DXd is now the preferred option for second-line treatment of HER2+ advanced breast cancer.

The DESTINY-Breast11 study included approximately 500 HER2-positive metastatic breast cancer patients who had

Table 1 Comparison between first-, second-, and third-generation ADCs

Properties/Generation	First-generation ADCs	Second-generation ADCs	Third-generation ADCs
Antibody type	Murine or chimeric antibodies	Human-mouse chimeric antibodies, humanized monoclonal antibodies	Fully human monoclonal antibodies
Linker	Unstable	Cleavable and non-cleavable	More stable, site-specific
Cytotoxin	Lower toxicity	Higher toxicity	Various highly effective small molecule toxins
Drug-to-antibody ratio	Non-uniform	Non-uniform	Uniform
Targeting	Lower	Higher	Highest
Immunogenicity	High	Lower	Lowest
Safety	Stronger toxicity/side effects	Stronger side effects	Lower toxicity
Clinical efficacy	Poor effect	Better effect	Best effect
Clinical application	Few clinical applications	Widespread clinical application	Widespread application with significant effects
Features	Non-site-specific conjugation, short half-life	Site-specific conjugation, improved efficacy	Site-specific conjugation, wider therapeutic window

ADCs, antibody-drug conjugates.

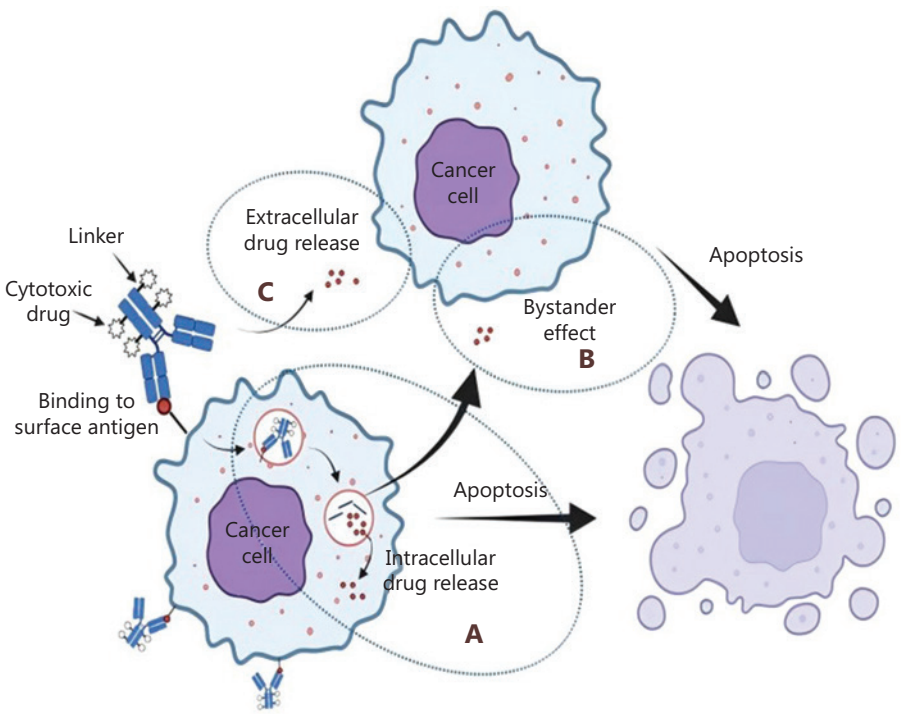


Figure 1 Third-generation antibody-drug conjugates: the rationale and mechanisms. (A) After antibody-drug conjugates (ADCs) enter the bloodstream, the antibody component binds to the antigen on the surface of the target cell. The ADC is then internalized through receptor-mediated endocytosis and subsequently releases the cytotoxic payload *via* the endosome-lysosome pathway, killing the tumor cells. (B) Payloads with membrane permeability also exert a bystander effect, leading to the death of surrounding antigen-negative cells. (C) In the acidic environment caused by high metabolism in tumors, the ADC linker undergoes cleavage at the toxin end, releasing the payload to kill tumor cells.

previously received up to 2 lines of treatment and > 50% of the patients had brain metastases (BM) at baseline[6]. The results showed that the median PFS in the BM cohort reached 17.3 months with a 12-month PFS rate of 61.6%. The objective response rate (ORR) in the non-BM cohort was 62.7% and the 12-month OS rate was also high in both cohorts (approximately 90%). The results of the DESTINY-Breast11 study are interesting and significant and are expected to change existing guidelines and clinical practice.

Additionally, the results of the TROPiCS-02[7] and ASCENT studies[8] demonstrated that the sacituzumab govitecan (SG) group had significantly improved median PFS and OS compared to the treatment of physician's choice (TPC) group. The EVER-132-002[9] and EVER-132-001 studies[10] confirmed this conclusion. Therefore, SG has emerged as a valuable option for later-line treatment in advanced HR+/HER2− and TNBC.

Early-stage breast cancer

Within the realm of adjuvant therapy for HER2-positive early-stage breast cancer the KATHERINE study[11] demonstrated that patients who do not achieve a non-pathologic complete response (non-pCR) after neoadjuvant therapy (NAT) containing trastuzumab, T-DM1 significantly improves invasive disease-free survival (IDFS) compared to trastuzumab. This finding has established T-DM1 as the standard adjuvant reinforcement therapy in this setting. The ongoing head-to-head DESTINY-Breast05 study[12] seeks to compare the clinical benefits of T-DXd *vs.* T-DM1 as adjuvant therapy for HER2+ breast cancer.

Combining trastuzumab and pertuzumab has consistently improved pCR rates in NAT for HER2+ early-stage breast cancer[13], solidifying the role of trastuzumab and pertuzumab combination therapy as the standard approach. Achieving a pCR is a critical prognostic factor for early-stage breast cancer and ADCs may offer further potential for improvement. The DESTINY-Breast11 study[14] is the first clinical trial to evaluate the application of T-DXd in NAT for patients with HER2+ early-stage, high-risk breast cancer. The DESTINY-Breast11 study uses a standard NAT regimen consisting of anthracycline-containing chemotherapy followed by Taxotere-Herceptin-Perjeta (THP) as the control compared to regimens in which T-DXd replaced anthracycline-containing chemotherapy followed by THP and T-DXd monotherapy. If successful, the DESTINY-Breast11 study may introduce a more effective and less toxic "anthracycline-free" and even "chemotherapy-free" anti-HER2 NAT regimen for clinical use.

The NeoSTAR study[15] was the first clinical trial to evaluate ADCs as neoadjuvant therapy for early-stage TNBC. The pCR rate was 30% in the single-agent SG treatment cohort. This finding confirms that single-agent SG has good clinical efficacy in NAT for TNBC. Future studies are needed to determine the optimal combination strategies with SG and the ideal duration of therapy.

The use of ADCs have progressively advanced from late-stage palliative care to adjuvant and even NAT, offering the potential to transform the diagnosis and treatment status of advanced and early-stage breast cancer.

ADCs contribute to the precise classification of breast cancer

Breast cancer is a highly heterogeneous malignancy at the molecular level. Precision classification based on molecular typing has become the standard for diagnosing and treating breast cancer. Traditional molecular subtypes include luminal A, luminal B, HER2+, and TNBC. In recent years the rapid development of ADCs has not only advanced the treatment of HER2+ and TNBC but also introduced new treatment options for patients with HER2-low- and ultra-low-expressing breast cancer, which has led to an update of standards for determining HER2 expression status.

As the first phase III clinical trial to yield positive results in HER2-low-expressing breast cancer, the DESTINY-Breast04 study[16] showed that patients with HR+ and HER2-low-expressing breast cancer treated with T-DXd had significantly improved median PFS (10.1 months *vs.* 5.4 months) and median OS (23.9 months *vs.* 17.5 months) compared to the treatment of physician's choice (TPC) group. In addition, HR- and HER2-low-expressing patients treated with T-DXd also experienced better outcomes with a median PFS of 8.5 months compared to 2.9 months in the TPC group and a median OS of 18.2 months in the T-DXd group compared to 8.3 months in the TPC group[16]. These benefits of T-DXd in the HR− population were consistent with the overall population, indicating that the benefits of the overall population were not solely driven by the HR+ group. Therefore, T-DXd benefits HR+ or HR− patients with HER2-low-expressing breast cancer. This revolutionary ushering of traditional anti-HER2 treatment into the "trichotomy" era defines a new treatment category

(HER2-low-expressing) and promotes the innovation of precision treatment for breast cancer. Based on the above results the FDA updated the prescribing information for T-DXd, further adding an indication for treating patients with unresectable or metastatic HER2-low-expressing breast cancer and expanding on the previous approval for HER2-positive disease.

Building on the success of the DESTINY-Breast04 study, the pivotal phase III clinical trial DESTINY-Breast06 aimed to advance HER2-low-expressing treatment to the frontline and further expand the population benefiting from anti-HER2 therapy[17]. The DESTINY-Breast06 study reported that the median PFS in the T-DXd group was 13.2 months in the HER2-low-expressing population, a 5.1-month extension compared to the TPC group with a 38% reduction in the risk of disease progression or death (HR = 0.62, 95% CI: 0.51–0.74). In the intention-to-treat (ITT) population, the median PFS in the T-DXd group was 13.2 months, a 5.1-month extension compared to the TPC group with a 37% reduction in the risk of disease progression or death (HR = 0.63, 95% CI: 0.53–0.75). An exploratory analysis further showed that patients with HER2 ultra-low expression benefited from T-DXd to the same extent as patients with HER2-low expression. The results provide robust evidence-based medical support for the application of T-DXd in the treatment of advanced breast cancer with HR+ and HER2-low expression and HER2 ultra-low expression. Moreover, the DESTINY-Breast06 trial adopted the administration of T-DXd to patients who had not received chemotherapy and had advanced endocrine therapy. This finding means that T-DXd provides a more effective follow-up treatment option for patients treated with CDK4/6 inhibitors.

The remarkable performance of T-DXd in patients with HER2-low-expressing breast cancer has sparked interest in HER2-low expression as an independent molecular subtype. The current definition of HER2 low expression is rooted in clinical practice even though HER2 low expression has significant value in guiding the use of ADCs. Nevertheless, researchers have not formed a consensus on whether there are differences between HER2 non-expressing breast cancer and HER2 low-expressing breast cancer in terms of patient prognosis and tumor biological characteristics[18-21]. As a result, whether HER2 low expression can serve as an independent molecular subtype still requires additional evidence. The updated *2023 American Society of Clinical Oncology and College of American Pathologists Breast Cancer HER2 Testing Guideline* recognizes that it is premature to create new categories, such as HER2 low expression and HER2 ultra-low expression. However, the distinction between immunohistochemistry (IHC) scores of 0 and 1+ remains clinically significant, indicating that while HER2-low expression may not be a molecular subtype, HER2-low expression can serve as a valuable clinical subgroup for treatment decisions[22].

Biological mechanism underlying resistance to ADCs

Although ADCs have demonstrated potent activity in antitumor treatment and have clear advantages in improving targeting and reducing side effects, ADCs still face the issue of treatment resistance. A thorough understanding of the mechanisms underlying resistance to ADCs can guide the formulation of subsequent treatment strategies, which is of great clinical significance.

Heterogeneity of antigen expression

Long-term exposure to treatment may lead to a decrease in HER2 receptor expression or structural changes, thereby affecting the efficacy of ADCs. For example, the KRISTINE trial reported that patients with HER2 expression heterogeneity had a lower pCR rate when treated with T-DM1[23].

Antigen dimerization

Dimerization of antigens with another cell surface receptor may mediate resistance to ADCs. NRG-1β, a ligand that can induce HER2/HER3 heterodimerization, inhibits the cytotoxic activity of T-DM1 in a subpopulation of HER2-amplified breast cancer cell lines. This resistance can be overcome by adding pertuzumab, a monoclonal HER2 antibody that blocks HER2/HER3 dimerization and downstream signal transduction, which has a synergistic effect with T-DM1[24].

Downregulation of antigen expression

ADCs rely heavily on antigen expression to exert targeted cytotoxic effects. Therefore, downregulation of target antigen expression in cancer cells after long-term drug exposure may be one of the reasons for ADC resistance. The SePHER study showed that in breast cancer cell lines and patient tissue samples the combination of trastuzumab and pertuzumab as first-line treatment reduced HER2 expression, thereby

affecting the efficacy of T-DM1 in second-line treatment[25]. The DAISY study also showed that in HER2-positive breast cancer patients who progressed after T-DXd treatment, HER2 expression decreased in 65% of patients[26].

Disruption of ADC internalization and recycling

Cancer cells may also develop resistance through disruption of the internalization and transport of ADCs to lysosomes. Endocytosis followed by lysosomal degradation is the main pathway for processing ADCs. Researchers assessing T-DM1 resistance found that ADCs were internalized into caveolin-1 (CAV-1)-positive spots in resistant cells, which altered ADC transport to lysosomes. After internalization into CAV-1-positive spots, proper enzymatic processing of the T-DM1 non-cleavable linker could not be carried out. Moreover, due to the neutral pH of these CAV-1-positive compartments, the charged payload could not penetrate the membrane to act on adjacent cells, thereby reducing the bystander activity of the ADCs[27].

Payload resistance

The payload is the main component of ADCs responsible for antitumor activity. Resistance to the payload can lead to acquired resistance to ADCs. Studies have shown that T-DXd-resistant cells exhibit reduced sensitivity to topoisomerase inhibitors, suggesting that loss of sensitivity to the ADC payload may be a cause of acquired resistance to T-DXd[28]. Tumor cells can also avoid cytotoxic effects by altering the payload targets. The TOP1 E418K missense mutation can cause the SG SN-38 payload to lose the target site in triple-negative breast cancer. Moreover, in subclones carrying the TOP1 E418K missense mutation, TOP1-related frameshift mutations have also occurred, which may further enhance cancer cell secondary resistance to SG[29].

ADC combination therapy

Although ADC monotherapy has demonstrated significant survival benefits in cancer treatment, unmet needs remain. Maximizing the anti-tumor effects of ADCs is crucial but addressing resistance to ADC monotherapy presents a challenge. As a result, ADC combination therapy has become a key area of exploration. Previous research[30,31] indicated that combining ADCs with chemotherapy is not satisfactory, therefore it is still necessary to explore other combined treatment plans.

ADCs combined with monoclonal antibodies

ADCs combined with monoclonal antibodies may be more effective than ADCs alone and may overcome resistance by inducing effective internalization and degradation of HER2, but previous studies have shown different results. Previous clinical studies, such as KAITLIN, KRISTINE, and MARIANNE, which investigated T-DM1 combined with pertuzumab, did not yield positive outcomes[32-34]. However, an interim analysis of the DESTINY-Breast07 study presented at the 2024 American Society of Clinical Oncology (ASCO) conference had promising data from the expanded dose phase of T-DXd monotherapy or T-DXd combined with pertuzumab as a first-line treatment plan for patients with HER2+ metastatic breast cancer[35]. The ORR for the T-DXd monotherapy and combination groups was 76.0% and 84.0%, respectively, and the 12-month PFS rate for both groups was 80.8% and 89.4%, respectively. Currently, the DESTINY-Breast09[36] is further exploring the efficacy of this combination strategy in HER2+ patients in the first-line setting.

ADCs combined with tyrosine kinase inhibitors (TKIs)

Dual HER2 blocking is more effective than monotherapy and small molecule TKIs bind to HER intracellular domains. TKIs combined with ADCs improve receptor internalization, increase uptake of ADCs payloads, and overcome drug resistance associated with reduced HER2 expression. The HER2CLIMB-02 study, a randomized double-blind phase III clinical trial, revealed the therapeutic potential of combining ADCs with small molecule TKIs in HER2+ advanced breast cancer patients at the 2023 San Antonio Breast Cancer Symposium[37]. The HER2CLIMB-02 study showed that in patients who had previously received trastuzumab and taxane treatments, as well as patients with a history of brain metastasis at the locally advanced/metastatic breast cancer stage, the combination of T-DM1 and tucatinib significantly prolonged the median PFS compared to T-DM1 alone [9.5 months *vs.* 7.4 months (HR = 0.76)]. Among patients with brain metastases, which accounted for 40% of the study population, the median PFS was also notably improved [median PFS: 7.8 months *vs.*

5.7 months (HR = 0.64)]. Importantly, no new safety risks associated with combination therapy were observed compared to T-DM1 monotherapy.

The *Annals of Oncology* published the results of cohort 4 from the TBCRC 022 study in July 2024[38], which evaluated the efficacy of combining neratinib with T-DM1 in patients with HER2+ brain metastases. The TBCRC 022 study reported that the T-DM1 and neratinib combination showed clear efficacy (approximately one-third of the patients achieved partial remission in the central nervous system and 38.1%–50.0% of the cohort patients achieved stable disease or remission lasting at least 6 months) whether or not the patients had undergone radiotherapy, extensive pre-treatment, or prior T-DM1 therapy.

ADCs combined with immune therapy

ADCs promote dendritic cell maturation in the process of killing tumor cells, which migrate to the lymph nodes and activate immature T cells, then recognize and kill tumor cells. In addition, ADCs activate the immune system through antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity effects. The combined regimen has the potential to exhibit a synergistic role in overcoming or preventing drug resistance in conjunction with the mechanism underlying immune checkpoint inhibitors. The first phase II KATE2 study exploring ADCs combined with immunotherapy showed[39] no significant median PFS difference between the T-DM1 combined with atezolizumab and control groups (8.2 months *vs.* 6.8 months; $P = 0.33$). However, the median PFS for both groups was 8.5 months and 4.1 months, respectively, in the PD-L1 positive subgroup. Although the difference was not statistically significant ($P = 0.099$), the T-DM1 plus atezolizumab group reduced the risk of disease progression by 60%, incentivizing further exploration. Consequently, the phase III KATE3 study involving T-DM1 combined with atezolizumab[40] is currently underway.

The SACI-IO clinical study, which was presented at the 2024 ASCO conference, examined ADCs combined with immunotherapy[41]. The results showed that SG combined with pembrolizumab did not significantly improve efficacy compared to SG alone. A subgroup analysis indicated a beneficial trend in PFS and OS in the PD-L1-positive population but without statistical significance. The OS data are still immature, requiring longer follow-up. The safety profile of SG combined with pembrolizumab in the SACI-IO study was consistent with the expected safety of both drugs and no new safety signals were observed. There may be intrinsic subtypes of HR+ and HER2– advanced breast cancer that benefit from immunotherapy but further exploration is needed to identify predictive factors for the effectiveness of ADCs combined with immunotherapy in this population.

Additionally, the NAT results of Dato-DXd monotherapy or in combination with durvalumab (Durva) in the I-SPY2.2 study[42,43] showed that among 103 patients in the Dato-DXd monotherapy cohort, 33 (32%) underwent early surgery, while 35 (33%) of 106 patients in the Dato-DXd + Durva cohort also underwent early surgery. In the NAT with Dato-DXd + Durva, the pCR rate in patients with positive immune markers reached 43% (20/47) and the model pCR rate was as high as 65%, both exceeding the threshold (40%). These findings suggest that in populations with predicted residual cancer burden and positive immune markers, Dato-DXd + Durva significantly improves efficacy. The question remains whether ADCs combined with immunotherapy will eventually replace preoperative immunotherapy plus chemotherapy. The upcoming results from the phase III TROPION-Breast04 study[44], which compares Dato-DXd + Durva to paclitaxel + carboplatin + pembrolizumab as a preoperative treatment, will be crucial in answering this question.

Maximizing the therapeutic potential of ADCs is a hot topic, with key research directions including expansion of the eligible patient population, overcoming resistance, and identifying the best combination strategies. The latter direction in particular is attracting significant attention. However, the success of ADC combination strategies to date has been limited, which can lead to the non-specific expression of targets leading to adverse reactions in normal tissues, overlapping toxic reactions, and newly emerging resistance mechanisms. Therefore, future efforts must focus on identifying optimal partners for ADCs, gaining a deeper understanding of the pharmacology, and integrating predictive biomarkers to enhance treatment efficacy.

New ADCs

Following the approval of the first ADC in the early 21st century, the pace of developing ADCs has accelerated significantly. Today, more than 15 ADCs have been approved and > 100 ADCs are in clinical development. The design and development of new ADCs are expected to further refine precision, enhance therapeutic efficacy, and reduce adverse effects.

HER2 ADCs

The results of another exploratory study (ACE-Breast-02) on ARX788, a new type of HER2-targeting ADC, was announced at the 2024 ASCO conference[45]. The ACE-Breast-02 study included advanced-stage patients who had received two or fewer lines of anticancer therapy. The median PFS in the ARX788 group was 11.33 months, extending the duration by 3.08 months compared to the lapatinib combined with capecitabine group with a 36% reduction in the risk of disease progression or death. Although the OS data is not mature, preliminary analysis suggests a trend favoring the ARX788 group. There was no significant difference in treatment-related adverse events between the two groups. In addition, several new HER2-targeting ADCs, such as SHR-A1811, MRG002, and DP303c, are also undergoing clinical trials, the results of which are eagerly awaited.

TROP2 ADCs

TROP2 has emerged as a promising target for ADCs, second only to HER2 in importance. Currently, TROP2 ADCs have also made remarkable progress in the field of breast cancer. One of the representative drugs, Dato-DXd, has achieved statistically and clinically significant PFS results in the phase III TROPION-Breast01 study[46]. The study aimed to evaluate the efficacy and safety of Dato-DXd *vs.* TPC in patients with HR+ and HER2− inoperable or metastatic breast cancer, offering a potential new treatment option for patients who have developed treatment resistance. Additional safety analysis from the TROPION-Breast01 study was announced at the 2024 European Society for Medical Oncology (ESMO) BC conference[47], showing that the median treatment duration in the Dato-DXd group was longer than the TPC group (6.7 months *vs.* 4.1 months). Furthermore, the grade 3 or higher treatment-related adverse event rates, treatment discontinuation due to adverse events, and the overall discontinuation rate were lower than the TPC group, confirming the good safety of Dato-DXd, which is generally controllable in clinical practice. Patient-reported outcomes (PROs) from the TROPION-Breast01 study, which were disclosed at the 2024 ASCO conference[48], showed that the time-to-deterioration of all secondary endpoints was delayed in the Dato-DXd group compared to the TPC group. These data confirmed that Dato-DXd has a potential advantage in improving the quality of life for patients, providing additional references for application in HR-positive and -negative advanced breast cancer.

Sacituzumab tirumotecan (SKB264/MK-2870) is a new type of TROP2 ADC. The specific data from the phase III OptiTROP-Breast01 study of this drug were reported at the 2024 ASCO conference[49]. The OptiTROP-Breast01 study assessed the efficacy of SKB264 in patients with locally recurrent or metastatic TNBC who had previously received treatment. The results showed a median PFS of 5.7 months for the SKB264 group compared to 2.3 months for the TPC group. The OS in the SKB264 group was significantly better than the TPC group (HR = 0.53; $P = 0.0005$) in the first planned interim OS analysis on 30 November 2023. SKB264 may provide a promising new option for second-line treatment of advanced TNBC patients.

HER3 ADCs

HER3-DXd is a HER3-targeting ADC consisting of an anti-HER3 monoclonal antibody (patritumab) and a topoisomerase I inhibitor. HER3-DXd monotherapy in patients with HR+ and HER2− breast cancer with high HER3 expression achieved an ORR of 30.1% and a PFS of 7.4 months in the U31402-A-J101 study[50]. The ORR was 22.6% with a median PFS of 5.5 months in TNBC, while the ORR reached 42.9% and the median PFS was 11.0 months in HER2+ breast cancer. The data suggest that HER3-DXd demonstrates preliminary anti-tumor efficacy in breast cancer with a low correlation to HER3 expression.

The ICARUS Breast01 study[51] presented the efficacy of HER3-DXd in patients with HR+ and HER2− advanced breast cancer after CDK4/6 inhibitor and first-line chemotherapy at the 2024 ESMO conference. The ICARUS Breast01 study reported an ORR of 53.0% and a median PFS of 9.4 months, demonstrating clinically meaningful activity and manageable safety in this population after ≥ 2 lines of therapy.

Nectin-4 ADCs

Enfortumab vedotin (EV) is an ADC targeting Nectin-4. The results of the EV-202 study[52], which were presented at the 2024 ASCO conference. The EV-202 study evaluated the efficacy of EV monotherapy in the HR+ and HER2− and TNBC breast cancer populations. The confirmed ORRs for the HR+/HER2− and TNBC cohorts were 15.6% and 19.0%, respectively, although these ORRs did not meet the pre-specified ORR thresholds. However, the disease control rates and median PFS for the HR+/HER2− and TNBC breast

cancer cohorts were 51.1% and 57.1%, and 5.4 months and 3.5 months, respectively. The overall safety profile of EV was manageable.

Bispecific ADCs

Bispecific ADCs are designed to simultaneously target two different epitopes or molecules, which enables more precise tumor targeting. Data from the phase I JSKN003 clinical study[53], a bispecific ADC targeting two HER2 epitopes for the treatment of HER2-expressing solid tumors, was presented at the 2024 ASCO conference. The ORR was 51.1% with a disease control rate was 93.3% among the 45 evaluable subjects. Specifically, the ORR was 73.3% (11/15) in patients with HER2+ breast cancer, while the ORR was 33.3% (3/9) in those with HER2-low-expressing breast cancer. Additionally, bispecific ADCs, such as BL-B01D1, TQB2102, and KM501, are also conducting related clinical trials, the results of which are eagerly anticipated. Bispecific ADCs hold substantial therapeutic potential, especially in overcoming resistance to traditional ADCs, and are expected to have a critical role in future treatment strategies.

Summary

The continuous development and evolution of ADCs are offering increasingly diverse options for the comprehensive treatment of breast cancer, significantly reshaping the current treatment landscape. As an innovative therapy, ADCs have shown immense potential in overcoming the limitations of traditional treatments. ADCs have not only achieved breakthroughs in the management of advanced breast cancer but are also gradually being integrated into the treatment of early-stage breast cancer, including neoadjuvant and adjuvant therapy. In addition, the precise targeting capabilities of ADCs have driven an update of standards for determining HER2 expression status, providing new treatment options for patients with HER2-low-expressing breast cancer. Although ADCs have shown efficacy as monotherapies, ongoing research is exploring combinations with other treatments, such as large molecule monoclonal antibodies, TKIs, and immunotherapy, to improve treatment outcomes and address drug resistance issues. Moreover, new types of ADCs are being developed that aim to further enhance both efficacy and safety. In summary, the development of ADCs provides new strategies for the treatment of breast cancer, promising to improve patient prognosis and quality of life.

Grant support

This work was supported by grants from the National Natural Science Foundation of China (Grant No. 81672638).

Conflict of interest statement

No potential conflicts of interest are disclosed.

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Cite this article as: Shi Z, Lu Y, Zhao Q, Wang Y, Qiu P. Antibody-drug conjugates in breast cancer: advances and prospects. Cancer Biol Med. 2025; 22: 83-92. doi: 10.20892/j.issn.2095-3941.2024.0486