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ADVANCES AND FUTURE DIRECTIONS IN HER2-POSITIVE BREAST CANCER: A NARRATIVE REVIEW

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ABSTRACT

HER2-positive breast cancer, characterized by the overexpression of the human epidermal growth factor receptor 2, accounts for 15-20% of all breast tumors and has historically been associated with a more aggressive phenotype. However, the prognosis for patients with HER2-positive metastatic breast cancer has dramatically improved in recent years due to significant therapeutic advancements. The development of HER2-directed therapies has revolutionized breast oncology, with trastuzumab marking a pivotal moment in 1998 with its FDA approval as the first-line adjuvant therapy (Chilà et al., 2021; Gampenrieder et al., 2020; Tarantino et al., 2021; Najjar et al., 2022). This narrative review summarizes the current and emerging therapeutic landscape for HER2-positive breast cancer, including novel anti-HER2 therapies such as monoclonal antibodies with enhanced properties, bispecific antibodies, and small molecules. This narrative review discusses the basic biology of HER2, its signaling pathways, and the mechanisms of action of available anti-HER2 modalities. A particular focus will be placed on the impact of novel antibody-drug conjugates (ADCs) and tyrosine kinase inhibitors (TKIs), which have shown remarkable efficiency, particularly in challenging scenarios like brain metastasis. These therapies, exemplified by trastuzumab deruxtecan and tucatinib, represent significant progress in overcoming resistance and improving patient outcomes. This review will also explore current and future trends in systemic therapy for HER2-positive metastatic breast cancer, aiming to highlight innovative strategies to overcome resistance and improve long-term patient outcomes (Gampenrieder et al., 2020; Mercogliano et al., 2023; Najjar et al., 2022; Rao et al., 2025; Guidi et al., 2023; Cano et al., 2023). Ultimately, it aims to provide clinicians and researchers with a concise, updated synthesis of emerging HER2-targeted strategies and their clinical implications.

KEYWORDS

HER2-positive Breast Cancer, Antibody–Drug Conjugates, Tyrosine Kinase Inhibitors, Trastuzumab Deruxtecan

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1.Introduction

1.1 Background of HER2-Positive Breast Cancer

1.1.1 Molecular Biology and Clinical Relevance

Human epidermal growth factor receptor 2 (HER2) positive cancers constitute approximately 15-20% of all breast tumors. Overexpression of HER2 is a critical molecular characteristic influencing disease progression and therapeutic strategies. Understanding the molecular biology of HER2 and its downstream signaling pathways is fundamental for the development of effective targeted therapies (Chilà et al., 2021; Najjar et al., 2022).

1.1.2 Global Epidemiology

The consistent global prevalence of HER2-positive status across breast cancer subtypes highlights its major clinical and public health importance. Despite the presence of regional differences, HER2-positivity represents an important category of breast cancers globally (15-20%) (Chilà et al., 2021).

1.1.3 Rationale for Targeting HER2 and Historical Context

Research into the oncogenic function of HER2 and the resulting creation of targeted therapies has revolutionized breast cancer treatment in recent years. The rationale for targeting HER2 lies in its critical role in tumor growth and progression (Tarantino et al., 2021).

1.2 Historical Context of HER2-Directed Therapy

The development of trastuzumab marked a significant milestone, becoming FDA-approved in 1998 as an adjuvant first-line therapy for HER2-positive breast cancer due to its overwhelming efficacy. This breakthrough established HER2-directed therapy as a cornerstone of treatment. Since then, the prognosis for patients with HER2-positive metastatic breast cancer has dramatically improved, driven by the successive generations of effective therapies, including monoclonal antibodies and small molecules targeting HER2.

Further advancements have included novel anti-HER2 therapies such as monoclonal antibodies with improved properties, bispecific antibodies, and antibody-drug conjugates, alongside small molecules (Jørgensen, 2023; Najjar et al., 2022; Gampenrieder et al., 2020). HER2-positive breast cancer, once considered a highly aggressive subtype, now represents a model of precision oncology. This review explores the evolution of HER2-targeted therapy, focusing on emerging ADCs and TKIs and their impact in shaping the future of treatment.

2. Methodology

This narrative review includes 26 studies published between 2015 and 2025, encompassing randomized controlled trials, pilot studies, and clinical protocols relevant to HER2-positive breast cancer. Articles were identified through a systematic search of the PubMed database using the following keywords: HER2-positive breast cancer, antibody–drug conjugates, tyrosine kinase inhibitors, and trastuzumab deruxtecan. Eligible studies were selected based on their clinical relevance, methodological quality, and contribution to the evolving therapeutic landscape of HER2-positive disease. No language or geographical restrictions were applied. Data from these studies were synthesized to highlight current advances and future directions in HER2-targeted therapy, with a focus on personalized treatment approaches and strategies to overcome therapeutic resistance.

3. Current Therapeutic Landscape of HER2-Targeted Therapies

The therapeutic landscape of HER2-positive breast cancer has evolved remarkably over the past two decades with the development of diverse HER2-targeted agents, including monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody–drug conjugates (ADCs). Collectively, these therapies have transformed the natural history of HER2-positive disease, substantially improving survival outcomes and paving the way for more personalized treatment approaches (Jørgensen, 2023; Suppan & Balic, 2022; Azar et al., 2021).

3.1 Monoclonal Antibodies

Monoclonal antibodies (mAbs) like **trastuzumab** and **pertuzumab** are foundational HER2-targeted treatments (Aapro et al., 2022; Rinnerthaler et al., 2019). Trastuzumab was the first HER2-directed monoclonal antibody to demonstrate a significant survival benefit in both early and metastatic breast cancer, establishing HER2 blockade as a fundamental treatment strategy. Pertuzumab, which binds to a distinct epitope on the HER2 extracellular domain, provides complementary inhibition and, when combined with trastuzumab and chemotherapy, has become the standard first-line regimen for HER2-positive metastatic disease. More recently, margetuximab, an Fc-engineered monoclonal antibody designed to enhance immune activation, has been approved for use in patients previously treated with multiple HER2-directed therapies (Jørgensen, 2023; Rinnerthaler et al., 2019; Aapro et al., 2022).

Efficacy and Limitations

Despite their proven clinical benefit, resistance to monoclonal antibodies remains a major therapeutic challenge. Mechanisms of resistance often involve molecular alterations in downstream signaling pathways, particularly within the MAPK and PI3K/AKT cascades, which can attenuate the antitumor efficacy of trastuzumab and pertuzumab. Understanding these mechanisms is essential for guiding the development of next-generation HER2-targeted agents and combination treatment strategies (Guidi et al., 2023).

3.2 Tyrosine Kinase Inhibitors (TKIs)

Small-molecule tyrosine kinase inhibitors (TKIs) represent another major class of HER2-targeted agents, designed to inhibit the intracellular kinase activity of the HER2 receptor and its downstream signaling pathways. By binding to the adenosine triphosphate (ATP)–binding site of the HER2 tyrosine kinase domain, these agents effectively block receptor autophosphorylation and subsequent activation of proliferative signaling cascades (Jørgensen, 2023; Azar et al., 2021). Key HER2-directed TKIs include lapatinib, neratinib, tucatinib, and pyrotinib. Lapatinib was among the first to be clinically approved, showing efficacy in trastuzumab-resistant metastatic breast cancer. Neratinib has demonstrated benefit in the extended adjuvant setting following trastuzumab-based therapy, while tucatinib—characterized by its high selectivity for HER2—has shown substantial improvement in progression-free and overall survival, particularly in patients with brain metastases, as evidenced by the HER2CLIMB trial. Pyrotinib, developed more recently, has shown encouraging results in Asian populations, further expanding the therapeutic options within this class (Aapro et al., 2022; Rinnerthaler et al., 2019).

Efficacy and Limitations

TKIs offer valuable alternatives for patients with disease progression following monoclonal antibody–based therapy and have demonstrated activity against central nervous system metastases. However, their integration into clinical practice is challenged by drug-specific toxicities such as diarrhea, hepatotoxicity, and dermatologic reactions. Additionally, determining the optimal sequencing of TKIs relative to antibody–drug conjugates (ADCs) remains an area of active investigation (Rao et al., 2025).

3.3 Antibody-Drug Conjugates (ADCs)

Antibody–drug conjugates (ADCs) represent one of the most transformative advances in the management of HER2-positive breast cancer, combining the high specificity of monoclonal antibodies with the potent cytotoxicity of linked payloads (Najjar et al., 2022). By conjugating a cytotoxic agent to an anti-HER2 antibody via a cleavable or stable linker, ADCs enable targeted delivery of chemotherapy to HER2-expressing tumor cells, thereby enhancing antitumor activity while attempting to limit systemic toxicity (Najjar et al., 2022). The first clinically approved ADC, trastuzumab emtansine (T-DM1), improved progression-free and overall survival in patients previously treated with trastuzumab and taxanes, but its efficacy can be limited by resistance mechanisms and a relatively modest drug-to-antibody ratio (DAR) (Rinnerthaler et al., 2019). These limitations spurred the development of next-generation ADCs featuring higher DARs, optimized linkers and more potent payloads.

Trastuzumab deruxtecan (T-DXd) is a second-generation ADC characterized by a high DAR and a membrane-permeable topoisomerase-I inhibitor payload, producing potent direct cytotoxicity and a bystander effect that can target heterogeneous or low-HER2 expressing tumor cells (Najjar et al., 2022; Ji et al., 2023). Pivotal trials (e.g., DESTINY series) have demonstrated superior efficacy of T-DXd in heavily pretreated populations, leading to its establishment as the preferred second-line therapy in many settings (Fehm et al., 2024). Notably, T-DXd has shown intracranial activity, broadening options for patients with brain metastases (Zhou et al., 2025). Interstitial lung disease (ILD), however, remains a clinically important toxicity requiring proactive monitoring and management (Hackshaw et al., 2020; Morgovan et al., 2024).

Other ADCs, such as disitamab vedotin (RC48), have demonstrated encouraging activity in trastuzumab-resistant and HER2-low tumors and are under continued clinical evaluation (Pourjamal et al., 2024). Current research priorities include optimizing ADC sequencing relative to monoclonal antibodies and TKIs, elucidating predictive biomarkers of response and resistance, and developing strategies to mitigate ADC-specific toxicities (Guidi et al., 2023a; Guidi et al., 2023b).

Efficacy and limitations

ADCs have substantially improved outcomes in HER2-positive disease, even in refractory cases, but durable benefit can be limited by distinct resistance mechanisms (e.g., HER2 downregulation, altered intracellular trafficking, efflux pumps) and safety concerns such as ILD and hematologic toxicity. Ongoing work focuses on rational combinations and novel ADC designs to overcome these challenges (Tapia et al., 2023).

3.4 Overall Comparison and Landscape

The advent of three principal classes of HER2-directed therapies—monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and antibody–drug conjugates (ADCs)—has fundamentally altered the prognosis and management of HER2-positive breast cancer, producing substantial gains in disease control and survival (Cano et al., 2023; Suppan & Balic, 2022). Each class offers distinct mechanistic advantages: monoclonal antibodies (e.g., trastuzumab, pertuzumab, margetuximab) provide extracellular blockade and immune-mediated effects and remain central to first-line regimens; TKIs (e.g., lapatinib, neratinib, tucatinib, pyrotinib) inhibit intracellular kinase signaling and can address certain resistance mechanisms and central-nervous-system disease; ADCs (notably T-DM1 and T-DxD) deliver potent cytotoxics selectively to HER2-expressing cells and have produced pronounced activity even in heavily pretreated populations (Fehm et al., 2024; Ji et al., 2023; Zhou et al., 2025). Collectively, these agents have reshaped HER2 biology from a uniformly poor-prognosis subtype into a model of precision oncology (Cano et al., 2023; Guidi et al., 2023a).

Optimal sequencing and combination of these modalities remain central clinical questions. In routine practice, dual HER2 antibody blockade with trastuzumab and pertuzumab plus chemotherapy is widely used in the first-line metastatic setting, ADCs- especially trastuzumab deruxtecan, have assumed a pivotal role in subsequent lines due to superior efficacy in several pivotal trials, and TKIs are often favored when CNS control is a priority or following antibody resistance (Fehm et al., 2024; Rao et al., 2025). Decisions about sequencing must balance prior therapies, disease distribution (including brain metastases), toxicity profiles (for example,

the risk of interstitial lung disease with certain ADCs), and drug availability, and should be individualized to patient- and tumor-level factors (Suppan & Balic, 2022; Morgovan et al., 2024).

The landscape continues to expand and diversify. Emerging ADC constructs, novel bispecific and Fc-engineered antibodies, and more selective TKIs are widening therapeutic options and prompting reassessment of biomarkers and treatment algorithms (Guidi et al., 2023a; Pourjamal et al., 2024; Ji et al., 2023). Concurrently, recognition of HER2-low disease and efforts to identify predictive biomarkers of response and resistance are redefining candidate populations for HER2-directed approaches. Future progress will depend on prospective evaluation of sequencing strategies, careful safety monitoring in real-world populations, and biomarker-driven patient selection to maximize benefit while minimizing harm (Cano et al., 2023; Rao et al., 2025; Guidi et al., 2023b).

4. Evolution and Efficacy of Antibody-Drug Conjugates (ADCs)

Antibody-Drug Conjugates (ADCs) represent a class of targeted therapy that combines monoclonal antibodies (mAbs) with cytotoxic drugs (payloads) via chemical linkers. This design aims to deliver potent anticancer agents directly to cancer cells, leading to fewer side effects and a broader therapeutic window compared to conventional chemotherapy. ADCs have demonstrated effectiveness even when target proteins are expressed in small amounts. The field of HER2+ breast cancer treatment was significantly advanced by the introduction of T-DM1, and ongoing ADC development seeks to provide even better treatment options (Morgovan et al., 2024; Mercogliano et al., 2023).

4.1 Trastuzumab Emtansine (T-DM1)

Trastuzumab emtansine (T-DM1) was a revolutionary ADC in the treatment of HER2+ breast cancer, marking a significant advancement in the field. T-DM1 demonstrated clinically meaningful improvements in progression-free and overall survival compared with prior regimens and established ADCs as a viable therapeutic modality in this setting. Despite its impact, limitations such as acquired resistance mechanisms and a relatively modest drug-to-antibody ratio (DAR) prompted the pursuit of ADCs with enhanced designs (Rinnerthaler et al., 2019; Mercogliano et al., 2023).

4.2 Trastuzumab Deruxtecan (T-DXd)

Trastuzumab deruxtecan (T-DXd), also known as DS-8201a, is an ADC composed of trastuzumab linked to eight molecules of deruxtecan, a topoisomerase I inhibitor, via a cleavable tetrapeptide-based linker. This design enables selective intracellular release of the cytotoxic payload, which induces apoptosis and double-strand DNA breaks (Mercogliano et al., 2023; Gampenrieder et al., 2020).

Superiority over T-DM1: T-DXd has demonstrated superior performance compared to T-DM1 in preclinical models of both HER2+ and HER2-low breast cancer, highlighting its broader therapeutic potential (Mercogliano et al., 2023).

Mechanism of Action: Its effectiveness is attributed to higher payload permeability and a potent bystander killing effect on neighboring cancer cells, allowing cytotoxic activity even in heterogeneous tumor environments (Mercogliano et al., 2023) (Gampenrieder et al., 2020).

Drug-to-Antibody Ratio (DAR): T-DXd possesses a higher drug-to-antibody ratio (approximately 8) compared to T-DM1 (3-4), which contributes to its greater cytotoxic potency. (Gampenrieder et al., 2020)

Systemic Exposure: The short half-life of deruxtecan helps minimize systemic exposure (Gampenrieder et al., 2020).

4.3 Other Promising ADCs

Several other ADCs are currently in development, demonstrating promising results in preclinical studies and early-phase clinical trials for HER2+ breast cancer and other cancers:

Trastuzumab-duocarmycine (SYD985) is considered the most developed after T-DXd. It consists of trastuzumab conjugated to duocarmycine, an irreversible DNA alkylating agent. It is effective in both dividing and non-dividing cells and exhibits a potent bystander killing effect. (Mercogliano et al., 2023)

XMT-1522 utilizes HT-19, an antibody that binds to a distinct HER2 epitope (IV domain) from trastuzumab, conjugated with 12 molecules of an auristatin derivative (AF-HPA). A phase 1 clinical trial (NCT03284723) in heavily pretreated HER2+ tumor patients showed manageable toxicity and promising antitumor effects. (Mercogliano et al., 2023)

PF-06804103 is composed of a trastuzumab-derived antibody with a potent auristatin Preclinical and early-phase studies have reported antitumor activity across HER2-positive and HER2-low breast, lung, and gastric cancers, supporting its potential as a broad-spectrum HER2-targeted agent (Mercogliano et al., 2023).

BAY2701439 features a trastuzumab-derived antibody conjugated to TTCs. It is currently being evaluated in clinical trials (NCT04147819) for patients with HER2+ breast, gastric, or gastroesophageal tumors (Mercogliano et al., 2023).

These ADCs represent the ongoing efforts to develop more effective and targeted therapies for various cancers, building upon the foundational success of earlier ADCs like T-DM1 and the enhanced capabilities of newer agents such as T-DXd. Current research continues to focus on improving drug delivery, minimizing systemic toxicity, and optimizing patient outcomes (Mercogliano et al., 2023).

Beyond clinical evidence, comparative preclinical analyses have deepened our understanding of ADC performance in HER2-positive breast cancer. A recent study directly evaluated trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd), and disitamab vedotin in a multiresistant lung metastasis model, revealing marked differences in tumor penetration, cytotoxicity, and antitumor activity. The data demonstrated that T-DXd exhibited superior efficacy in overcoming drug resistance, likely due to its high drug-to-antibody ratio and membrane-permeable payload, while disitamab vedotin showed favorable distribution and internalization kinetics. Such findings underscore the mechanistic heterogeneity among ADC generations and their implications for optimizing patient selection and therapeutic sequencing (Pourjamal et al., 2024).

5. Mechanisms of Resistance and Challenges in HER2-Targeted Therapy

Resistance to HER2-targeted therapies is a major clinical challenge in cancer treatment, often leading to acquired resistance with prolonged therapy. This resistance can arise from various molecular mechanisms, including alterations in HER2 expression, activation of alternative signaling pathways, and tumor heterogeneity. (Najjar et al., 2022)

5.1 Molecular Mechanisms of Resistance

5.1.1 HER2 Downregulation and Alterations

Decreased levels or structural alterations of the HER2 receptor, which is necessary for the activity of some HER2-targeting agents like T-DM1, can lead to resistance after extended drug exposure (Guidi et al., 2023).

5.1.2 PI3K/AKT Pathway Alterations

Activation of alternative intracellular pathways, such as the PI3K/AKT/mTOR pathway, represents one of the most frequent mechanisms of resistance to HER2-targeted therapy (Rao et al., 2025). The AXL protein can activate downstream signaling pathways like PI3K/AKT and MAPK/ERK, which are crucial for cancer cell growth and survival, contributing to resistance (Tapia et al., 2023).

5.1.3 Tumor Heterogeneity

HER2 heterogeneity within tumors poses a barrier to effective treatment, as different cells may respond differently to targeted agents (Suppan & Balic, 2022) (Rao et al., 2025). Understanding these mechanisms is essential for developing strategies to overcome resistance and improve treatment strategies in HER2-positive breast cancer patients.

Additional mechanisms contributing to HER2 therapy resistance include:

- **Overexpression of HER ligands and receptors** that can lead to alternative dimerization, allowing downstream pathways to continue signaling despite partial inhibition (Najjar et al., 2022).
- **Reactivation of signaling pathway**, which can occur through the loss of downstream negative regulators or the gain of activating mutations (Najjar et al., 2022).
- **Impaired drug binding** due to receptor masking or mutation, reducing antibody affinity (Tarantino et al., 2021).
- **Constitutive activation of parallel pathways**, allowing cells to bypass HER2 inhibition (Tarantino et al., 2021).
- **Metabolic reprogramming or reduced immune system activation,** both of which can diminish treatment sensitivity (Tarantino et al., 2021).
- **Upregulation of drug efflux pumps,** that can reduce the intracellular concentration of therapeutic agents (Rao et al., 2025).

5.2 Strategies to Overcome Resistance

5.2.1 Combinatorial Therapeutic Regimens

Given the common development of resistance, investigating combinatorial therapeutic regimens that combine anti-HER2 monoclonal antibodies with chemotherapeutic agents is a promising approach (Najjar et al., 2022).

5.2.2 Targeting Alternative Pathways

Preclinical models indicate that inhibiting AXL, which activates PI3K/AKT and MAPK/ERK pathways, can overcome resistance to HER2-targeted therapies (Tapia et al., 2023).

5.2.3 Novel Anti-HER2 Agents and ADCs

Ongoing research aims to understand resistance mechanisms to both traditional and novel anti-HER2 agents, including Antibody-Drug Conjugates (ADCs), to improve clinical outcomes (Tarantino et al., 2021; Guidi et al., 2023).

Emerging therapies, including next-generation antibody–drug conjugates (ADCs), aim to circumvent classical resistance mechanisms through improved payload delivery, bystander effects, and activity in HER2-low disease. Ongoing investigations seek to elucidate resistance pathways specific to these novel agents and identify predictive biomarkers for treatment selection.

Further work is needed to fully comprehend and overcome these complex resistance mechanisms, especially for novel anti-HER2 agents and ADCs, to enhance patient outcomes in metastatic breast cancer (Tarantino et al., 2021; Guidi et al., 2023).

6. Emerging Strategies and Future Directions in HER2-Positive Brain Metastases Management

The management of HER2-positive breast cancer brain metastases is undergoing a significant paradigm shift due to the emergence of innovative targeted therapies, particularly antibody-drug conjugates (ADCs) and tyrosine kinase inhibitors (TKIs). These advancements are increasingly recognized for their potential to change treatment philosophies for brain metastasis (Rao et al., 2025).

6.1 Novel Agents and Targeted Therapies

6.1.1 Antibody-Drug Conjugates (ADCs)

ADCs, such as trastuzumab deruxtecan (T-DXd), represent a new class of anti-tumor drugs that combine monoclonal antibodies with cytotoxic agents via linkers. The 2023 ESMO guidelines recommend T-DXd for stable brain metastases in HER2-positive breast cancer. ADCs are highlighted for their superior intracranial response rates and survival benefits (Rao et al., 2025; Ji et al., 2023).

6.1.2 Tyrosine Kinase Inhibitors (TKIs)

Small molecule TKIs have shown excellent therapeutic efficacy in patients with active brain metastasis. Drugs like pyrotinib and tucatinib have demonstrated effective intracranial activity. Tucatinib, in combination with chemotherapy, is also recommended by the 2023 ESMO guidelines for HER2-positive breast cancer brain metastases (Rao et al., 2025).

6.1.3 Dual-Target Treatment

Combining monoclonal antibodies like pertuzumab and trastuzumab has proven more effective than trastuzumab alone in controlling brain metastasis. Trastuzumab itself has been shown to prolong overall survival and prolong the median time to brain metastasis onset in HER2-overexpressed patients (Rao et al., 2025).

6.2 Ongoing and Upcoming Clinical Trials

6.2.1 Zenocutuzumab Trial

A Phase II trial (NCT03321981) investigated zenocutuzumab in combination with trastuzumab and vinorelbine for patients who had progressed on prior trastuzumab/pertuzumab and T-DM1. The study reported a clinical benefit rate (CBR) of 35.1% at 24 weeks and an overall response rate (ORR) of 18.9%, including one complete response (Gampenrieder et al., 2020).

6.2.2 Pivotal Clinical Trials

Clinical trials such as HER2CLIMB and DESTINY-Breast03, along with real-world studies, have been instrumental in demonstrating the superior intracranial response rates and survival benefits of these therapies (Rao et al., 2025).

6.3 Future Perspectives

Future research is focusing on genetic signatures, mechanisms of brain tropism in breast cancer cells, and potential biomarkers to predict brain metastasis. The growing role of ADCs and TKIs is expected to further integrate these therapies into standard care, influencing future guideline updates (Guglielmi et al., 2024; Rao et al., 2025).

In the context of rapidly evolving ADC-based therapies, expert consensus and multidisciplinary discussions have increasingly focused on optimal sequencing strategies. A round table of leading oncologists recently highlighted the paradigm shift toward ADC-centric treatment planning in HER2-positive advanced breast cancer, emphasizing the integration of T-DXd and next-generation ADCs with tyrosine kinase inhibitors, immunotherapy, and precision biomarkers. The experts underscored that balancing efficacy, safety, and resistance mechanisms requires a personalized, data-driven approach to maximize patient outcomes (Yan et al., 2022).

In conclusion, ADCs and TKIs are at the forefront of novel strategies for HER2-positive breast cancer brain metastases, offering significant improvements in intracranial response and survival, supported by ongoing clinical research and evolving treatment guidelines.

7. Safety and Adverse Events of Antibody-Drug Conjugates (ADCs), with a Focus on T-DXd

Trastuzumab deruxtecan (T-DXd) is an Antibody-Drug Conjugate (ADC) that has shown high response rates and clinical benefits across various malignant diseases. However, its use is associated with specific safety concerns, particularly interstitial lung disease (ILD)/pneumonitis, and other toxicities (Nakano, 2023; Najjar et al., 2022).

7.1 Interstitial Lung Disease (ILD) and Pneumonitis

7.1.1 Prevalence and Severity

Interstitial lung disease (ILD) or pneumonitis is a notable adverse event (AE) associated with T-DXd therapy. Across clinical studies, the incidence of ILD has ranged from 10% to 13.6%, with approximately 2.2% of cases being fatal (Tapia et al., 2023). Most events are Grade 1 or 2, although Grade 5 toxicities have been reported in some trials (Stanowicka-Grada & Senkus, 2023). In a smaller cohort, ILD/pneumonitis occurred in 13.3% of patients, all of which were Grade 1 (Zhou et al., 2025). Comparative analyses consistently indicate that T-DXd carries a higher risk of ILD or pneumonitis than trastuzumab emtansine (T-DM1) (Morgovan et al., 2024; Najjar et al., 2022).

7.1.2 Mechanism

The proposed mechanism for T-DXd-related lung injury involves off-target uptake into alveolar macrophages, leading to diffuse lymphocytic infiltrates and mild fibrosis (Najjar et al., 2022).

7.1.3 Management

While ILD/pneumonia are significant risks, most events can be managed with careful monitoring and fast intervention. The FDA label regards Grade 2 or higher ILD as a treatment-terminating factor (Morgovan et al., 2024; Najjar et al., 2022).

7.2 Other Toxicities Associated with T-DXd

7.2.1 Common Adverse Events

Beyond pulmonary toxicity, Grade III adverse events are typically gastrointestinal (e.g., nausea, vomiting) and hematologic (e.g., neutropenia) in nature (Tapia et al., 2023). Despite these concerns, clinical trials for T-DXd generally report that it is well-tolerated with a relatively low incidence of AEs, although high-grade ILD is a significant clinical issue. Several studies concluded that T-DXd demonstrates an acceptable safety profile across multiple tumor types, with treatment-related AEs occurred in a small percentage of patients (e.g., 11.1%) (Najjar et al., 2022; Azar et al., 2021).

7.2.2 Dose Modifications

Dose reductions are occasionally required, particularly for persistent Grade 2 nausea or vomiting (Zhou et al., 2025).

7.3 Pharmacovigilance Data and Management Recommendations

Pharmacovigilance data, including analyses from the FAERS database, indicates a higher frequency of severe pulmonary adverse effects associated with T-DXd compared to T-DM1. Similarly, the EudraVigilance database showed that 12% of reported adverse drug reactions for approved ADCs were related to T-DXd, compared to 24% for T-DM1 (Morgovan et al., 2024).

Monitoring of pulmonary events is strongly recommended for patients treated with T-DXd. Early recognition and prompt intervention are crucial to minimize morbidity and prevent fatal outcomes. The management of adverse events, especially ILD, remains a major clinical challenge (Morgovan et al., 2024) (Nakano, 2023).

While clinical trials have established the efficacy of T-DXd and other ADCs, real-world evidence continues to highlight critical safety concerns. In particular, interstitial lung disease (ILD) and pneumonitis remain clinically significant complications, with reported rates varying across populations and treatment histories. A large real-world observational cohort study evaluating post–trastuzumab deruxtecan therapies confirmed a substantial incidence of ILD, particularly in heavily pretreated patients, alongside diminished effectiveness of subsequent regimens. These findings reinforce the need for vigilant pulmonary monitoring and early intervention, as well as more comprehensive guidelines for managing toxicity in real-world settings (Nozawa et al., 2025).

T-DXd offers significant clinical benefits but requires careful monitoring for adverse events, particularly ILD and pneumonitis, which can be severe or fatal. While generally well-tolerated, effective management of its specific toxicities, guided by pharmacovigilance data and clinical recommendations, is essential for patient safety.

Table 1 provides an overview of key HER2-targeted therapies, summarizing their mechanisms of action, efficacy outcomes, and major adverse events. This contextual comparison underscores the evolving landscape of ADC development, illustrating how improvements in linker chemistry, payload potency, and pharmacokinetics have contributed to both enhanced efficacy and distinct toxicity profiles.

Table 1. Summary of key HER2-targeted therapies, their mechanisms, and clinical outcomes

Therapy	Drug class	Mechanism	Clinical Outcomes
Trastuzumab (Stanowicka-Grada & Senkus, 2023; Jørgensen, 2023)	Monoclonal antibody (mAb)	Binds to HER2 extracellular domain IV, inhibits dimerization, and mediates ADCC	Improved OS and PFS in early and metastatic HER2+ BC; standard backbone of therapy
Pertuzumab (Gampenrieder et al., 2020; Suppan & Balic, 2022)	mAb	Inhibits HER2–HER3 dimerization and downstream signaling	Synergistic with trastuzumab; improved PFS in CLEOPATRA trial
T-DM1 (Trastuzumab emtansine) (Rinnerthaler et al., 2019; Ji et al., 2023)	ADC (mAb + DM1 payload)	HER2-targeted delivery of maytansine; microtubule inhibitor	PFS improvement post-trastuzumab; effective in resistant disease
T-DXd (Trastuzumab deruxtecan) (Fehm et al., 2024; Zhou et al., 2025; Hackshaw et al., 2020; Morgovan et al., 2024)	ADC (mAb + topoisomerase I inhibitor)	High DAR, cleavable linker, bystander effect	Superior ORR and OS vs. T-DM1 (DESTINY-Breast03, DESTINY-Breast02); intracranial efficacy; risk of ILD
Disitamab vedotin (Najjar et al., 2022; Pourjamal et al., 2024)	ADC (mAb + MMAE payload)	Targets HER2-low tumors; induces apoptosis via MMAE	Promising activity post-TKI resistance; favorable distribution kinetics
Tucatinib (Rao et al., 2025; Guglielmi et al., 2024)	Tyrosine kinase inhibitor (TKI)	Selectively inhibits HER2 kinase activity	Significant intracranial benefit; improved OS in HER2CLIMB
Pyrotinib (Zhou et al., 2025; Tapia et al., 2023)	TKI	Pan-HER inhibitor; blocks EGFR/HER2/HER4	Effective post-trastuzumab; activity in brain metastases
Neratinib+ Capecitabine (Chilà et al., 2021)	TKI + chemotherapy	Irreversible pan-HER inhibitor; blocks HER1, HER2, HER4	Effective in trastuzumab/pertuzumab-pretreated disease; GI toxicity common
Zongertinib (Beamion BCGC-1) (Hurvitz et al., 2025)	Novel TKI	Potent HER2/EGFR inhibitor; CNS-penetrant	Ongoing trial (phase Ib/II); encouraging CNS control
Novel ADCs (e.g., ARX788, SYD985) (Guidi et al., 2023; Ji et al., 2023)	ADCs (next-gen)	Enhanced linker–payload stability, improved DAR	Improved response post-T-DM1; manageable toxicity

Building upon the current understanding of T-DXd safety and adverse event profiles, additional research insights provide a broader perspective on methodological rigor, clinical trial data, and study disclosures relevant to HER2-targeted therapies.

8. Additional Research Insights

This section summarizes various aspects of research, including methodological approaches, clinical trial specifics, and declarations of interest based on the analyzed publications.

8.1 Clinical Trial Information

8.1.1 DESTINY-Breast02 Trial

This phase 3 trial evaluated the antibody-drug conjugate trastuzumab deruxtecan against physician's choice treatment (capecitabine with trastuzumab or lapatinib) for HER2-positive metastatic breast cancer. The trial focused on patients whose disease had progressed after trastuzumab emtansine (Fehm et al., 2024).

8.1.2 Ongoing Trials

An open-label, dose escalation, phase 1 trial for ALT-P7 is currently underway, investigating its use in patients with HER2-positive metastatic breast cancer who have progressed on prior trastuzumab-based therapies. Another trial (NCT04020575) is investigating a CAR-T cell therapy (huMNC2-CAR44) targeting MUC1* in HER2+ breast cancer patients with MUC1-positive advanced tumors (Rinnerthaler et al., 2019; Mercogliano et al., 2023).

8.1.3 Biomarker Analysis Requirements

For Phase II studies, archival tissue from the tumor sample used for enrollment is a prerequisite for biomarker analysis (Hurvitz et al., 2025).

8.1.4 Bispecific Antibodies (bsAbs)

Zanidatamab (ZW25) is an anti-HER2 bispecific antibody that binds to both ECD2 and ECD4 domains of the HER2 receptor. It has been tested in a phase 1 trial involving various HER2+ and HER2-low tumor histologies that had progressed after standard care (Tarantino et al., 2021).

8.2 General Research Context

8.2.1 Drug-induced ILD

Drug-induced interstitial lung disease (ILD) represents a group of severe, potentially life-threatening pulmonary conditions marked by fibrosis and inflammation within the lung interstitium (Hackshaw et al., 2020).

8.2.2 Study Limitations

One study noted a limitation in that it did not include a quality assessment of the included studies, such as those related to respiratory failure. (Hackshaw et al., 2020)

9. Therapeutic Progress and Challenges in HER2-Positive Breast Cancer

Significant therapeutic progress has been made in the treatment of HER2-positive breast cancer, particularly with the advent of HER2-targeted therapies and antibody-drug conjugates (ADCs). However, challenges remain, necessitating continued research and novel strategies.

9.1 Therapeutic Progress

9.1.1 Improved Prognosis and Survival

Over the past two decades, the approval of numerous anti-HER2 agents has significantly improved cure rates in early-stage disease and greatly extended survival in the advanced setting. The prognosis for patients with HER2-positive advanced breast cancer (ABC) has dramatically improved since the introduction of HER2-targeted therapies (Tarantino et al., 2021; Aapro et al., 2022).

9.1.2 Revolutionary Impact of ADCs

The emergence of ADCs in the last decade has revolutionized the management of HER2-positive breast cancers. These agents, such as trastuzumab deruxtecan (T-DXd), have transformed the treatment landscape, especially for challenging complications such as brain metastasis (Najjar et al., 2022; Rao et al., 2025).

9.1.3 Mechanism of ADCs

ADCs utilize the specificity of HER2-targeting antibodies to deliver cytotoxic payloads directly to HER2-overexpressing tumors. Their unique pharmacokinetic and pharmacodynamic properties provide

therapeutic opportunities for high-risk, heavily pretreated patients and can potentially overcome limitations of HER2 resistance to conventional HER2-targeted therapy (Najjar et al., 2022).

9.1.4 Multidisciplinary Approach

Continuous advancements in systemic and localized therapies, integrated within a multidisciplinary treatment framework, hold great promise for improving both prognosis and quality of life, particularly for patients with brain metastases (Rao et al., 2025).

9.2 Remaining Challenges

9.2.1 Brain Metastasis

Brain metastasis remains a common and challenging complication in HER2-positive advanced breast cancer, significantly impacting patient prognosis and quality of life (Rao et al., 2025).

9.2.2 Treatment Resistance

Despite major therapeutic breakthroughs, the benefit of anti-HER2 ADCs is limited by the occurrence of acquired and de novo resistances. Most patients ultimately experience disease progression during or after treatment with approved HER2-targeted agents (Guidi et al., 2023) (Aapro et al., 2022).

9.2.3 Lack of Evidence in Specific Populations

Clinical evidence regarding the efficacy and safety of currently available HER2-targeted therapies in certain patient populations is scarce, making real-world data critical for treatment decisions (Aapro et al., 2022).

9.2.4 Therapy Sequencing Complexity

Rapid developments in available HER2-directed treatments have increased the complexity of therapy sequencing, often complicating the establishment of clear and evidence-based clinical guidelines (Gampenrieder et al., 2020).

9.3 Clinical Importance of ADCs and Future Research Priorities

ADCs represent a significant therapeutic milestone, offering solutions for high-risk, heavily pretreated patients and demonstrating increased response to HER2-targeted therapy. Their development has been pivotal in revolutionizing the treatment landscape for HER2-positive breast cancer (Najjar et al., 2022; Guidi et al., 2023; Rao et al., 2025).

A further effort is required to overcome resistance through novel strategies and approaches. Research is ongoing into combination strategies, such as combining tyrosine kinase inhibitors (TKIs) with monoclonal antibodies (mAbs) or ADCs, which may offer higher antitumor efficacy, though a survival benefit for ADC and TKI combinations has not yet been reported. Addressing the challenges of brain metastasis and developing strategies for managing treatment resistance are crucial areas for future research (Guidi et al., 2023; Hurvitz et al., 2025).

While treatment in HER2-positive breast cancer has advanced remarkably- particularly through the development of ADCs- ongoing investigation is essential to address therapeutic resistance, improve management of brain metastases, and refine treatment strategies. Future therapeutic methods should focus on optimizing sequencing, enhancing central nervous system penetration, and integrating biomarker-driven approaches to personalize care and improve long-term outcomes.

10. Conclusions

Over the past two decades, the treatment of HER2-positive breast cancer has changed profoundly. The introduction of targeted therapies- from monoclonal antibodies and tyrosine kinase inhibitors to antibody–drug conjugates (ADCs) has transformed a once highly aggressive disease into one that can often be effectively controlled. The approval of trastuzumab in 1998 marked the beginning of this progress and opened the door to continuous innovation in HER2-directed treatment.

Despite these advances, important challenges remain. Many patients still experience treatment resistance or develop brain metastases, which limit long-term outcomes. The development of newer ADCs, such as trastuzumab deruxtecan, has provided new hope for patients who previously had few effective options, demonstrating strong activity even in heavily pretreated cases.

Looking ahead, future research should focus on understanding and overcoming resistance, improving sequencing of available therapies, and ensuring that new treatments are safely and effectively integrated into routine clinical care. Continued collaboration between researchers, clinicians, and patients- supported by real-world data will be essential to further improve survival and quality of life for people living with HER2-positive breast cancer.

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