Review

Next-Generation HER2-Targeted ADCs for Treatment of Breast Cancer: Precision Oncology's New Frontier

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Review

Next-Generation HER2-Targeted ADCs for Treatment of Breast Cancer: Precision Oncology's New Frontier

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Simple Summary: Antibody-drug conjugates (ADCs) represent a promising therapeutic category in oncology. In the treatment of HER2-positive metastatic breast cancer, trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) have been pivotal, demonstrating superior clinical outcomes over previous conventional treatments. This review focuses on approaches to overcome resistance to T-DM1 and T-DXd, while also shedding light on the emergence of innovative HER2-targeted ADCs. We discuss the characteristics and available efficacy and safety data on RC48, ARX-788, SYD985, BL-M0701, and the bispecific ADC zanidatamab zovodotin (ZW25). Clinical trials are crucial in determining the optimal dosing regimens, understanding resistance mechanisms, and identifying patient populations that would derive the most benefit from these treatments. With a focus on innovation and precision, these novel ADCs are at the forefront of a new era in targeted cancer therapy, holding the potential to improve outcomes for patients with HER2-positive and HER2-Low breast cancer.

Abstract: The HER2-targeted antibody-drug conjugates (ADCs) trastuzumab emtansine (T-DM1) and Trastuzumab deruxtecan (T-DXd) improved outcomes in breast cancer. Novel combinations and sequential approaches are under investigation to overcome resistance to T-DM1 and T-DXd. Furthermore, the landscape of HER2-targeted therapy is rapidly advancing with the development of ADCs designed to attack cancer cells with greater precision and reduced toxicity. Disitamab Vedotin (RC48) incorporates a HER2 antibody with unique binding epitope and a potent microtubule inhibitor as its cytotoxic moiety. ARX-788 comprises a non-cleavable linker and a novel maytansinoid derivative as the cytotoxic drug, engineered for increased stability and a higher drug-to-antibody ratio. SYD985, a duocarmycin-based ADC, is designed to be activated only in the acidic environment of the tumor, thus reducing off-target effects. BL-M0701 targets a different epitope on the HER2 protein, which might be beneficial in circumventing resistance that affects the binding of other ADCs and incorporate a camptothecin derivative as its payload. Zanidatamab zovodotin (ZW25) is an ADC that binds to two different HER2 epitopes simultaneously, enhancing the internalization and delivery of its cytotoxic payload. These and other ADCs in phase I trials hold the potential to improve outcomes for HER2-positive and HER2-Low breast cancer and possibly other solid tumors.

Keywords: HER2; breast cancer; breast neoplasms; antibody-drug conjugate; ADCs; trastuzumab emtansine; trastuzumab deruxtecan; disitamab Vedotin; ARX-788; SYD985; BL-M0701; zanidatamab zovodotin.

1. Introduction

Amplification and/or overexpression of the human epidermal growth factor receptor 2 (HER2) is a well-established prognostic marker for aggressive disease progression in patients with breast cancer [1]. The approval of trastuzumab, a monoclonal antibody targeting HER2, in 1998, marked a significant advancement in the therapeutic landscape for HER2-positive breast cancer [2].

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Subsequently, there has been a substantial increase in the clinical development of innovative therapies aimed at this specific cancer subtype [3]. The strategic incorporation of monoclonal antibodies and tyrosine kinase inhibitors, along with chemotherapy, endocrine therapy, and immunotherapy, has profoundly transformed the clinical outcomes for individuals diagnosed with HER2-positive breast cancer [4]. This paradigm shift has been evidenced at both the early and advanced stages of the disease [5].

Antibody-drug conjugates (ADCs) are an advanced modality in oncological treatment, integrating the specificity of monoclonal antibodies with the cytotoxic power of potent drugs [6]. As targeted therapeutics, ADCs are designed to selectively home in on and neutralize cancer cells expressing antigens, with a notable focus on HER2. This targeted approach amplifies treatment efficacy while minimizing the widespread adverse effects typically associated with conventional chemotherapy. The realm of ADCs has experienced exponential progress, characterized by substantial advancements in research and development, culminating in regulatory approvals that highlight their transformative role in medical oncology. To date, two ADCs directed against HER2 - trastuzumab emtansine (T-DM1, Kadcyla) [7] and trastuzumab deruxtecan (T-DXd, DS-8201a, Enhertu) [8]- have been approved by the Food and Drug Administration (FDA) and other regulatory agencies throughout the world for the management of HER2-positive breast cancer. In addition, T-DXd was approved for patients with HER2-Low metastatic breast cancer [9]. The DESTINY-Breast06 trial is testing the efficacy of T-DXd in patients with HER2-Ultra-Low breast cancer (IHC score 0, with 1-10% cells staining weakly).

The intricate action of ADCs is orchestrated by three integral elements: a monoclonal antibody, a chemical linker with stability or cleavability properties, and a cytotoxic agent [10]. The engineered monoclonal antibody is fine-tuned to detect and bind to an antigen prevalently expressed on the surface of cancer cells (e.g., trastuzumab). Following attachment, the antibody-drug complex is internalized via receptor-mediated endocytosis, a selective ingress contingent on distinctive cellular receptors [11]. While pinocytosis may also facilitate ADC uptake in the absence of the target antigen, the conjugated antibody's considerable size and hydrophilic character significantly mitigate nonspecific absorption, thereby augmenting the specificity and safety of ADCs.

Upon cellular entry, the ADC is trafficked to endosomes and lysosomes, where enzymatic cleavage of the linker ensues, culminating in the release of the cytotoxic payload. This release enables the drug to unleash its cell-killing potential. The therapeutic agents employed in ADCs are diverse, ranging from microtubule disruptors to topoisomerase inhibitors. A pivotal feature of ADCs is the 'bystander effect,' wherein the liberated toxins can permeate and exterminate neighboring tumor cells that may not express the target antigen, thereby facilitating a more thorough elimination of malignant cells [12].

ADCs targeting HER2 have emerged as a vanguard in the therapeutic arsenal against breast cancer. HER2 is a vital receptor implicated in cellular proliferation and growth regulation. ADCs targeting HER2 typically utilize trastuzumab as the antibody constituent, which specifically antagonizes the HER2 receptor, thus melding the precision of targeted therapy with the destructive force of chemotherapeutic agents (Table 1).

Table 1. Key Characteristics of Selected HER2 ADCs.

ADC Name	mAb	Payload	Linker	DAR	Clinical Phase
Trastuzumab emtansine (T-DM1)	Trastuzumab	DM1	Non-cleavable SMCC linker	3.5	Approved for metastatic HER2-positive breast cancer, residual disease after neoadjuvant therapy
Trastuzumab deruxtecan (DS-8201a)	Trastuzumab	DXd	Cleavable GGFG linker	8	Metastatic HER2-positive breast cancer
Trastuzumab duocarmazine (SYD985)	Trastuzumab	seco-DUBA	Cleavable vc linker	2.7	Phase I/II - Advanced Breast Cancer

ARX-788	Anti-HER2 mAb (ARX269)	MMAF	Non-cleavable linker conjugated to pAcF	1.9	Phase II - Advanced Breast Cancer
ALT-P7	Trastuzumab biobetter (HM2)	MMAE	Cleavable cysteine-containing peptide	2	Phase I
BL-M07D1	Trastuzumab	Ed-04	Cathepsin B cleavable linker	8	Phase I - Advanced Breast Cancer
Disitamab Vedotin (RC48)	Hertuzumab	MMAE	mc-val-cit PABC linker	4	Phase I
Zanidatamab zovodotin	Zanidatamab	Zovodotin	Cleavable linker vc	2-4 (variable)	Phase II

Abbreviations: mAb: Monoclonal Antibody; DAR: Drug-to-Antibody Ratio; DM1: Derivative of Maytansine 1; SMCC: Succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate; DXd: Derivative of Exatecan; GGFG: Glycine-Glycine-Phenylalanine-Glycine; vc: Valine-Citrulline; seco-DUBA: Seco-Duocarmycin HydroxyBenzamide Azaindole; MMAF: Monomethyl Auristatin F; pAcF: para-Acetylphenylalanine; MMAE: Monomethyl Auristatin E; mc-val-cit PABC: Maleimidocaproyl-valine-citrulline-p-aminobenzylcarbamate.

2. Trastuzumab Emtansine (T-DM1)

Trastuzumab emtansine (T-DM1) represents a seminal advancement in the treatment of breast cancer, acting as the archetype ADC approved for this indication, both in the metastatic and adjuvant settings.

Maytansine is a highly potent cytotoxic agent derived from the Ethiopian plant Maytenus serrata. Due to its high toxicity, it's not used directly as a cancer treatment but rather as a part of a targeted therapy. Emtansine (also known as DM1) is a derivative of maytansine that has been chemically modified to be less toxic and more stable in the bloodstream. It is used as the cytotoxic component of T-DM1, where it is attached to the antibody trastuzumab through a stable linker. T-DM1 retains trastuzumab's inhibitory functions—especially the blockade of the PI3K/AKT pathway. In addition, trastuzumab facilitates T-DM1's internalization and subsequent disintegration to unleash the potent microtubule-inhibitory action of the MCC-DM1 complex [13].

The EMILIA trial showcased the preferential outcomes of T-DM1, demonstrating its ability to improve progression-free survival (PFS) rates compared to a regimen that combined lapatinib and capecitabine in patients with HER2-positive metastatic breast cancer who had received a prior taxane [7]. The KATHERINE trial showed improvement in disease-free survival (DFS) rates in patients with early-stage HER2-positive breast cancer with residual disease following neoadjuvant trastuzumab-based treatment [14]. This randomized trial validated the role of T-DM1 in this setting, compared to continued trastuzumab therapy.

In the KRISTINE trial, T-DM1 therapy was compared to sequential anthracycline-based chemotherapy followed by taxane in combination with trastuzumab and pertuzumab, or the TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab) regimen in the neoadjuvant setting. In this study, T-DM1 demonstrated a reduced pathologic complete response rate compared to the other regimens [15]. Nevertheless, the KRISTINE trial linked it to a more favorable safety profile, achieving pathologic complete responses in 44% of patients without conventional chemotherapy.

The most prevalent adverse effects associated with T-DM1 treatment are thrombocytopenia and liver enzyme elevation, highlighting the necessity for vigilant laboratory monitoring throughout the therapy [7,14,15].

2.1. Mechanisms of Resistance to T-DM1

The immune-related mechanisms of action of T-DM1 is mediated by a complex interplay involving the IgG1 framework, which prompts antibody-dependent cellular cytotoxicity (ADCC), and HER2 binding that impedes PI3K/AKT signaling. The cytotoxicity of the drug is delivered by emtansine, which disrupts microtubules following its release into the cytosol. Resistance may be

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precipitated by defective binding, as well as impaired intracellular processing and metabolism, potentially augmenting the cellular expulsion of T-DM1 or altering its lysosomal degradation [16].

Key factors contributing to resistance encompass HER2 expression downregulation, intracellular routing changes, lysosomal function debilitation, drug removal through efflux pumps, and activation of compensatory signaling pathways. Genetic mutations, such as those in PIK3CA or PTEN loss, can activate the PI3K-AKT-mTOR pathway, furthering resistance [17]. Additionally, diminished colocalization with caveolin-1 (CAV1), essential for endocytic transport, might impair drug binding and sensitivity [17,18]. Finally, tumor cells might evade immunological detection, resisting T-DM1 therapy [19]. Immunomodulatory strategies are under investigation to counteract this resistance [20].

Given the patient-specific nature of resistance mechanisms, a spectrum of these factors may concurrently influence treatment response. Addressing T-DM1 resistance remains a formidable challenge in treating HER2-positive breast cancer.

2.2. T-DM1 Combination Therapies

Current research strives to devise approaches to surmount these mechanisms to improve patient prognosis. Personalized medicine strategies, including targeted and immune-based therapies, are under exploration to effectively counter resistance. In efforts to surmount resistance to Trastuzumab-DM1 (T-DM1) in treating HER2-positive breast cancer, the integration of T-DM1 with diverse therapeutic agents has been extensively investigated. This strategy targets specific resistance mechanisms, proposing alternate modalities to boost treatment efficacy.

A multitude of agents have been assessed for their potential synergistic effects in tandem with T-DM1, including monoclonal antibodies (e.g., pertuzumab), tyrosine kinase inhibitors (e.g., lapatinib, neratinib, tucatinib), PI3K Pathway Inhibitors (e.g., alpelisib), PD1/PDL1 checkpoint inhibitors (e.g., pembrolizumab, atezolizumab) as well as CDK4/6 inhibitors (e.g., palbociclib, ribociclib, abemaciclib) [21–25].

The logic behind these combinations is to mount a diversified onslaught on HER2-positive breast cancer cells, targeting various pathways and resistance mechanisms. Utilizing T-DM1 with these agents is anticipated to ameliorate treatment results and confront the hurdles posed by drug resistance. Future clinical studies will shed light on the success of these combination treatments, propelling advancements in care for patients with HER2-positive breast cancer.

3. Trastuzumab Deruxtecan (T-DXd)

Trastuzumab deruxtecan (T-DXd) stands as a novel ADC in the treatment arsenal against breast cancer, comprising an anti-HER2 antibody conjugated to a cytotoxic payload. T-DXd distinguishes itself by utilizing a topoisomerase I inhibitor derivative (i.e., deruxtecan) as its payload, connected via a cleavable tetrapeptide-based linker [26]. This cleavable linker is selectively severed within tumor cells, reducing off-target release and associated toxicities. T-DXd possesses a notably higher drug-to-antibody ratio (DAR) relative to T-DM1, an attribute that contributes to its potent efficacy [27].

Clinical investigations, including the pivotal DESTINY-Breast01 and DESTINY-Breast03 trials, have demonstrated T-DXd's efficacy in significantly prolonging progression-free survival (PFS) over T-DM1, leading to its endorsement by the FDA as a second-line therapy for HER2-positive metastatic breast cancer [8,28]. Furthermore, T-DXd's approval for HER2-low breast cancer signals the recognition of a new subset within the breast cancer spectrum, expanding the therapeutic landscape [29].

While T-DXd has shown promising clinical efficacy in HER2-positive breast cancer, its use is accompanied by potential adverse effects which require vigilant monitoring. Paramount among these is the risk of drug-related interstitial lung disease (ILD) or pneumonitis, inflammatory conditions that may progress to severe impairment of lung function and significant respiratory compromise. Other toxicities include gastrointestinal symptoms, hematological abnormalities, and rare cardiac toxicities.

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Regular monitoring and appropriate supportive treatments are essential for managing these side effects [8].

3.1. T-DXd: Mechanisms of Resistance

Trastuzumab deruxtecan (T-DXd) has emerged as a significant therapeutic agent in the treatment of HER2-positive and HER2-Low metastatic breast cancer, exhibiting considerable clinical efficacy. Nonetheless, resistance to T-DXd poses a significant obstacle in clinical settings. A thorough comprehension of the resistance mechanisms is crucial to devising informed therapeutic strategies to improve patient outcomes.

HER2 Receptor Modifications: Modifications of the HER2 receptor are a primary resistance mechanism, including mutations, gene amplification, or structural alterations, which can diminish the receptor's affinity for T-DXd. These modifications may reduce the drug's efficacy by impairing target binding, necessitating the investigation of methods to overcome these changes in HER2 [30].

ADC Internalization and Intracellular Trafficking: The internalization and intracellular trafficking of T-DXd are critical to its cytotoxic action. Resistance may develop from disruptions in these processes, impeding the delivery of the cytotoxic payload. Enhancing T-DXd internalization and trafficking could be a strategic approach to bypass this resistance mechanism [31].

Drug Efflux Transporters: The expression of efflux transporters, such as P-glycoprotein (P-gp), which expel the payload (deruxtecan) from cells, can decrease its intracellular concentration and cytotoxic impact. Inhibition or circumvention of these transporters is under investigation to enhance deruxtecan's intracellular retention [32].

Tumor Microenvironment and Stromal Factors: The tumor microenvironment, including stromal cell-secreted factors, can confer survival advantages to cancer cells, fostering resistance to T-DXd. Targeting the tumor microenvironment through combination therapies or immune-modulating agents may address this resistance mechanism [33].

Alternative Signaling Pathways: The activation of alternative signaling pathways, such as the PI3K/AKT/mTOR pathway, can provide survival advantages to cancer cells, undermining T-DXd's effectiveness. Co-targeting HER2 and these alternative pathways may be essential to counteract resistance [3,34–36].

Tumor Heterogeneity: The intrinsic heterogeneity of tumors, both among patients and within a single tumor, can result in cancer cell populations with varying sensitivities to T-DXd, contributing to the complex nature of resistance. Personalized treatments, considering the unique molecular and phenotypic profiles of tumors, may be promising in overcoming resistance [37].

In summary, resistance to Trastuzumab deruxtecan in breast cancer is complex and involves diverse interactions between the tumor cells and their surrounding microenvironment. Current research is focused on elucidating these mechanisms in detail and developing targeted strategies to counter resistance. Anticipated advancements in T-DXd-based treatments for HER2-positive and HER2-Low breast cancer include personalized medicine, combination therapies, and an enhanced understanding of tumor biology.

Therapeutic combinations are being rigorously evaluated to surmount resistance to Trastuzumab deruxtecan (T-DXd) in HER2-positive breast cancer therapy. These research efforts aim to refine treatment regimens and enhance patient prognoses. A range of combinations are in various stages of clinical trials, following the same paradigm as T-DM1 above. The objectives of these clinical trials are to establish the safety profiles, efficacy, and appropriate dosing regimens for these combination treatments. The forthcoming results are expected to yield critical insights into the most efficacious combinations and patient demographics best suited for these therapies. The overarching aim is to personalize treatment approaches, thereby advancing the care and outcomes for patients with HER2-positive breast cancer who exhibit resistance to T-DXd.

3.2. T-DXd in HER2-Low Breast Cancer

In the realm of breast cancer treatment, the categorization of tumors as HER2-positive or negative has been traditionally binary. However, a subset of tumors exhibit low levels of HER2

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("HER2-Low"), which is found in 45-60% of cases without HER2 amplification or overexpression [38]. These HER2-low tumors are identified by an immunohistochemical (IHC) score of 1+ or a score of 2+ accompanied by a negative in situ hybridization (ISH) result. In the pivotal DESTINY-Breast 04 trial, Trastuzumab Deruxtecan (T-DXd) showed significant effectiveness in treating HER2-low metastatic breast cancer, achieving a 52.6% objective response rate among patients who had undergone one or two prior lines of therapy [9].

While HER2-0 breast cancers are often less amenable to monoclonal antibody therapy, a subset known as HER2-ultra-low has been recognized, characterized by minimal HER2 protein expression. Ongoing studies are exploring the use of ADCs for this group. For example, the DESTINY-Breast06 trial is investigating the efficacy of T-DXd in patients with HER2-ultra-low metastatic breast cancer. Additionally, certain genetic mutations, like the V777L ERBB2 mutation, and MutL deficiency — related to mismatch repair system changes — suggest potential responsiveness to anti-HER2 therapies, even in HER2-negative breast cancers.

Ongoing research is assessing T-DXd against chemotherapy in hormone receptor-positive HER2-low metastatic breast cancer and exploring its combination with immune checkpoint inhibitors. Early data indicate favorable safety and efficacy, with high response rates [39]. The combination of T-DXd with immune therapies such as PD-L1 and PD-1 inhibitors is being evaluated, showing promising activity, although questions about the incremental benefit over T-DXd alone persist. These studies underscore the potential of T-DXd as a key therapeutic for HER2-low breast cancer, offering hope for improved outcomes in this diverse patient population.

4. New HER2-Targeting ADCs on the Horizon

Emerging ADCs are being developed to enhance the therapeutic landscape of HER2-positive breast cancer treatments. The advent of such ADCs has been revolutionizing the field, particularly by expanding the potential applications beyond traditional HER2-positive cancers to include tumors with lower expression levels of HER2 or with ERBB2 mutations. These novel ADCs are characterized by their refined pharmaceutical properties, including the use of antibodies with greater affinity and specificity to the HER2 protein and potent cytotoxic payloads capable of effectively targeting cancer cells.

The innovative ADCs are designed with modifications that optimize the delivery and release of cytotoxic agents within tumor cells, aiming to leverage the tumor microenvironment to enhance anti-tumor activity. Advancements in ADC technology are not only improving the effectiveness of these therapies but also aiming to reduce resistance and adverse effects. These improvements are the result of meticulous engineering that includes the selection of high-affinity antibodies, development of potent payloads, and the creation of stable linkers that bind the payload until it reaches the tumor site (Figure 1). The mechanism of ADCs involves the targeted delivery of these components to cells expressing specific cancer antigens, followed by the release of a cytotoxic payload to eliminate the cancer cells [40].

The research and development of HER2 ADCs are expected to continue improving the therapeutic index, offering a broader spectrum of treatment options for patients with HER2-positive and HER2-low breast cancer. These advancements signal a shift towards precision medicine, where treatment strategies can be personalized for better clinical outcomes and an enhanced quality of life for patients with breast cancer (Table 2).

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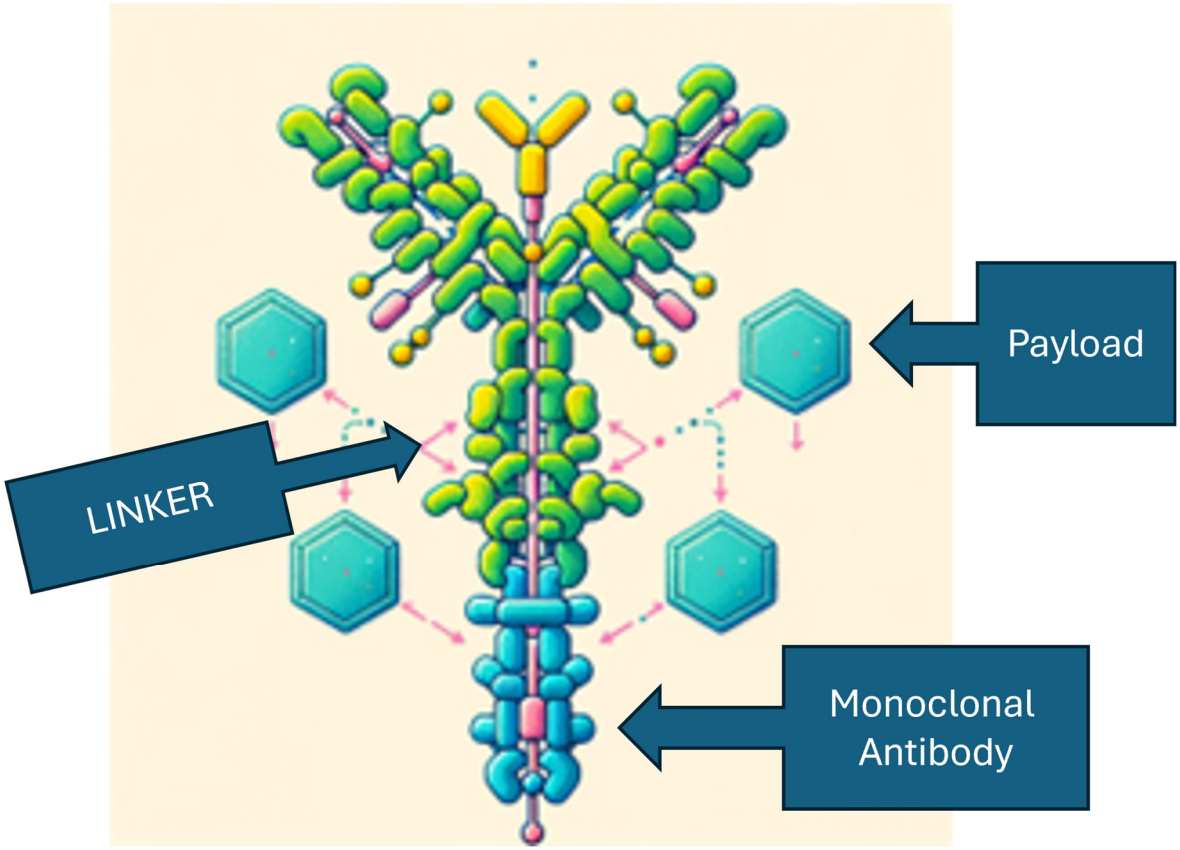

Figure 1. Molecular structure of ADCs.

Table 2. New HER2-Targeted ADCs in Clinical Trials.

Study Title	Key Eligibility	Intervention	Primary Endpoint	Phase	n
Clinical Study of ALT-P7 to Determine Safety, Tolerability and Pharmacokinetics in Breast Cancer Patients [NCT03281824]	HER2-Positive MBC	ALT-P7 (HM2-MMAE)	DLT, MTD	I	27
Efficacy and Safety of Pyrotinib Maleate Combined with ARX788 Neoadjuvant Treatment in Breast Cancer Patients [NCT04983121]	stage II-III HER2-positive breast cancer patients experiencing a poor efficacy of trastuzumab and pertuzumab.	ARX788	Residual tumor burden (RCB)	II	30
ARX788 in HER2-positive, Metastatic Breast Cancer Subjects (ACE-Breast-03) [NCT04829604]	HER2-Positive MBC previously treated with T-DXd	ARX788	ORR	II	71
ARX788 in HER2-positive Breast Cancer Patients with Brain Metastases [NCT05018702]	HER2-Positive MBC resistant or refractory to Tyrosine kinase inhibitors (TKI)	ARX788	Central nervous system (CNS) clinical benefit rate (CBR)	II	32
ARX788 in Breast Cancer with Low Expression of HER2 [NCT05018676]	HER2-Low MBC	ARX788	ORR	II	54
A Study of BL-M07D1 in Patients with Locally Advanced or Metastatic HER2 Positive/Low Expression Breast Cancer and Other Solid Tumors [NCT05461768]	Locally advanced or metastatic HER2-positive/low-expression breast cancer and other solid tumors	BL-M07D1	DLT, MTD	I	26

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A Study of Disitamab Vedotin in Previously Treated Solid Tumors That Express HER2 [NCT06003231]	HER2-Positive metastatic solid tumors	disitamab vedotin	ORR	II	190
Different Targeted Antibody-drug Conjugates For HER2 Ultra-low or No Expression Advanced Breast Cancer [NCT05824325]	HER2 ultra-low or no expression advanced breast cancer	SHR-A1811 vs. TROP2 ADC	Toxicity, ORR	I|II	56
SYD985 vs. Physician's Choice in Participants with HER2-positive Locally Advanced or Metastatic Breast Cancer (TULIP) [NCT03262935]	HER2-Positive MBC	SYD985 vs. SOC	PFS	III	437
A Study of TQB2102 for Injection in Patients with Recurrent/Metastatic Breast Cancer [NCT06115902]	HER2-Positive MBC	TQB2102	Toxicity, ORR	I	150
Study of Antibody Drug Conjugate in Patients with Advanced Breast Cancer Expressing HER2 [NCT02952729]	HER2-Positive MBC	XMT-1522	MTD, DLT	I	120

Abbreviations: MMAE: Monomethyl Auristatin E; DLT: Dose-Limiting Toxicity; MTD: Maximum Tolerated Dose; RCB: Residual Cancer Burden; T-DXd: Trastuzumab Deruxtecan; ORR: Objective Response Rate; TKI: Tyrosine Kinase Inhibitor; CNS: Central Nervous System; CBR: Clinical Benefit Rate; SOC: Standard Of Care; PFS: Progression-Free Survival.

4.1. Disitamab Vedotin (RC48)

Disitamab Vedotin (DV), known as RC48, is a novel ADC directed against HER2-expressing cancer cells. The architecture of DV is characterized by a humanized anti-HER2 monoclonal antibody linked to the cytotoxic agent monomethyl auristatin E (MMAE) through a cleavable linker [41]. This design ensures that the monoclonal antibody binds selectively to the HER2 epitope, facilitating the internalization of MMAE, which then mediates cell death. DV's binding affinity for HER2, which is higher than that of other therapeutic agents like trastuzumab, potentially increases its therapeutic impact. Furthermore, DV can induce cytotoxicity in adjacent cells—a phenomenon known as the bystander effect. Early clinical evaluations of DV have shown promising efficacy, particularly in patients with HER2 2+/ISH-negative status, indicating a potential for tailored therapy based on HER2 expression levels [42].

Disitamab Vedotin and similar next-generation ADCs represent a significant advance in cancer therapeutics, combining precise tumor targeting with innovative payload mechanisms and improved linker technologies. These developments contribute to ADCs with variable DARs, refined safety profiles, and expanded potential for treating diverse cancer types and disease stages. It should be noted that DV is currently approved in China for gastric cancers [43].

4.2. ARX788

ARX788 represents an innovative ADC comprising an anti-HER2 monoclonal antibody, a non-cleavable linker, and a modified monomethyl auristatin F (MMAF), known as Amberstatin 269 (AS269) [44]. This ADC exhibits a DAR of 1.9. Preclinical studies, including those reported by Barok et al. in 2020, demonstrate ARX788's superior efficacy over T-DM1 in trastuzumab-resistant breast cancer xenograft models [45]. A phase I trial showed ARX788 is well tolerated and has promising anti-tumor activity in patients with HER2-positive advanced gastric adenocarcinoma (ChinaDrugTrials.org.cn: CTR20190639) [46]. Current phase II clinical trials are evaluating ARX788's efficacy in various HER2-positive breast cancer contexts. Trial NCT05018676 is investigating its impact on HER2-low breast cancers, while NCT05018702 focuses on patients with HER2-positive cancers that have metastasized to the brain. Additionally, NCT04829604, known as ACE-Breast-03,

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aims to determine the effectiveness of ARX-788 in patients with HER2-positive metastatic breast cancer who have previously undergone treatment with T-DXd [43].

4.3. SYD985

Trastuzumab duocarmazine (SYD 985) is a novel ADC that combines trastuzumab with a cleavable valine-citrulline linker and a duocarmycin derivative, seco-DUBA, which is activated by proteases to cause DNA alkylation and cell death. It exhibits a bystander effect and has a DAR of 2.7 [47]. It showed efficacy in HER2-low breast cancer models, surpassing T-DM1. In a phase 1 trial, it demonstrated antitumor activity with ORRs of 28% for HR+ and 40% for HR− MBC patients . Ocular side effects were noted [43].

The Phase III TULIP® study compared SYD985 with physicians' choice of treatment in participants with HER2-positive locally advanced or metastatic breast cancer. The trial met its primary endpoint, showing a statistically significant improvement in progression-free survival (PFS) for SYD985 over the physicians' choice. PFS is the duration from randomization to disease progression or death from any cause. Additionally, the study reported preliminary supportive results for overall survival (OS) [48].

4.4. BL-M0701

BL-M07D1 is a new ADC targeting HER2 with a structure comprising the humanized antibody trastuzumab, a cathepsin B cleavable linker, and Ed-04, a camptothecin-derived topoisomerase I inhibitor. This inhibitor impedes the cell cycle in the S phase, inducing apoptosis. BL-M07D1 has a DAR of 8:1, akin to T-DXd, but with a more stable linker.

Preclinical evaluations using xenograft models revealed BL-M07D1's superior tumor inhibition, outperforming T-DXd in low HER2-expressing models and both T-DM1 and T-DXd in HER2-positive models. Notably, BL-M07D1 demonstrated potent bystander effects, suggesting an enhanced efficacy against mixed HER2-positive/negative tumors [49]. These findings posit BL-M07D1 as a promising candidate in the treatment of a wider spectrum of breast cancers, surpassing the current HER2-targeting ADCs. A Phase I trial is ongoing in patients with metastatic breast cancer.

4.5. Zanidatamab zovodotin

Zanidatamab zovodotin, also referred to as ZW49, is an innovative bispecific ADC aimed at treating HER2-expressing or HER2-amplified cancers, including breast cancer. It is currently undergoing clinical evaluation to determine its efficacy and safety profile. The first-in-human phase I trial was designed to determine the maximum tolerated dose, characterize its safety and tolerability, and evaluate its anti-tumor activity as monotherapy [50]. Among eight patients with breast cancer, Zanidatamab zovodotin achieved a confirmed overall response rate (ORR) of 13%, which included a partial response (PR) rate of 13% and a stable disease (SD) rate of 38%. This indicates a promising activity profile, although the response rates suggest there is a need for continued development and investigation to fully understand the potential of this ADC.

The emergence of Zanidatamab zovodotin represents a significant step forward in the treatment of HER2-positive cancers, potentially offering a new therapeutic option for patients with advanced disease who have limited treatment choices. As clinical trials progress, the oncology community eagerly anticipates further data to evaluate the full potential of this novel ADC in the treatment landscape of breast cancer [51].

4.6 . Other ADCs in Clinical Trials

There are many other ADCs in clinical trials, including ALT-P7, SHR-A1811, TQB2102, XMT-1522 (Table 2). The therapeutic benefit of these molecules will be determined by the results of these trials and additional future clinical trials.

5. Future Directions

HER2-targeted ADCs have emerged as a promising strategy for breast cancer treatment, with a particular focus on enhancing outcomes for both patients with HER2-positive and HER2-low breast cancer. The field of ADC research continues to advance. Ongoing clinical trials are exploring novel ADCs to further improve breast cancer therapy. Furthermore, one of the exciting frontiers in this field is the exploration of novel therapeutic sequences or combinations involving ADCs.

The benefit of sequencing HER2-targeted ADCs upon disease progression is an area of active investigation. It is possible ADCs may continue to be effective by delivering a cytotoxic payload to tumor cells through a targeted antibody, even if the antibody remains the same (e.g., trastuzumab).

By combining ADCs with other targeted agents, such as tyrosine kinase inhibitors or immune checkpoint inhibitors, multiple pathways involved in tumor growth and immune response can be simultaneously targeted. This synergistic approach aims to overcome drug resistance and maximize treatment efficacy.

The concept of precision medicine becomes even more potent with combination therapies. By identifying specific patient subgroups that may benefit from certain combinations, we can tailor treatments to individual patients based on their molecular and genetic profiles. Next generation sequencing remains an important tool in understanding the biology of each patient's individual tumor.

In the coming years, it will be crucial to understand the benefits and potential toxicities of each HER2 ADC in clinical development. Tailored monitoring and treatment adjustments will be key to minimizing risks and enhancing the therapeutic outcome for patients with HER2-positive breast cancer treated with a specific ADC or sequence of ADCs.

6. Conclusions

The exploration of novel combinations with ADCs represents a promising frontier in cancer therapy. These combinations have the potential to expand the therapeutic reach, overcome resistance mechanisms, modulate the immune system, and offer tailored treatments to specific patient subgroups. Ongoing clinical trials and research efforts are essential in advancing our understanding of these combinations and their potential to improve patient outcomes in the complex landscape of cancer treatment.

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