 DOI: 10.35382/TVUJS.16.1.2026.156

ADVANCES IN THE TREATMENT OF HER-2 POSITIVE BREAST CANCER: AN OVERVIEW

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Abstract – *HER2-positive breast cancer is identified as a significant subtype, accounting for approximately 15–20% of cases, and was historically associated with a poor prognosis. However, patient outcomes have been revolutionized by the development of targeted therapies. This review provides a comprehensive overview of recent therapeutic advancements and analyzes persistent challenges in clinical management. A synthesis of data from pivotal clinical trials and systematic reviews published over the past decade was conducted, focusing on treatment modalities for HER2-positive breast cancer in both early and metastatic settings. The treatment paradigm has evolved from antibody monotherapy to complex regimens involving dual blockade and next-generation antibody-drug conjugates. Notably, trastuzumab deruxtecan has been established as a new standard of care in the metastatic setting. Furthermore, novel tyrosine kinase inhibitors, such as tucatinib, have provided effective treatment options for patients with brain metastases. Although survival rates have been significantly improved, critical challenges remain, including the management of drug toxicity and the overcoming of resistance mechanisms. Future research must be focused on personalizing treatment based on predictive biomarkers.*

Keywords: breast neoplasms, pertuzumab, trastuzumab deruxtecan, trastuzumab emtansine, tucatinib.

I. INTRODUCTION

Breast cancer remains one of the most prevalent malignancies and a leading cause of cancer-related mortality among women globally. The classification of breast cancer based on its specific molecular markers has revolutionized treatment strategies. Among these classifications, human epidermal growth factor receptor 2 (HER2)-positive breast cancer constitutes a critical clinical subtype, accounting for approximately 15–20% of all cases [1, 2].

Historically, the HER2-positive subtype was associated with a relatively poor prognosis, characterized by rapid cellular proliferation and a high risk of recurrence [3]. However, the development of HER2-targeted therapies, pioneered by trastuzumab (Herceptin), marked a paradigm shift, transforming this disease from a major challenge into one with significantly improved outcomes [4].

Over the last decade, the landscape of HER2-positive breast cancer treatment has witnessed exponential advances with the introduction of numerous novel agents. These include next-generation monoclonal antibodies, tyrosine kinase inhibitors (TKIs), and notably, the emergence of antibody-drug conjugates (ADCs). Yet, this rapid pace of development presents clinicians and researchers with a complex and growing body of data. Optimizing treatment sequencing and managing mechanisms of acquired resistance pose significant clinical challenges. Therefore, a comprehensive and up-to-date overview is essential to synthesize the most critical findings and guide clinical decision-making, particularly in light of the recently updated 2024 ESMO clinical practice guidelines [5, 6].

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Received date: 9 December 2025; Revised date: 29 March 2026; Accepted date: 31 March 2026

II. LITERATURE REVIEW

Molecular background and function of HER2

The human epidermal growth factor receptor 2 (HER2) is identified as a transmembrane glycoprotein belonging to the ErbB family [7]. The ErbB signaling network is recognized as a complex system where HER2 functions primarily as a preferred heterodimerization partner, particularly for HER3 – a member of the ErbB family characterized as a pseudokinase due to its lack of intrinsic tyrosine kinase activity [8]. Following activation, stable heterodimeric complexes are formed, triggering a cascade of downstream signaling pathways, including PI3K/AKT/mTOR, which are fundamental to cellular survival [7–9].

Aberrant expression and cancer pathogenesis

The involvement of HER2 in cancer pathogenesis is predominantly characterized by ERBB2 gene amplification, leading to the overexpression of the HER2 protein on the cell surface [3, 7]. This overexpression results in a high abundance of functional receptors, which drives constitutive, unregulated intracellular signaling. This promotes a tumor phenotype characterized by uncontrolled cell growth, high invasive potential, and metastatic potential.

Basically, HER2-positive breast cancer has been regarded as having a less favorable prognosis. However, the HER2 status serves critically as a robust predictive biomarker, indicating the tumor's susceptibility to targeted therapies. This profound understanding of HER2 molecular biology has paved the way for the development of modern monoclonal ADC therapies [4, 10].

The treatment landscape of HER2-positive breast cancer in the pre-targeted therapy era

Prior to the advent of targeted therapies, the management of HER2-positive breast cancer faced significant challenges due to the aggressive biological nature of this subtype [3, 7]. During this period, treatment protocols relied primarily on a combination of surgery, radiotherapy, and traditional cytotoxic chemotherapy, typically involving anthracyclines and taxanes [4]. Because HER2 overexpression drives rapid cell division, these tumors often exhibited poor responses to endocrine (hormonal) therapy, leaving chemotherapy as the only viable systemic treatment option [1, 5].

The prognosis for HER2-positive patients during this era was considered the poorest among all breast cancer subtypes [3]. The high rate of tumor cell proliferation resulted in significantly shorter disease-free survival (DFS) [3, 4]. Patients were faced with a high clinical risk of visceral metastasis (liver, lungs) and, notably, central nervous system (brain) involvement. Before the introduction of trastuzumab (the first monoclonal antibody targeting HER2) in the late 1990s, the 5-year survival rate for this group was observed to be substantially lower than that of HER2-negative or hormone receptor-positive patients [4, 6].

The subsequent emergence of targeted therapies has completely redefined the clinical landscape, through which HER2-positive breast cancer has been transformed from the subtype with the worst prognosis into one with some of the most effective treatment options and best disease control in modern oncology [4, 5].

III. RESEARCH METHODS

A dual-track search strategy was implemented to ensure both historical depth and clinical currency. First, a systematic search was conducted via PubMed for peer-reviewed articles published between January 2010 and December 2025. The search string was constructed as follows: ('breast neoplasms') AND ('trastuzumab deruxtecan') OR ('trastuzumab emtansine') OR ('pertuzumab') OR ('tucatinib'). The selection was restricted specifically to randomized controlled trials (RCTs) and meta-analyses. Then, foundational molecular research and landmark studies were identified through hand-searching of reference lists from high-impact review articles. The systematic selection process is visually summarized in the PRISMA 2020 flow diagram (Figure 1). A total of 178 records were initially identified, comprising 173 records from the PubMed database and 5 additional records through manual

searching of reference lists. Before the screening phase, 146 records were removed for specific reasons: 45 focused exclusively on HER2-low populations; 49 were sub-analyses of previously included trials; and 52 lacked final clinical outcomes. The remaining 32 records were then screened, leading to the exclusion of 10 records identified as duplicate data or interim analyses of trials already accounted for. Consequently, 22 full-text reports were assessed for eligibility. Out of these, 4 studies were excluded due to an inadequate follow-up period for survival analysis. Ultimately, 18 studies met all inclusion criteria and were included in this review, consisting of 13 pivotal clinical studies and 5 foundational landmark studies.

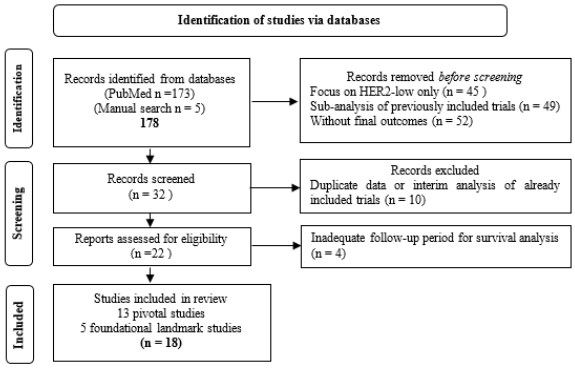

Fig. 1: PRISMA 2020 flow diagram illustrating the selection process for randomized controlled trials and meta-analyses on HER2-positive breast cancer treatments

IV. RESULTS AND DISCUSSION

A. Therapeutic strategies in early-stage disease

Neoadjuvant and adjuvant treatment strategies are identified as pivotal in the curative management of early-stage HER2-positive breast cancer. Innovation in this segment is defined by maximizing the pathological complete response (pCR) rate in the neoadjuvant setting, which is recognized as a robust surrogate biomarker for favorable long-term survival outcomes [5, 10].

Establishing dual HER2 blockade as the standard of care

The current gold standard for neoadjuvant treatment of high-risk HER2-positive tumors (>T1c or node-positive) is comprised of taxane-based chemotherapy combined with dual HER2 blockade. The addition of pertuzumab to trastuzumab-based regimens was shown to significantly improve outcomes by inhibiting HER2/HER3 heterodimerization. The efficacy of this approach was demonstrated in the NeoSphere and TRYPHAENA trials, where increased pCR rates were achieved compared to single-agent anti-HER2 therapy [10, 11]. Subsequently, the APHINITY trial confirmed the benefit of adjuvant dual blockade, demonstrating a statistically significant improvement in invasive disease-free survival (iDFS) in the high-risk, node-positive population [12].

Treatment escalation strategies for targeting residual disease

A breakthrough has been achieved through the implementation of intensified adjuvant therapy for patients with residual disease following neoadjuvant treatment. The KATHERINE trial is established as the foundational study for this strategy. It was demonstrated that substituting trastuzumab with trastuzumab emtansine (T-DM1) significantly reduces the risk of recurrence or death [13]. Currently, T-DM1 is utilized as the standard of care for patients failing to achieve pCR, regardless of hormone receptor status. Furthermore, the potential of next-generation agents such as trastuzumab deruxtecan (T-DXd) to further enhance outcomes in high-risk settings is currently being investigated in ongoing clinical trials [5, 14].

Treatment de-escalation to balance efficacy and toxicity

A growing trend toward treatment de-escalation is observed to mitigate long-term toxicities, such as anthracycline-related cardiotoxicity. The adjuvant paclitaxel and trastuzumab (APT) trial validated the high efficacy of a non-anthracycline regimen (paclitaxel and trastuzumab) for small (T1), node-negative tumors, yielding an iDFS rate exceeding 95% [15]. Additionally, the attainment

of pCR is now utilized as a predictive tool to personalize adjuvant therapy, allowing for treatment individualization based on early therapeutic response [5, 13].

B. Advances in metastatic HER2-positive breast cancer

The management of HER2-positive metastatic breast cancer has undergone a revolutionary shift, transforming prognosis and extending overall survival (OS). This section delineates the established first-line standard and examines the profound impact of second- and subsequent-line targeted agents.

Dual blockade as the standard for first-line therapy

The benchmark for first-line (1L) treatment remains established by the CLEOPATRA trial. It was demonstrated that the combination of pertuzumab, trastuzumab, and docetaxel significantly improves both progression-free survival (PFS) and OS. This synergistic effect is attributed to the complementary mechanisms of the two antibodies, where downstream signaling pathways are more effectively blocked [16].

The pivotal role of antibody-drug conjugates

ADCs have redefined subsequent lines of therapy. While T-DM1 was initially established as the preferred second-line (2L) option based on the EMILIA trial [17], it has been surpassed by T-DXd. The DESTINY-Breast03 trial definitively established T-DXd as the new 2L standard, showing an unprecedented reduction in the risk of progression or death (HR for PFS: 0.28) [14]. Furthermore, T-DXd is now utilized in the HER2-low population, significantly expanding the clinical utility of targeted agents beyond traditional boundaries [5, 14].

Management of central nervous system metastases

The management of central nervous system (CNS) metastases remains a critical challenge due to the blood-brain barrier (BBB). Small-molecule TKIs, such as tucatinib, are critically utilized due to their superior BBB penetration. The HER2CLIMB trial confirmed that the addition of tucatinib to trastuzumab and capecitabine improves OS in patients with active brain metastases, and this regimen is now incorporated into the 2024 ESMO guidelines [5, 6].

To provide a clear clinical pathway, the current standards for treatment sequencing are outlined in Table 1. The treatment landscape for HER2-positive breast cancer is strategically categorized into early-stage and metastatic settings. In the neoadjuvant phase, the combination of a taxane with dual HER2 blockade (trastuzumab and pertuzumab) remains the standard to achieve pCR. Post-surgery, adjuvant therapy is tailored based on the presence of residual disease. Patients achieving pCR continue with trastuzumab-based regimens, while those with residual disease are switched to T-DM1 to mitigate recurrence risk. For metastatic disease, the paradigm shifts toward a sequenced approach, starting with trastuzumab-pertuzumab-taxane in the first line, followed by T-DXd as the preferred second-line therapy. In later lines or specifically for patients with CNS involvement, the tucatinib-based triplet regimen is prioritized due to its proven efficacy in improving survival for active brain metastases.

C. Challenges in the clinical management of HER2-positive breast cancer

Management of specific toxicities

The efficacy of treatment has been significantly improved by the introduction of new targeted therapies, particularly ADCs and TKIs; however, new challenges regarding the management of specific toxicities have been presented [5, 6].

Interstitial lung disease (ILD): ILD is recognized as the most prominent and alarming toxicity associated with T-DXd, with severity ranging from mild (grade 1) to fatal (grade 5). The high incidence of ILD reported in the DESTINY-Breast03 and DESTINY-Breast04 trials is considered a major clinical concern, necessitating strict monitoring protocols [5, 14]. The precise mechanism is hypothesized to involve the premature release of the cytotoxic payload (DXd) in lung

Table 1: Summary of evidence-based treatment sequencing

Setting	Clinical scenario	Recommended regimen (Standard of care)	Key clinical outcomes	Pivotal evidence (RCTs)
Early-stage	Neoadjuvant (Tumor > 2cm or N+)	Taxane + Trastuzumab + Pertuzumab	Improved pCR	NeoSphere [10], TRYPHAENA [11]
	Adjuvant (pCR achieved)	Trastuzumab ± Pertuzumab (to complete 1 year)	Increased iDFS	APHINITY [12]
	Adjuvant (Residual disease/non-pCR)	Trastuzumab Emtansine (T-DM1)	Significant reduction in recurrence risk	KATHERINE [13]
Metastatic	First-line	Taxane + Trastuzumab + Pertuzumab	Superior OS and PFS	CLEOPATRA [16]
	Second-line	Trastuzumab Deruxtecan (T-DXd)	Remarkable PFS	DESTINY-Breast03 [14]
	Third-line/CNS disease	Tucatinib + Trastuzumab + Capecitabine	Improved survival in brain metastases	HER2CLIMB [18]

Note: pCR – pathological complete response; iDFS – invasive disease-free survival; OS – overall survival; PFS – progression-free survival

tissue, leading to pulmonary cellular damage and subsequent interstitial inflammation [14]. High vigilance is demanded, requiring regular chest CT scans and the immediate initiation of high-dose corticosteroids upon suspicion of grade 2 or higher ILD [5].

Cardiovascular toxicity: Cardiovascular health is identified as a general concern, particularly with HER2-targeted therapies and prior anthracycline exposure. Trastuzumab was identified as the first anti-HER2 therapy to cause left ventricular ejection fraction (LVEF) dysfunction. This mechanism is believed to involve the blockade of HER2 signaling, which is essential for cardiomyocyte survival [11]. Frequent LVEF monitoring is mandated every three to six months during treatment, and anti-HER2 therapy must be interrupted if LVEF drops below safety thresholds [5, 6].

Acquired drug resistance

Treatment failure in metastatic disease is primarily driven by complex mechanisms of drug resistance. Alterations in the HER2-HER3 axis and the development of p95-HER2 (a truncated receptor lacking the antibody-binding domain) are known to reduce the efficacy of trastuzumab [7, 8]. Furthermore, the activation of alternative signaling pathways, such as the PI3K/AKT/mTOR pathway via PIK3CA mutations, is identified as a key bypass mechanism [7]. Resistance to ADCs is also observed, potentially due to decreased HER2 expression, impaired drug release, or enhanced drug efflux mechanisms [14, 17].

Central nervous system metastasis

Central nervous system metastasis is identified as a frequent complication, occurring in 30% to 50% of patients with HER2-positive metastatic disease [5, 6]. A unique therapeutic challenge is presented by the BBB, which impedes the penetration of large molecular weight agents like trastuzumab and T-DM1 [14]. Consequently, local failure in CNS disease control is frequently observed despite systemic response.

D. Future perspectives on overcoming resistance

As T-DXd is increasingly established as the standard-of-care in second-line metastatic settings [14], the management of disease progression following ADC therapy has emerged as a critical and unresolved clinical challenge. Current research is extensively focused on several strategic pathways to circumvent acquired resistance, particularly addressing payload-related evasion and HER2 downregulation.

One promising approach is identified as the deployment of next-generation ADCs, such as trastuzumab duocarmazine (SYD985) and disitamab vedotin (RC48). These agents are currently being evaluated for their efficacy in patients with prior T-DXd exposure, aiming to bypass cross-resistance through novel linker-payload technologies [5]. Furthermore, the potential for synergistic combination strategies is

being rigorously explored, notably through the integration of anti-HER2 agents with immune checkpoint inhibitors. Ongoing trials, such as KATE3 and HER2CLIMB-05, are investigating whether agents like pembrolizumab can enhance the immune-mediated antitumor response in the presence of HER2 blockade [5].

In parallel, TKI-mediated rescue protocols are being assessed to bypass secondary signaling pathways. Specifically, the use of the highly selective inhibitor tucatinib in combination with other ADCs is being scrutinized not only to overcome systemic resistance but also to provide superior CNS control [6]. Through the integration of these novel regimens, a more durable and personalized therapeutic landscape is intended for patients who have exhausted current ADC options, ultimately aiming to transform the management of refractory HER2-positive breast cancer.

V. CONCLUSION

The therapeutic landscape for HER2-positive breast cancer has undergone an extraordinary transformation, transitioning from an aggressive phenotype with poor prognosis to a highly manageable disease. This progress is anchored by the integration of dual HER2 blockade as a standard of care alongside the emergence of next-generation ADCs and CNS-penetrant TKIs. In clinical practice, treatment escalation with T-DM1 is now considered mandatory for patients with residual disease post-neoadjuvant therapy to effectively mitigate recurrence risks. Furthermore, T-DXd has established itself as the preferred second-line standard for metastatic disease, extending its utility even to the emerging 'HER2-low' cohort. For patients with active brain metastases, triple therapy incorporating tucatinib should be prioritized due to its superior blood-brain barrier penetration. At the same time, robust protocols for monitoring interstitial lung disease remain essential for those receiving T-DXd. Ultimately, the next phase of clinical care will shift from the development of individual agents toward the intelligent sequencing of these powerful drugs, supported by the identification of predictive biomarkers to achieve durable remissions.

Nonetheless, such progress must be viewed within the context of certain inherent limitations. While this review comprehensively synthesizes revolutionary advances, the dynamic nature of the field – driven by ongoing pivotal trials evaluating T-DXd in early-stage settings and post-T-DXd regimens – means that recommendations on optimal sequencing continue to evolve. The rapid arrival of novel agents further underscores the necessity for periodic systematic updates, ensuring that clinical decisions remain consistently informed by the latest high-level evidence.

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