Review Article

A Review of Clinical Evolution, the DESTINY-Breast 09 Trial, and Management Strategies for the Modern ADC Era

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Abstract: The treatment landscape for HER2-positive metastatic breast cancer (mBC) has remained relatively static for over a decade, defined by the combination of a taxane with dual HER2 blockade (Trastuzumab and Pertuzumab) established by the CLEOPATRA trial. However, the emergence of antibody-drug conjugates (ADCs) with higher drug-to-antibody ratios and membrane-permeable payloads has redefined expectations for durability and efficacy. The landmark DESTINY-Breast09 trial presented in 2025 has demonstrated that first-line treatment with Trastuzumab Deruxtecan (T-DXd) plus Pertuzumab achieves an unprecedented median progression-free survival (PFS) exceeding 40 months, a nearly 14-month improvement over the traditional standard. This review provides a comprehensive analysis of the mechanistic synergy between T-DXd and Pertuzumab, evaluates the efficacy data across key patient subgroups, and addresses the critical safety management of interstitial lung disease (ILD). As T-DXd plus Pertuzumab ascends to the first-line setting, clinicians must balance superior clinical outcomes with a shifted toxicity profile, marking a definitive transition from traditional chemotherapy toward payload-driven targeted therapy.

Keywords: clinical evolution, destiny-breast 09 trial, management strategies, modern era

1. INTRODUCTION

Human epidermal growth factor receptor 2 (HER2), encoded by the ERBB2 gene, is a transmembrane receptor tyrosine kinase belonging to the epidermal growth factor receptor (EGFR/ErbB) family, a signaling axis that plays a central role in regulating cellular proliferation, survival, differentiation, and motility [1]. Unlike other EGFR family members, HER2 lacks a known ligand and exists in a constitutively active conformation, rendering it a preferred dimerization partner for other ErbB receptors. This unique biology amplifies downstream signaling through the PI3K–AKT–mTOR and MAPK pathways, promoting oncogenic transformation when HER2 is overexpressed or amplified [2]. HER2 gene amplification or protein overexpression occurs in approximately 15–20% of breast cancers and was historically associated with aggressive tumor biology, early relapse, and markedly reduced overall survival in the metastatic setting. Prior to the advent of HER2-directed therapy, HER2-positive metastatic breast cancer (mBC) was among the most lethal breast cancer subtypes, characterized by rapid disease progression and limited responsiveness to conventional cytotoxic chemotherapy [3]. The therapeutic landscape was fundamentally transformed in 1998 with the clinical introduction of trastuzumab, a monoclonal antibody targeting the extracellular domain of HER2. Trastuzumab not only inhibited HER2-driven signaling but also engaged immune-mediated mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), redefining HER2-positive mBC as a biologically targetable disease [4]. This landmark advance converted what was once an acutely fatal malignancy into a chronically manageable condition, setting the stage for iterative improvements in survival over subsequent decades. This paradigm shift

reached a new apex with the CLEOPATRA trial, which established the combination of docetaxel, trastuzumab, and pertuzumab (THP) as the first-line standard of care. Pertuzumab, by inhibiting HER2 dimerization at a distinct epitope from trastuzumab, delivered complementary blockade of HER2 signaling. CLEOPATRA demonstrated a median overall survival approaching five years, an unprecedented outcome in metastatic breast cancer and a benchmark that remained unchallenged for over a decade [5]. The durability of benefit observed with THP entrenched taxane-based dual HER2 blockade as the foundational first-line regimen worldwide. Despite this success, the limitations of the THP paradigm gradually became apparent. The vast majority of patients ultimately experience acquired resistance, driven by mechanisms such as HER2 signaling reactivation, pathway redundancy, receptor heterogeneity, and adaptive tumor evolution. As a result, therapeutic innovation shifted toward more potent HER2-directed agents capable of overcoming resistance while minimizing cumulative toxicity [6]. The second-line treatment landscape underwent two major paradigm shifts. The first came with trastuzumab emtansine (T-DM1), an antibody–drug conjugate (ADC) that coupled HER2 targeting with intracellular delivery of a cytotoxic payload. More recently, the field was irrevocably altered by the emergence of trastuzumab deruxtecan (T-DXd), a next-generation ADC distinguished by a high drug-to-antibody ratio, a cleavable linker, and a membrane-permeable payload capable of inducing a bystander effect [7]. Across the DESTINY-Breast01, 02, and 03 trials, T-DXd demonstrated striking improvements in response rates and progression-free survival compared with existing standards, rapidly establishing itself as the preferred therapy in later lines of treatment. Given the magnitude and consistency of benefit observed with T-DXd in previously treated populations, the oncology community increasingly questioned whether the traditional sequencing paradigm—reserving the most potent therapy for later lines—remained justified. This rationale catalyzed the design of DESTINY-Breast09, a pivotal first-line trial evaluating whether ADC-based therapy could outperform the long-dominant CLEOPATRA regimen in treatment-naïve HER2-positive metastatic disease [8]. DESTINY-Breast09 represents the first randomized trial in more than 12 years to meaningfully surpass the efficacy benchmarks established by CLEOPATRA, marking a watershed moment in the evolution of HER2-positive mBC therapy. By demonstrating superior disease control in the frontline setting, the trial fundamentally reshapes the therapeutic algorithm, signaling a transition away from chemotherapy-centered regimens toward ADC-driven precision oncology as the new standard. This shift not only redefines expectations for progression-free survival but also underscores a broader conceptual evolution: from incremental optimization of existing regimens to a wholesale rethinking of how HER2-driven disease should be treated from the outset.

2. MECHANISTIC FOUNDATIONS OF T-DXD AND PERTUZUMAB SYNERGY

The efficacy of the T-DXd plus Pertuzumab combination stems from distinct yet complementary mechanisms of action. T-DXd is a second-generation ADC composed of a humanized anti-HER2 IgG1 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload (DXd) via a tetrapeptide-based cleavable linker [9]. Unlike its predecessor T-DM1, T-DXd possesses a high drug-to-antibody ratio (DAR) of approximately 8, ensuring a dense delivery of the cytotoxic payload to the tumor site. The DXd payload is highly potent and has a short systemic half-life, which minimizes off-target toxicity. Crucially, DXd is membrane-permeable, allowing it to exit the target cell upon lysosomal release and penetrate adjacent cells in the tumor microenvironment—a phenomenon known as the bystander effect [10]. Pertuzumab complements this by binding to subdomain II of the HER2 extracellular domain. While Trastuzumab (the antibody backbone of T-DXd) binds to subdomain IV, Pertuzumab specifically prevents the heterodimerization of HER2 with other members of the HER family, particularly HER3. This dual epitope targeting results in more comprehensive inhibition of downstream PI3K/AKT and MAPK signaling pathways [11]. Preclinical models suggested that the addition of Pertuzumab to T-DXd could

enhance receptor internalization and stabilize the HER2-ADC complex, providing a biological rationale for the combination in the DESTINY-Breast09 trial.

3. THE CLINICAL EVOLUTION TOWARD THE FIRST-LINE ADC

The transition of ADCs to the first-line setting was built upon a foundation of success in pre-treated patients. In the DESTINY-Breast01 Phase 2 trial, T-DXd showed an objective response rate (ORR) of 60.9% in patients who had received a median of six prior lines of therapy. This was followed by the DESTINY-B reast03 trial, which compared T-DXd head-to-head against T-DM1 in the second-line setting [12]. T-DXd demonstrated a 72% reduction in the risk of progression or death (HR 0.28), an efficacy signal so strong it necessitated a re-evaluation of the frontline standard. Furthermore, the DESTINY-Breast12 trial provided critical data on the central nervous system (CNS) activity of T-DXd, showing substantial intracranial responses in patients with both stable and active brain metastases [7]. These cumulative data points provided the impetus for DESTINY-Breast09, a trial designed to determine if T-DXd could displace taxanes entirely in the treatment-naïve population.

4. DESTINY-BREAST09: STUDY DESIGN AND EFFICACY ANALYSIS

DESTINY-Breast09 was a global, randomized, Phase 3 trial that enrolled 1,157 patients with previously untreated HER2-positive metastatic or unresectable breast cancer. Patients were randomized in a 1:1:1 ratio to receive T-DXd plus Pertuzumab, T-DXd plus placebo, or the investigator's choice of THP (standard CLEOPATRA regimen) [13]. The primary endpoint was PFS by blinded independent central review (BICR). At the 2025 ASCO interim analysis (median follow-up of 29.2 months), the trial met its primary objective. The T-DXd plus Pertuzumab arm achieved a median PFS of 40.7 months, compared to 26.9 months in the THP arm (HR 0.56; 95% CI 0.44–0.71; $p < 0.00001$). This represented a 44% reduction in the risk of disease progression or death [14]. Secondary endpoints further supported the superiority of the ADC-based regimen. The confirmed ORR was 85.1% for the combination arm versus 78.6% for THP. Notably, the complete response (CR) rate was nearly doubled (15.1% vs 8.5%). The duration of response (DOR) for T-DXd plus Pertuzumab exceeded 39 months, underscoring the durability of the treatment effect in the treatment-naïve setting.

5. SUBGROUP PERSPECTIVES: DE NOVO DISEASE, HR STATUS, AND MUTATIONS

The benefit of T-DXd plus Pertuzumab was remarkably consistent across all prespecified subgroups. In patients with de novo metastatic disease (52% of the cohort), the median PFS in the combination arm was not yet reached, with a Hazard Ratio of 0.49 compared to THP. For patients with recurrent disease, the PFS was 38.0 months vs 22.5 months [9]. Hormone receptor (HR) status and PIK3CA mutation status did not attenuate the benefit of the ADC combination. Even in patients with PIK3CA mutations—a group historically associated with resistance to HER2-targeted therapy— the HR was 0.57, suggesting that the potent cytotoxic delivery of T-DXd can overcome intracellular signaling mutations that typically hinder traditional monoclonal antibody efficacy [15].

6. THE SAFETY HORIZON: MANAGING ILD AND OTHER TOXICITIES

The superior efficacy of T-DXd is accompanied by a unique toxicity profile that requires a change in clinical management. The most significant adverse event is adjudicated drug-related interstitial lung disease (ILD) or pneumonitis. In DESTINY-Breast09, ILD occurred in 12.1% of patients in the T-DXd plus Pertuzumab arm, compared to 1.0% in the THP arm. While the majority of cases were low-grade (Grade 1 or 2), the trial reported two Grade 5 (fatal) events. This incidence is consistent with previous T-DXd trials but highlights the absolute necessity of rigorous monitoring [13]. Management guidelines as of 2026 emphasize early detection via imaging and patient education. For any Grade 1 asymptomatic ILD,

T-DXd must be interrupted, and systemic steroids should be considered. For Grade 2 or higher symptomatic ILD, T-DXd must be permanently discontinued. Emerging real-world data presented in 2025 suggests that careful rechallenge in patients who successfully resolved Grade 1 ILD may be safe, but this remains a high-risk intervention that requires expert multidisciplinary oversight [16]. Other frequent toxicities included nausea (72%), neutropenia (65%), and fatigue. Interestingly, the absence of taxane-induced alopecia and peripheral neuropathy was a significant positive factor for patient quality of life, potentially offsetting the gastrointestinal and hematologic challenges of the ADC [17]. The success of T-DXd plus Pertuzumab in the first-line setting raises critical questions about treatment sequencing. If the most potent agent is used upfront, what remains for the second-line? Potential options include T-DM1, Tucatinib combinations (the HER2CLIMB regimen), or novel ADCs currently in development. Additionally, the role of T-DXd in the 'HER2-low' space (IHC 1+ or 2+/ISH-) is expanding, suggesting that the threshold for 'HER2-positivity' may become increasingly fluid as these drugs move toward earlier lines of therapy [18]. Economic considerations and 'financial toxicity' also cannot be ignored. The cost of long-term ADC therapy—given a median PFS of over 40 months—represents a substantial challenge for healthcare systems globally. Future studies evaluating fixed-duration treatment or induction-maintenance strategies (similar to the PATINA trial) will be essential to optimize the value and sustainability of these breakthroughs [19].

7. CONCLUSION

The U.S. Food and Drug Administration’s approval of trastuzumab deruxtecan (T-DXd) in combination with pertuzumab in late 2025 represents a decisive inflection point in the therapeutic landscape of HER2-positive metastatic breast cancer (mBC), effectively signaling the end of the taxane-based triplet as the universal first-line standard of care. For more than a decade, the combination of trastuzumab, pertuzumab, and a taxane served as the cornerstone of first-line therapy, offering meaningful survival benefits but at the cost of cumulative toxicity and an eventual plateau in efficacy. The emergence of antibody–drug conjugate (ADC)–based regimens now redefines both clinical expectations and therapeutic priorities in this disease. The pivotal DESTINY-Breast09 trial demonstrated an unprecedented improvement in progression-free survival (PFS), with median disease control extending beyond three years—a threshold that was previously inconceivable in the first-line metastatic setting. This magnitude of benefit not only surpasses historical benchmarks established by taxane-containing regimens, but also challenges long-standing assumptions about the durability achievable with systemic therapy in HER2-driven metastatic disease. Importantly, these gains were observed across clinically relevant subgroups, reinforcing the robustness of the ADC-based strategy and its broad applicability within the HER2-positive population. Mechanistically, the success of the T-DXd plus pertuzumab combination reflects the convergence of potent intracellular cytotoxic delivery, sustained HER2 pathway blockade, and bystander killing effects that may overcome intratumoral heterogeneity. Unlike conventional chemotherapy, T-DXd exploits high drug-to-antibody ratios and membrane-permeable payloads, enabling activity even in tumors with variable HER2 expression. When paired with pertuzumab, which disrupts HER2 dimerization and downstream signaling, the regimen achieves both molecular precision and cytotoxic intensity, redefining the therapeutic ceiling for metastatic disease control. Notwithstanding these advances, interstitial lung disease (ILD)/pneumonitis remains a clinically significant and non-trivial toxicity associated with T-DXd. While the majority of ILD events are low-grade and manageable with early detection and prompt intervention, the potential for severe or fatal outcomes necessitates vigilant monitoring and structured management algorithms. Importantly, within the context of DESTINY-Breast09, the overall benefit–risk profile strongly favored the ADC combination, particularly when weighed against the cumulative neurotoxicity, alopecia, myelosuppression, and quality-of-life burdens historically associated with prolonged taxane exposure. As clinician familiarity with ILD risk mitigation continues to improve, the therapeutic index of T-DXd-based regimens is likely

to further widen. Looking ahead, the approval of T-DXd plus pertuzumab shifts the central challenge from whether superior disease control is achievable to how best to optimize and individualize its delivery. Future efforts will increasingly focus on refined patient selection, including identification of clinical, radiographic, and molecular predictors of benefit and toxicity. Parallel advances in toxicity surveillance, including standardized ILD screening protocols and real-world pharmacovigilance, will be essential to safely extend these benefits to broader patient populations. Finally, this milestone establishes a new therapeutic foundation upon which next-generation HER2-directed strategies can be built. Ongoing exploration of novel ADCs, bispecific antibodies, immune-modulating combinations, and rational sequencing approaches will determine whether even greater durability—and potentially functional cure for select patients—can be achieved. In this context, the T-DXd plus pertuzumab paradigm does not represent the culmination of progress in HER2-positive mBC, but rather the opening of a new era in which prolonged disease control is no longer the exception, but the expectation.

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