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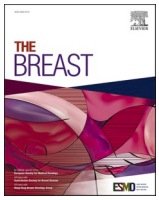

Unveiling the future of breast cancer therapy: Cutting-edge antibody-drug conjugate strategies and clinical outcomes

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ABSTRACT

Breast cancer has become the most prevalent malignant tumor worldwide and remains one of the leading causes of cancer-related mortality among women globally. The prognosis for patients with metastatic breast cancer remains poor, necessitating the exploration of novel therapeutic strategies to improve survival rates. In the era of precision medicine, antibody-drug conjugates (ADCs) have gained significant attention as a targeted therapeutic strategy in breast cancer treatment. ADCs, a relatively new treatment for breast cancer, deliver cytotoxic drugs (payloads), directly into the tumor space, turning chemotherapy into a targeted agent, which enables patients to experience significant improvements with manageable drug toxicity. For the treatment of breast cancer, there are three ADCs approved for breast cancer treatment: Trastuzumab emtansine (T-DM1), Trastuzumab Deruxtecan (T-Dxd) targeting HER-2, and Sacituzumab Govitecan (SG) targeting Trop-2. Recent clinical studies have demonstrated that the benefits of ADC therapies extend beyond HER2-positive breast cancer toinclude hormone receptor (HR)-positive breast cancer, triple-negative breast cancer (TNBC), and HER2-low expressing breast cancer. Notably, the DESTINY-Breast series of studies, particularly focusing on T-Dxd, encompass neoadjuvant, adjuvant, and multiple lines of therapy for advanced breast cancer. This marks the advent of a comprehensive ADC era in breast cancer treatment. This review summarizes the efficacy and adverse effects of ADC therapies that have completed or are currently undergoing phase I-III clinical trials. Additionally, it analyzes potential combination strategies to overcome ADC resistance, aiming to provide clinicians with a comprehensive clinical guide to the use of ADCs in breast cancer treatment.

1. Introduction

Breast cancer has emerged as the foremost prevalent malignancy among women globally [1]. Historically, the evolution of treatment modalities for breast cancer has been significantly influenced by advancements in molecular biology. Postoperative chemotherapy employing cytotoxic agents was the cornerstone of therapy aimed at minimizing tumor recurrence. Nevertheless, the limitations of chemotherapy, characterized by a narrow therapeutic window, pronounced systemic toxicity, and the propensity for drug resistance, necessitated alternative approaches [2]. Enhanced understanding of cellular carcinogenesis mechanisms, coupled with advancements in monoclonal antibody production technologies, has pivoted anti-tumor drug development towards targeted therapies targeting proteins that facilitate breast cancer cell growth, dissemination, and proliferation [3]. ADCs, colloquially termed "molecular missiles"—have undergone extensive research, particularly for Her-2-positive breast cancers [4]. ADCs ingeniously combine small-molecule cytotoxins with large-molecule monoclonal antibodies, yielding potent anti-tumor efficacy with minimal systemic toxicity. Recently, the exploration of cellular oncogenic signal transduction pathways and tumor markers has broadened the target repertoire of ADCs, exemplified by the advent of SG targeting Trop-2 in breast cancer, heralding the clinical emergence of novel targets [5]. This development underscores the potential of ADCs to undergo continual refinement and expansion, catering to new patient cohorts. This review aims to summarize the ADCs approved for breast cancer and describe the potential ADCs under investigation and new strategies of ADC in treating breast cancer.

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2. Basic characteristics of ADC

ADC represents a pivotal advancement in targeted cancer therapy, combining a monoclonal antibody specific to tumor antigens, a cytotoxic payload, and a linker. Upon administration, the antibody component of an ADC specifically binds to its antigen on the tumor cell surface, facilitating internalization via clathrin-mediated endocytosis [6]. This is followed by lysosomal degradation, releasing the payload within the cell to exert its cytotoxic effects, either by disrupting DNA or inhibiting tubulin function, thereby halting tumor cell division (Fig. 1). This dual mechanism—antigen-targeted blockade and payload-mediated cytotoxicity—enables ADCs to deliver targeted therapy with potentially superior clinical efficacy compared to conventional monoclonal antibodies or their fragments.

ADCs with different targets have different killing mechanisms which determine where the drug will be released and the adaptive populations. Her-2 overexpression occurs in 20%–30 % of breast tumors and predicts a poor clinical prognosis [7]. Therefore, Her-2 targeted ADCs, T-DM1 and T-Dxd, which have been approved by the U.S. Food and Drug Administration (FDA), the mechanism includes two parts: one is the anti-tumor effect mediated by trastuzumab: the Fab segment can block the extracellular domain of Her-2 on the cell surface and inhibit the proliferation of tumor cells by inhibiting the PI3K/AKT signaling pathway [8,9]; The Fc segment can induce antibody-dependent cell--mediated cytotoxicity (ADCC) to kill tumor cells [10]. The second is the anti-tumor effect mediated by payload. The payloads currently under development are mainly limited to tubulin inhibitors, DNA damage agents, and immunomodulators [11]. The payload of T-DM1 can block mitosis by destroying the microtubule network of target cells, resulting in mitotic disaster or apoptosis to inhibit tumor cell proliferation [12]. The second Her-2 targeted ADC approved for breast cancer, T-Dxd, the payload is a derivative of exatecan, has stronger membrane penetration, and can penetrate neighboring cells to eliminate neighboring antigen-negative tumor cells, a process known as the bystander effect, this process bears significance for tumor cells characterized by heterogeneous antigen expression [13].

Transmembrane calcium signal transducer Trop-2 is highly expressed in multiple tumor types, most notably in more than 90 % of breast cancer [14,15]. Trop-2 is related to a variety of transcription factors, resulting in the dysregulation of related pathways. It can increase the expression of CREB1, Jun, NF-κB, Rb, STAT1, and STAT3 by activating CyclinD1 and ERK/MEK pathways, thereby mediating tumor cell deterioration and metastasis [16]. Studies have shown that the use of small interfering RNA (siRNA) to silence the Trop-2 gene in breast cancer cell models can inhibit tumor cell deterioration, proliferation, invasion, and cell colony formation in vitro [17,18]. Therefore, Trop-2 as the target of SG can effectively block these signaling pathways, and the highly toxic payload SN-38 also has the bystander effect to kill the tumor cells with low expression of antigen [19,20].

3. For HER-2 positive breast cancer

3.1. Trastuzumab emtansine(T-DM1, Trastuzumab/DM1)

T-DM1, the first Her-2 targeted antibody-drug conjugate approved for BC, serves as a pivotal adjuvant therapy for Her-2+ BC. In the EMILIA trial, the findings revealed that the median progression-free survival (mPFS) in the T-DM1 monotherapy group exceeded that of the lapatinib plus capecitabine group by 3.2 months (9.6 months vs. 6.4 months), and median overall survival (OS) was 30.9 months compared

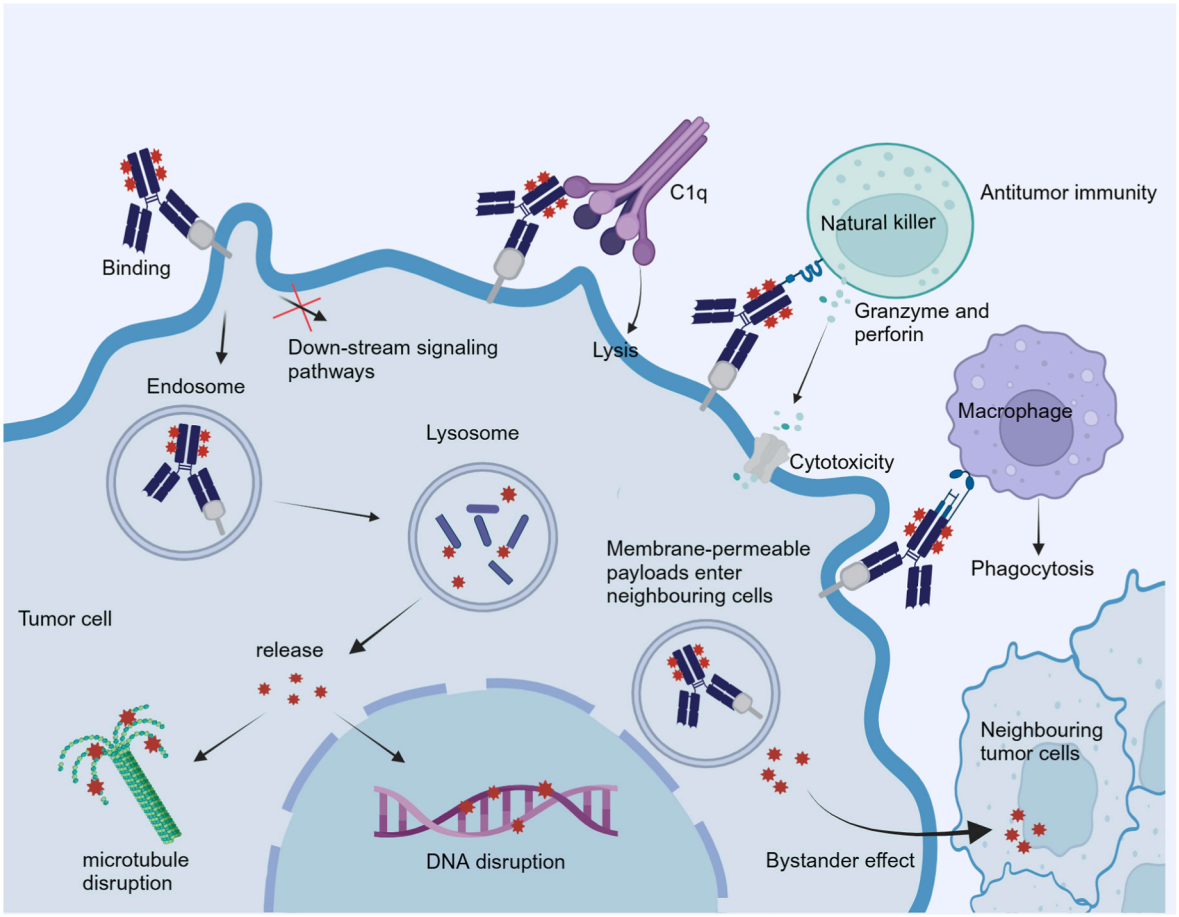

Fig. 1. Schematic presentation of the mechanism of action for an ADC.

to 25.1 months, respectively. This demonstrated a 32 % reduction in mortality risk with T-DM1 treatment [21]. Following this study, in 2013, FDA approved T-DM1 as the standard second-line treatment for patients with metastatic (Fig. 2), Her-2+ BC [22,23]. Subsequent research, the TH3RESA trial, evaluating T-DM1 against the treatment of physician's choice (TPC), supported these conclusions, showing a significant improvement in mPFS with T-DM1 (6.2 months vs. 3.3 months). The final mOS analysis indicated a considerable increase in survival for the T-DM1 group (22.7 months vs. 15.8 months) [24]. Importantly, the TH3RESA trial enrolled individuals who had received at least two prior anti-Her-2 therapies, suggesting the benefits of T-DM1 even after multiple lines of targeted Her-2 therapy. Further investigation has been conducted into the potential benefits of T-DM1 in earlier stages of treatment, specifically in the adjuvant setting. The KATHERINE trial found that for patients who did not achieve a pathological complete response (pCR), T-DM1 substantially lowered the recurrence risk by 50 % and increased the absolute invasive disease-free survival (iDFS) benefit by 11.3 % compared to trastuzumab, after a median follow-up of 41 months [25]. Consequently, the FDA has approved T-DM1 for monotherapy in the adjuvant treatment of Her-2+ early BC in patients with residual invasive disease post-neoadjuvant therapy involving taxanes and trastuzumab [26]. Moreover, the efficacy of T-DM1 in comparison to traditional chemotherapy combined with targeted therapy regimens in the neoadjuvant setting was assessed in the KRISTINE trial. It reported a higher probability of event-free survival (EFS) events in the T-DM1 group (13.9 %) compared to the control group (5.9 %), indicating that the traditional chemotherapy combined with dual anti-Her-2 blockade maintains its superiority [27]. Furthermore, the KAMILLA trial's exploratory subgroup analysis, representing the largest cohort of Her-2+ BC patients treated with T-DM1 in a prospective study, showed a median PFS and OS of 6.8 and 27.2 months, respectively [28].

Overall, the efficacy of T-DM1 in the adjuvant treatment of Her-2-positive early breast cancer and the multi-line treatment of advanced breast cancer is proved by robust evidence from trials such as EMILIA and TH3RESA. However, its comparative effectiveness against traditional chemotherapy, in conjunction with dual anti-Her-2 blockade as a neoadjuvant therapy, remains to be conclusively determined.

3.2. *Trastuzumab deruxtecan(T-Dxd, trastuzumab/Dxd)*

T-Dxd represents a pivotal shift in the therapeutic landscape for Her-2+ BC, emerging as a viable option for subsequent lines of therapy. In the DESTINY-Breast 01 study, patients with advanced Her-2 positive breast cancer treated with T-Dxd had a remarkable mPFS of 16.4 months [29]. Further validation came from the DESTINY-Breast 02 study, which supplemented the OS data for T-Dxd, the median OS of the T-Dxd group and the TPC group was 39.2 months and 26.5 months, respectively [30]. Moreover, data from the DESTINY-Breast 03 study unveiled that T-Dxd, when compared to T-DM1, significantly prolonged PFS in patients with advanced BC who had not responded to first-line therapy with trastuzumab, pertuzumab, and a taxane (THP), recording a PFS more than fourfold longer (28.8 months versus 6.8 months), at the 2024 ASCO Congress, the study published OS results, with 52.6 months of OS in the T-Dxd group, significantly longer than 42.7 months in the T-DM1 group [31,32]. In December 2019, FDA granted accelerated approval to T-Dxd for adult patients with unresectable or metastatic Her-2+ solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. Historically, monoclonal antibody therapies have demonstrated limited efficacy in patients with brain metastases (BMs). However, T-Dxd has transformed the treatment landscape

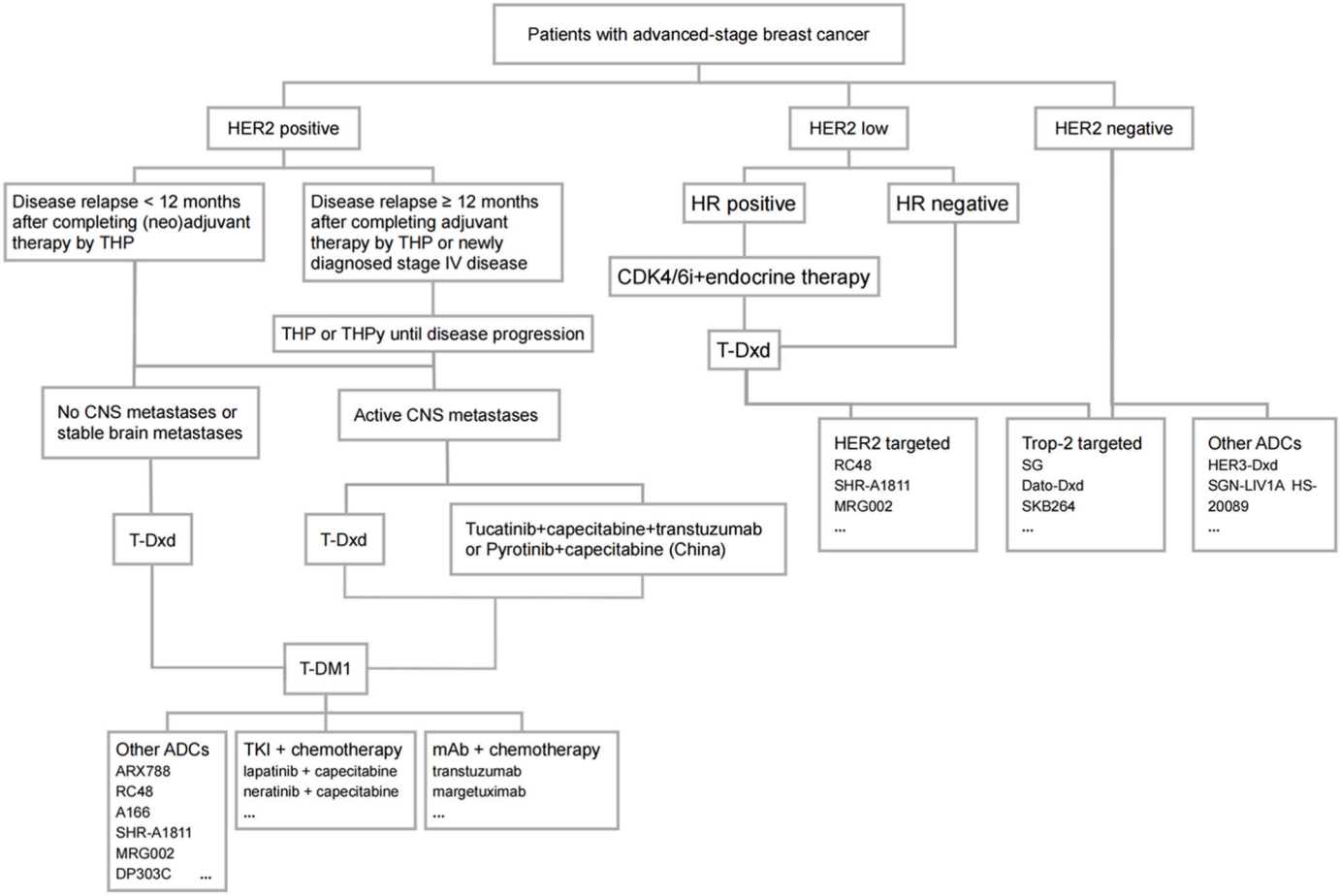

Fig. 2. Treatment algorithm for patients with advanced-stage breast cancer. T: taxane, H: transtuzumab, P: pertuzumab, Py: pyrotinib, CDK4/6i: CDK4/6 inhibitor.

for these patients. The recent DESTINY-Breast12 single-arm clinical trial further substantiated this potential, yielding promising results. In the cohort with BMs, the 12-month PFS rate was 61.6 % (95 % confidence interval [CI]: 54.9–67.6), while the 12-month central nervous system (CNS) PFS was 58.9 % (95 % CI: 51.9–65.3). Notably, among patients with active brain metastases, the 12-month PFS rate was even more impressive, reaching 66.7 % (95 % CI: 53.4–76.9) [33]. In comparison, the best prior results were observed in the HER2CLIMB trial, where the combination of tucatinib, trastuzumab, and capecitabine achieved a 12-month PFS of only 35 % [34]. Currently, no head-to-head clinical trials have compared T-Dxd with tucatinib, leaving the relative efficacy of these agents inconclusive. Nonetheless, we can derive some clinical insights from the patient populations in both studies. The DESTINY-Breast12 trial included a higher proportion of untreated patients with active brain metastases (33.05 %), and these individuals achieved a 12-month PFS of 47 % with T-DXd, whereas the HER2CLIMB trial primarily enrolled previously treated patients. Additionally, according to the results of the PERMEATE study, the combination of pyrotinib and capecitabine has also shown promising efficacy in the Chinese population with brain metastases, with a median PFS of 11.3 months [35](Fig. 2).

3.3. Trastuzumab duocarmazine (SYD985, trastuzumab/duocarmycin)

SYD985 incorporates the duocarmycin derivative as its payload through an innovative technology platform. This platform engineers a seco-DUBA structure, enhancing water solubility and optimizing alkylation rates. The drug's linker, a peptide susceptible to cleavage by cathepsin B within cellular environments, safeguards the seco-DUBA structure, thus ensuring its high stability in the bloodstream and minimizing off-target toxicity [36]. Recent outcomes from the TULIP trial, part of the ongoing Phase 3 clinical evaluation of SYD-985 in patients with Her-2+ BC, were unveiled at the 2023 ESMO Congress. These findings demonstrate that SYD985 significantly extends PFS compared to the control group (7.9 vs 4.9 months, HR = 0.63) [37]. While the survival benefits confirm SYD-985's efficacy in treating Her-2-positive breast cancer, its performance does not surpass that of the already available drug, T-Dxd. This finding could help to explain why, despite its earlier development, the FDA has not yet approved SYD985. SYD985 is highly effective in treating heterogeneous tumors via the bystander effect. It has a 54 times greater killing effect on Her-2 negative cells compared to T-DM1 [38]. Further research is necessary to determine whether SYD-985 can produce positive outcomes in populations with low Her-2 expression.

3.4. FS-1502(Trastuzumab/MMAF)

FS-1502, leveraging Monomethyl auristatin F as its payload—a member of the tubulin inhibitors class—disrupts the cytoskeletal structure of tumor cells, impeding mitotic division. This cytotoxic agent exhibits a potency 100 to 1000 times greater than that of doxorubicin. In a Phase I dose-escalation trial (NCT03944499) targeting advanced Her-2-overexpressing solid tumors, FS-1502 demonstrated favorable tolerability and significant antitumor efficacy [39]. Specifically, among patients with Her-2+ BC who had not responded to multiple lines of therapy, the ORR reached 53.7 %, with a mPFS of 15.5 months. Notably, only mild ocular toxicity was reported, and no instances of interstitial lung disease were observed. Currently, a Phase III clinical trial (NCT05755048) is in progress to further assess the effectiveness and safety of FS-1502 in treating advanced Her-2+ BC.

3.5. A166(Trastuzumab/Duo-5)

A166, an innovative Her-2-targeted ADC, integrates trastuzumab with the microtubule inhibitor auristatin derivative, duostatin-5 (Duo-5), through a cleavable linker [40]. In this phase I study, at the recommended dose, the drug demonstrated a good safety profile with an ORR of 73.9 % and a median PFS of 12.3 months [41]. On May 11, 2023, the National Medical Products Administration (NMPA) accepted the marketing application for A166 for the treatment of Her-2-positive unresectable locally advanced, recurrent, or metastatic breast cancer following failure of second-line or higher anti-Her-2 therapies. To determine whether it can be used as an alternative to T-DM1 or overcome drug resistance in ADCs, we must await the results of the phase III clinical trial (CTR20231740).

3.6. SHR-A1811(Trastuzumab/SHR9265)

SHR-A1811, a domestically developed ADC in China, exhibits a structural similarity to T-Dxd. Characterized by its innovative payload, SHR169265, and an optimized DAR, SHR-A1811 has demonstrated an impressive pharmacokinetic profile along with a favorable preclinical safety profile [42]. Notably, phase I clinical trial results revealed that SHR-A1811 achieved an ORR of 81.5 % for the follow-up treatment of Her-2+BC, compared to the 62 % ORR reported for T-Dxd in the DESTINY-Breast01 trial. These findings position SHR-A1811 as a potential best-in-class anti-Her-2 ADC [43,44].

3.7. ARX788(Trastuzumab/MMAF)

ARX788 intricately conjugates a monoclonal antibody specific to Her-2 with Ambrastatin269, a potent cytotoxic agent targeting tubulin [45]. The initial findings from a Phase I clinical trial (CTR20171162) underscored ARX788's capacity to attain a satisfactory ORR in patients, while maintaining a safety profile devoid of dose-limiting toxicity or serious adverse effects [46]. Bolstering its potential further, data from a Phase II trial (NCT04829604) revealed an ORR of 51.7 % and a disease control rate (DCR) of 100 % in patients with Her-2+ metastatic BC, including those resistant or refractory to T-DM1. In the latest results of Phase II/III trial ACE-Breast-02, ARX788 significantly extended PFS compared to lapatinib plus capecitabine in patients with HER2+ advanced breast cancer previously treated with trastuzumab and taxane (11.33 months vs 8.25 months, HR = 0.64, P = 0.0006) [47,48]. Advancing on these promising results, a Phase III clinical trial (NCT05426486) is currently in progress. This trial is designed to assess the combined efficacy and safety of ARX788 and pyrotinib as a neoadjuvant therapy for Her-2+ BC, further cementing ARX788's potential as a foundational element in treating this formidable disease.

3.8. MRG002(MAB802/MMAE)

MRG002, employing the Monomethyl auristatin E payload, has demonstrated initial anti-tumor efficacy in its first-in-human (FIH) study (MRG002-001) conducted in China, specifically in patients with Her-2+, late-stage BC. The ORR for 47 patients with evaluable HER2-positive breast cancer was 53 %, for 23 patients with liver metastasis it was 61 %, and for 5 patients with liver metastasis combined with brain metastasis it was 60 %, indicating that this drug has a high response rate in patients with metastasis, warranting further investigation [49]. A Phase III clinical trial is now in progress to assess the efficacy and safety of MRG002 for the treatment of Her-2+, unresectable locally advanced or metastatic BC.

3.9. RC-48(Hertuzumab/MMAE)

RC-48 is the first innovative ADC developed independently in China to enter clinical research. This innovative therapeutic has garnered regulatory approval for two distinct indications: the treatment of Her-2-overexpressing locally advanced or metastatic gastric cancer and gastroesophageal junction adenocarcinoma following at least two systemic chemotherapy regimens, as well as Her-2+ locally advanced or metastatic urothelial carcinoma in patients previously treated with

systemic chemotherapy [50]. In the realm of breast cancer, the ASCO released pivotal data in 2021 concerning patients with either Her-2+ or Her-2-low expressing breast cancer. The findings highlighted a superior benefit-risk profile within the 2.0 mg/kg dosing cohort. Furthermore, the results from the C001 study demonstrated a notable ORR of 42.9 % in patients with metastatic Her-2+ BC, accompanied by a median PFS of 5.7 months [51].

4. For HER-2 low breast cancer

Breast cancer is classified as Her-2-positive if there is evidence of Her-2 overexpression, indicated by a score of 3+ in immunohistochemistry (IHC) assays, or gene amplification as detected by in situ hybridization (ISH) assays in at least one tumor sample. Conversely, the absence of these markers categorizes BC as Her-2-negative. Recently, a revised nomenclature has been suggested for cases exhibiting IHC scores of 1+ or 2+ coupled with negative ISH results, now termed Her-2-low BC [52]. Subsequent studies have revealed that this subtype may benefit from Her-2-targeted therapies, as demonstrated by the efficacy of novel anti-Her-2 agents like T-Dxd.

4.1. T-Dxd

Based on the membrane-permeable nature of the payload and the properties of the linker, T-Dxd can provide cytotoxic activity against off-targeted cancer cells, called the bystander effect. The pivotal Phase III DESTINY Breast04 (DB04) trial, involving participants with low Her-2 expression, showcased significant improvements in OS and PFS across various hormone receptor statuses, with T-Dxd outperforming the treatment of physician's choice [53]. Subsequently, the NMPA approved the indication for T-Dxd: monotherapy for adult breast cancer patients with unresectable or metastatic Her-2 low expression (IHC 1+ or IHC 2+/ISH-) who have previously received at least one systemic therapy in the metastatic stage of disease or who relapsed during or within 6 months after completion of adjuvant chemotherapy (Fig. 2).

4.2. SHR-A1811

The ORR of SHR-A1811 when used for posterior line treatment of breast cancer with low Her-2 expression can reach 55.8 %. In terms of safety, the incidence of interstitial pneumonia caused by T-Dxd has been condemned by the public, whereas the incidence of SHR-A1811 is just 3.2 % [43]. In addition, Phase III clinical trials (NCT05814354, NCT06126640) are underway in patients with different subtypes of breast cancer to evaluate whether SHR-A1811 has a dual benefit in survival time and quality of life compared to conventional therapies.

4.3. MRG-002

In preclinical studies, MRG002 demonstrated efficacy against BC characterized by low Her-2 expression. Subsequently, a Phase II trial was initiated to assess both the safety and antitumor activity of MRG002 in this patient subset. The trial, involving 49 evaluable patients with low Her-2 expression, reported an ORR of 34.7 % and a DCR of 75.5 %. Notably, the study included 8 patients with TNBC who had undergone at least two prior lines of therapy. The results from this subgroup were particularly promising, further substantiating the significant efficacy and safety of MRG002 for BC patients exhibiting low Her-2 expression [54].

4.4. RC-48

Due to its remarkable bystander effect, RC48 also demonstrated obvious efficacy in BC with low Her-2 expression. The Phase Ib/II trial C003 CANCER (NCT03052634) enrolled 48 patients with Her-2 low expression, to receive treatment with RC48. The ORR and mPFS for patients treated with a dose of 2.0 mg/kg were 39.6 % and 5.7 months, respectively. Overall, RC48 has shown promising potential in treating Her-2-negative BC, potentially bridging a significant gap in current treatment options [51].

5. For HER2-ultro-low/negative breast cancer (ADC drugs targeting Trop-2)

5.1. Sacituzumab govitecan (SG, IMMU-132, hRS7/SN-38)

SG is the first Trop-2-targeted ADC approved by the FDA, demonstrating significant efficacy in patients with Her-2-negative BC, which include HR+/HER-2 BC patients and TNBC patient [55]. TROPiCS-02 study indicated that the SG group achieved an extension of mPFS over the TPC group (5.5 months vs 4.0 months, $P = 0.0003$). And the OS data for SG and TPC was 14.5 months vs. 11.2 months ($P = 0.01$).The patients included in this study were all treated with CDK4/6 inhibitors and had received 2–4 lines of chemotherapy, suggesting that SG could be a new treatment option for HR+/Her-2-BC patients with poor response to endocrine therapy [56]. Additionally, the accelerated approval of SG in 2020 has introduced a targeted treatment alternative for TNBC. In the IMMU-132-01 study, 108 patients with metastatic TNBC treated with SG as a third-line or subsequent therapy showed an ORR of 33 %, with significant improvements in mPFS and OS—5.5 months and 13 months, respectively [57]. In the phase III ASCENT trial, SG significantly outperformed single-agent chemotherapy chosen by physicians, with the mPFS at the primary endpoint reaching 4.8 months versus 1.7 months, and the mOS at the secondary endpoint extending to 11.8 months versus 6.9 months [58]. These results underscore SG's potential as an effective option for treating advanced TNBC post-initial treatment.

5.2. Datopotamab deruxtecan (DS-1062, hTINA1/Dxd)

Datopotamab deruxtecan is an innovative ADC targeting Trop-2, currently under clinical trial. It is specifically designed to address Her-2-negative BC. The first Phase III data from the TROPION-Breast01 trial, involving HR+/Her-2- advanced BC, was unveiled at the 2023 ESMO Meeting. The results revealed that the median PFS in the Dato-DXd group was significantly superior than that in the investigator's choice of chemotherapy group (6.9 months vs 4.9 months) [59]. Additionally, the use of Dato-DXd extends to the treatment of TNBC which has a higher expression of Trop-2. Ongoing clinical trials include TROPION-Breast02, which compares Dato-DXd's efficacy and safety against chemotherapy in the first-line treatment of unresectable locally advanced or metastatic TNBC unsuitable for PD-1/PD-L1 inhibitor therapy [60]. Another trial, TROPION-Breast03, is evaluating Dato-DXd as postoperative adjuvant therapy in TNBC patients with residual lesions after neoadjuvant therapy.

5.3. SKB-264

The first phase II clinical data for SKB-264 showed that the monotherapy was effective in treating metastatic TNBC after multiple prior treatments [61]. As a result, SKB-264 has received two "breakthrough therapy" designations from the Center for Drug Evaluation of the NMPA. These designations are for the treatment of locally advanced or metastatic TNBC, as well as locally advanced or metastatic HR+/Her-2- BC that has previously undergone at least second-line chemotherapy. Ongoing clinical trials are examining whether SKB-264, alone (NCT05347134, NCT06081959) or in combination with other therapies, such as PD-L1 monoclonal antibody KL-A167 (NCT05445908), can offer improved survival benefits for patients with advanced TNBC and advanced HR+/Her-2- BC.

6. Other ADCs under pre/phase-II clinical development

In the evolving landscape of BC treatment, researchers are broadening their horizons beyond the well-known Her-2 and Trop-2 targets to explore the potential of other tumor-associated antigens as novel targets for ADCs. Notably, Nectin-4, a type I membrane protein, has been identified as a promising candidate due to its role in stimulating tumor cell proliferation and invasion through activation of the PI3K/AKT pathway [62]. Similarly, the interaction of the membrane protein associated with folate metabolism, FRα, and its interaction with LYN tyrosine kinase plays a pivotal role in tumor genesis by regulating PEAK1 phosphorylation and consequently activating ERK and STAT3 signaling pathways [63]. Additionally, the immunomodulatory molecule B7-H4 presents a significant interest in its ability to suppress anti-tumor T cell activity, leading to T cell exhaustion or dysfunction, and thus facilitating tumor immune evasion [64]. These emerging targets, supported by preclinical research, herald a new development frontier for the next generation of ADC therapeutics. We summarized the potential ADC medicines based on their respective targets (Table 1), which is an important step forward in the search for more effective breast cancer treatments.

7. ADC combination medication regimens

As new targets are explored, the range of indications for ADCs is expanding. However, in clinical settings, resistance to drugs like T-DM1 remains an issue for some patients. Drug resistance can manifest at various stages, including the downregulation or loss of antigen expression, defects in endocytic trafficking pathways, impaired lysosomal function, and limited toxicity of the payload [65]. We have investigated several combination drug regimens to counteract ADC resistance and enhance its efficacy (Fig. 2). The optimal strategy involves selecting combinations that produce additive or synergistic effects on tumor cells or the tumor microenvironment while avoiding overlapping toxicities.

7.1. Combine with chemotherapeutics

Many ADCs utilize microtubule inhibitors as payloads. To enhance

Table 1
Potential ADC medicines based on their respective targets.

Drug	Target	Linker	Payload	DAR	Phase	Clinical trial number	Disease status
ALT-P7	HER-2	Cleavable	Microtubule polymerization inhibitor, auristatin analogueMMAE	2	I	NCT03281824	R/R Advanced HER2+ BC
PF-06804103	HER-2	Cleavable	Microtubule polymerization inhibitor, auristatin analogueAur0101	4	I	NCT03284723	R/R Advanced BC
ZW49	HER-2	Cleavable	Microtubule polymerization inhibitor, auristatin-basedpayload	NA	I	NCT03821233	R/R HER2+ cancer
XMT-1522	HER-2	Cleavable	Microtubule polymerization inhibitor, AF-HPA moiety	12	I	NCT02952729	R/R HER2+ cancer
BDC-1001	HER-2	Non-cleavable	TLR7/8 inhibitor	NA	II	NCT04278144	R/R Advanced HER2 expressing cancer
BB-1701	HER2	Cleavable	Eribulin	NA	II	NCT06188559	R/R Advanced HER2 ± BC
GQ1001	HER2	NA	Microtubule polymerization inhibitor, maytansinoidderivative DM1	2	II	NCT04450732 NCT05575804	R/R Advanced HER2+ cancer R/R Advanced HER-2 BC
U3-1402	HER-3	Cleavable	TOP1 inhibitor, camptothecin analogue DXd	8	I II II	NCT04610528 NCT04699630 NCT02980341	Preoperative hormone receptor+/HER2-BC R/R mBC R/R HER3+mBC
SGN-LIV1	LIV-1	Cleavable	Microtubule polymerization inhibitor, auristatin analogueMMAE	4	II I	NCT03310957 NCT01969643	First line mTNBC R/R mBC
MORAb-202	FRα	Cleavable	Microtubule inhibitor, eribulin	4	II	NCT04300556	R/R Advanced solid tumors
PRO1184	FRα	Cleavable	Exatecan	8	II	NCT05579366	R/R Advanced solid tumors
BAT8006	FRα	Cleavable	Topoisomerase I inhibitor (TOP1i)	8	I	NCT05378737	R/R Advanced solid tumors
CX-2009	CCD166	Cleavable	Microtubule polymerization inhibitor, maytansinoid derivative DM4	3.5	II II	NCT04596150 NCT03149549	R/R Advanced HER-2 BC R/R Advanced solid tumors
ASG-22ME	Nectin-4	Cleavable	Microtubule polymerization inhibitor, auristatin analogueMMAE	3–4	II	NCT04225117	R/R Advanced solid tumors
NBE-002	ROR1	Non-cleavable	Highly potent anthracycline derivative PNU-19682	NA	I	NCT04410224	R/R Advanced solid tumors
BA3021	ROR2	Cleavable	Microtubule polymerization inhibitor, auristatin analogueMMAE	NA	II	NCT03504488	R/R Advanced solid tumors
PF-0664720	PTK7	Cleavable	Microtubule polymerization inhibitor, auristatin-based payload Aur0101	4	I	NCT02222922	R/R Advanced solid tumors
AZD8205	B7-H4	Cleavable	topoisomerase I inhibitor (TOP1i)	8	II	NCT05123482	R/R Advanced solid tumors
SGN-B7H4V	B7-H4	Cleavable	Microtubule polymerization inhibitor, auristatin analogueMMAE	NA	I	NCT05194072	R/R Advanced solid tumors
PYX-201	ED-B	Cleavable	Microtubule polymerization inhibitor, auristatin-based payload Aur0101	4	I	NCT05720117	R/R Advanced solid tumors
MEN-1309	CD205	Cleavable	Microtubule polymerization inhibitor, maytansinoid derivative DM4	3.7	I	NCT04064359	R/R Advanced solid tumors
IMGC936	ADAM9	Cleavable	maytansinoid linker-payload,DM21-C	2	II	NCT04622774	R/R Advanced solid tumors
ASN-004	5T4	NA	Auristatin F hydroxypropylamide (AF-HPA)	10–12	I	NCT04410224	R/R Advanced solid tumors
TH1902	SORT1	Cleavable	Docetaxel	2	I	NCT04706962	R/R Advanced solid tumors

Abbreviations: DAR, drug-antibody ratio; FRα, folate receptor alpha; HER, human epidermal growth factor receptor; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; NA, not acquired; PTK7, protein tyrosine kinase 7; ROR, receptor tyrosine kinase orphan receptor; TOP, topoisomerase; TROP2, trophoblast cell surface antigen 2; R/R, relapse/refractory.

the blockade of the G2/M phase of the cell cycle, DNA-damaging agents can be combined with microtubule inhibitors, with improved efficacy noted when microtubule inhibitors are used sequentially after DNA-damaging agents [66,67]. Additionally, chemotherapy may influence the expression of surface antigens targeted by ADCs. For instance, in pancreatic cancer cells, combining gemcitabine with T-DM1 has shown increased efficacy due to gemcitabine's ability to up-regulate Her-2 expression [68]. In a phase Ib/IIa study, the combination of T-DM1 and Paclitaxel for Her-2+ BC resulted in an ORR of 47.8 % and a mPFS of 7.4 months [69]. However, this combination treatment significantly increased toxicity. Another study involving T-DM1 and Pegylated doxorubicin reported an ORR of 40 % [70]. These findings indicate that while ADC and chemotherapy combinations may offer survival benefits, the associated increase in toxic side effects cannot be overlooked [71].

7.2. Combine with targeted therapies

ADCs, when combined with targeted therapies, can significantly improve the inhibition of oncogenic signaling pathways. This combination enhances the utilization of surface antigens and increases the sensitivity of tumors with low antigen expression, while also modifying the tumor microenvironment [72]. Research is ongoing to explore the potential synergies between ADCs and existing targeted treatments, including macromolecular monoclonal antibodies, small molecule TKIs, PI3K inhibitors (PI3Ki), CDK4/6i, and PARP inhibitors (PARPi).

The monoclonal antibody pertuzumab binds to domain II of the extracellular region of the Her-2 receptor, inhibiting its ability to form dimers with other HER receptors, particularly the Her-2-HER3 complex. This prevents the ligand regulator NRG-1β from diminishing the cytotoxic effects of T-DM1 in BC cell lines [73]. In a Phase Ib/IIa trial combining T-DM1, pertuzumab, and docetaxel in patients with Her-2+ BC, the treatment significantly improved the objective response rate to 80 % compared to 43.6 % [74]. However, a subsequent Phase III trial (NCT02131064) combining T-DM1 with pertuzumab did not yield the desired outcomes. The three-year EFS rate for the combination treatment was 85.3 %, lower than the 94.2 % observed in the T-DM1 monotherapy group. The specific mechanisms behind these results require further investigation [75].

Small molecule TKIs such as lapatinib, nilotinib, and tucatinib, bind to ATP binding sites and inhibit downstream signal transduction. These inhibitors are particularly effective in enhancing the inhibition of the PI3K-AKT and MAPK pathways when used in combination with T-DM1 [76–78]. At the 2023 SABCS, results from the Phase III Her-2CLIMB-02 study were presented. The findings indicate that combining tucatinib with T-DM1 significantly improves PFS in patients with Her-2+ advanced BC, notably in those with brain metastases. The study showed a mPFS of 9.5 months with the combination therapy compared to 7.4 months with the control group [79]. Importantly, tucatinib plus trastuzumab and capecitabine is approved for patients with metastatic HER 2+ breast cancer who have previously received one or more HER2-targeted therapies [80]. It is also suggested as the first option for patients who have disease progression after T-Dxd treatment, especially those with active brain metastases [81,82]. However, this strategy lacks prospective cohort research evidence and requires additional investigation. Besides, excessive activation of the PAM signaling pathway is also a key mechanism of drug resistance in BC. The combination of T-DM1 and PI3Kis has been found to have a synergistic effect in inhibiting the PI3K/AKT/mTOR pathway [83]. In a Phase I study of T-DM1 combined with the PI3Ki Alpelisib for treating Her-2+ BC, the ORR was 43 %, and the mPFS was 8.1 months [84].

Additionally, CDK4/6 serves as a common downstream target for several growth-promoting signaling pathways, including RAS/MAPK, ER, and PI3K/mTOR [85]. CDK4/6i enhances cell cycle control and inhibits tumor cell proliferation by selectively targeting CDK4/6 [86]. In a phase I clinical trial, the combination of T-DM1 and the CDK4/6i Palbociclib for treating Her-2+ BC yielded an ORR of 33 % and a mPFS of 6 months [87]. When T-DM1 was combined with another CDK4/6i, Ribociclib, the ORR dropped to 16.7 % [88]. The efficacy of CDK4/6 inhibitors in combination with T-DM1 was not significant, this may be due to the CDK4/6i's role in preventing tumor cells from entering the S/M phase, thereby diminishing the impact of T-DM1 [89].

Recently, a Phase 1b study indicates that the PARP inhibitor Rucaparib effectively disrupts DNA repair in cancer cells with BRCA gene mutations, which enhances cancer cell mortality and hampers tumor progression. The result showed that SG and Rucaparib achieved an ORR of 50 % and a CBR of 100 %, suggesting a synergistic interaction [90–92].

7.3. Combine with immunotherapy

Numerous studies suggest that ADCs could boost the efficacy of immunotherapy. The induction of immunogenic cell death by ADC leads to the maturation of dendritic cells, increases T-lymphocyte infiltration, and enhances immune memory. Additionally, these studies indicate increased expression of immunomodulatory proteins like PD-L1 and MHC [93–96]. It is reported that T-DM1 could enhance tumor-specific immunity by increasing stromal tumor-infiltrating lymphocytes [97]. However, the Phase II KATE2 study, which investigated the combination of T-DM1 and Atezolizumab in treating Her-2- BC, did not yield significant improvements in PFS but instead showed a higher incidence of adverse effects [98,99]. Interestingly, a subset of patients with PD-L1 positive tumors did experience a PFS benefit, with an mPFS of 8.5 months for the T-DM1 plus Atezolizumab group compared to 4.1 months for the control group, though this finding was not statistically significant (HR = 0.60, 95 % CI: 0.32–1.11, P = 0.099) [99]. The limited sample size and variability at baseline temper these results, leaving the true benefit uncertain. Consequently, the ongoing Phase III KATE3 study continues to explore this combination [100]. Moreover, the preclinical study of Dato-Dxd has shown that combining its payload 'Dxd' with immunotherapy can enhance T-cell recognition of tumor cells, bolster the immune response, and increase anti-tumor activity, a finding supported by data from the BEGONIA study released at the 2023 ESMO [16,101]. When used with the immune checkpoint inhibitor Durvalumab in the first-line treatment of advanced TNBC, regardless of PD-L1 expression, Dato-Dxd demonstrated potential for additional benefits in ORR, warranting further investigation [102].

8. Discussion

HER2-targeted ADCs have established a pivotal role in treating both HER2-positive and HER2-low breast cancer patients, while TROP-2-targeted ADCs, such as SG, have demonstrated remarkable efficacy in TNBC. This review synthesizes clinical data to outline the therapeutic pathways for breast cancer patients treated with ADCs (Fig. 3). As depicted, ADCs exemplified by T-Dxd now span the full spectrum of breast cancer therapies. Although current clinical data for ADCs targeting HER2-low and TNBC patients are limited, the growing variety of ADCs in development holds promise for future breakthroughs. Target selection is pivotal in advancing effective ADCs [103]. While the development of HER2-targeted ADCs in breast cancer has progressed earlier and more comprehensively, a biomarker-agnostic strategy is currently applied to other ADCs targeting proteins like HER3 and Trop-2, which are highly expressed in breast cancer cells. In the TROPiCS-02 study, no significant differences in PFS and OS were observed between subgroups with high Trop-2 expression and low Trop-2 expression, potentially due to the bystander effect [104,105]. Notably, longitudinal evaluations revealed that anti-HER2 ADC agents, particularly T-DXd, displayed superior efficacy, specificity, and cytotoxicity compared to ADCs targeting non-driver oncogenes such as HER3-DXd and SG. The absolute difference in ORR among these drugs was substantial, ranging from 20% to 30 %, with mPFS and mOS differences nearly doubling. Despite similar designs between HER3-DXd

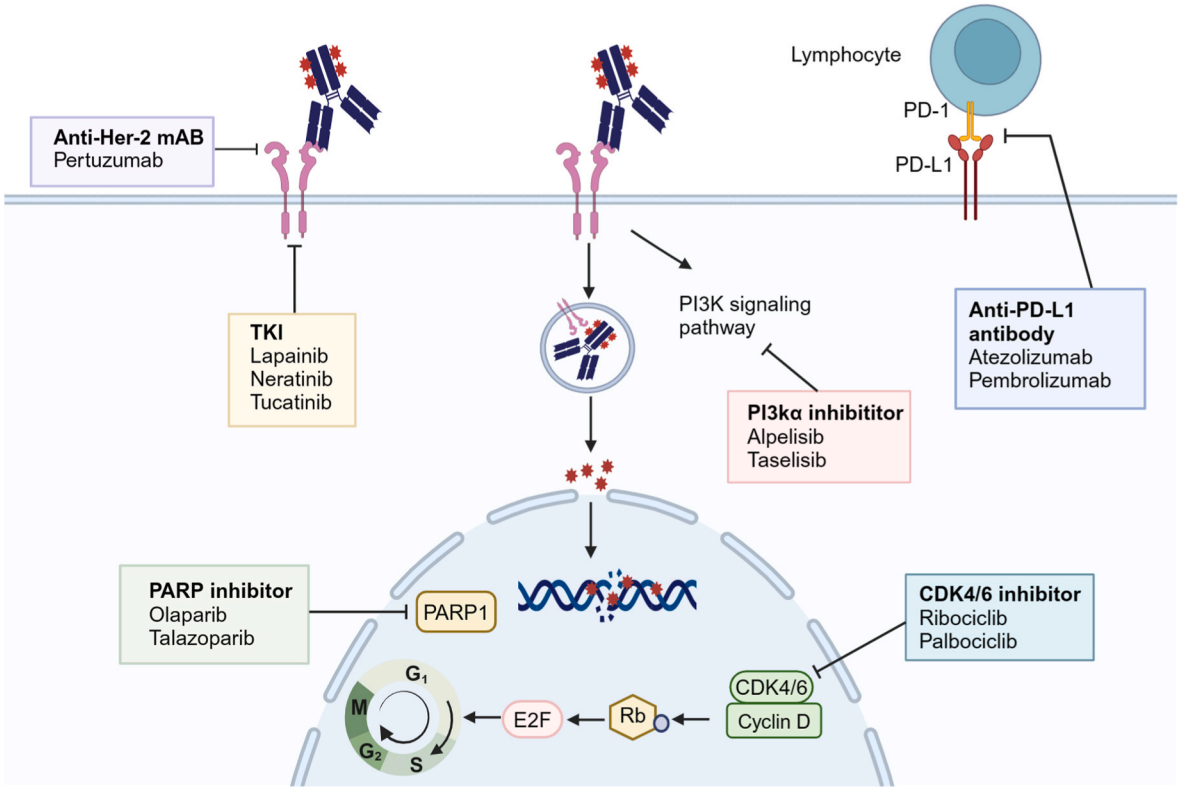

Fig. 3. ADC combination regimens to address ADC resistance and enhance efficacy.

and T-DXd, the primary difference lies in their antigen targets, while the linker, payload, and DAR remain consistent, highlighting the importance of target selection. Oncogenic targets significantly influence ADC behavior, potentially through enhanced internalization and ubiquitination of the target-ADC complex, reducing downregulation—a known ADC resistance mechanism that impairs drug uptake. Additionally, oncogenic drivers tend to be uniformly and highly expressed in tumor tissues due to evolutionary pressures [106]. ADCs targeting driver oncogenes also retain some intrinsic mAb functionality, impairing target protein function by blocking receptor ligands, disrupting dimerization, and inducing endocytosis and degradation. The Fc segment of ADC antibodies can engage with FcR on effector cells (e.g., NK cells, macrophages), promoting direct cytotoxic effects like ADCC, CDC, and ADCP, while inhibiting downstream antigen receptor signaling [8,107,108], reinforcing the hypothesis that ADCs targeting oncogenic or functional proteins may offer enhanced antitumor efficacy compared to those targeting non-functional proteins. Innovations in ADC drug development can be pursued in multiple dimensions: 1) Mechanism innovation: Combining novel ADC mechanisms, such as dual conjugation of cytotoxic agents or conjugating ADCs with PD-L1 inhibitors, especially for HER2-positive breast cancer. 2) Combination drug innovation: Concurrently conjugating cytotoxic agents with two large molecule monoclonal antibodies or combining ADCs with immune checkpoint inhibitors, monoclonal antibodies, or small molecule TKIs. 3) Combination therapy innovation: Integrating ADCs with immunotherapy, endocrine therapy, targeted therapy, or chemotherapy.

Resistance is a critical challenge in ADC therapy, driven by mechanisms such as antibody-mediated resistance, impaired drug transport, lysosomal dysfunction, and payload-specific resistance. Strategies to overcome resistance include developing drugs targeting novel mechanisms and exploring combination therapies addressing different resistance pathways. Designing effective ADC combination regimens should adhere to the following principles: minimizing additive toxicities to avoid exacerbating adverse effects, ensuring synergistic interactions to enhance therapeutic efficacy, and supporting the regimen with robust evidence-based feasibility. Current ADC combination regimens undergoing clinical trials encompass immunotherapy, endocrine therapy, targeted therapy, and chemotherapy. The advent of precision medicine has introduced a broader array of treatment options and reshaped the therapeutic landscape for breast cancer. From mechanistic innovations to clinical applications, ADCs continue to advance the frontier of breast cancer treatment, offering the potential for significant patient benefits.

CRediT authorship contribution statement

Lu Sun: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Xiaomeng Jia:** Visualization, Methodology, Investigation, Data curation. **Kainan Wang:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Man Li:** Writing – review & editing, Project administration, Methodology, Funding acquisition.

Ethical approval

Ethical approval was not required.

Declaration of competing interest

The authors declare no competing interests.

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