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Advances in Antibody–Drug Conjugate Therapy for Breast Cancer: Clinical and Mechanistic Insights into Trastuzumab Deruxtecan and Datopotamab Deruxtecan

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Abstract Antibody–drug conjugates (ADCs) have emerged as a transformative class of targeted therapies, offering new hope in the management of advanced breast cancer and other solid tumors. Among the most impactful developments are fam-trastuzumab deruxtecan-nxki (T-DXd) and datopotamab deruxtecan (Dato-DXd, also known as Datroway), both of which integrate precise tumor targeting with potent cytotoxic activity.

T-DXd, a HER2-directed ADC, has significantly advanced the treatment paradigm for HER2-positive and HER2-low metastatic breast cancer. Results from the DESTINY-Breast01, DESTINY-Breast03, and DESTINY-Breast04 trials demonstrated exceptional objective response rates (ORR) and substantial improvements in progression-free survival (PFS). The molecule's design—featuring a high drug-to-antibody ratio and a cleavable linker that allows for a bystander effect—enables it to effectively eliminate heterogeneous tumor populations and overcome resistance to prior HER2-targeted therapies. These findings have positioned T-DXd as a breakthrough option that extends the benefits of HER2-directed treatment beyond traditional HER2-positive disease categories.

Similarly, Dato-DXd, a novel ADC targeting TROP2, has shown considerable promise in hormone receptor (HR)-positive, HER2-negative breast cancer and non–small cell lung cancer (NSCLC). In the TROPION-Breast01 trial, Dato-DXd achieved a 37% reduction in the risk of disease progression, establishing its clinical potential as a new therapeutic standard. Like T-DXd, it employs a topoisomerase I inhibitor (DXd) payload, which, combined with its bystander killing capacity, ensures strong activity even in tumors with heterogeneous or low antigen expression.

Despite their remarkable efficacy, both agents face challenges that require careful management. The most significant among these are interstitial lung disease (ILD), a potentially serious adverse event, as well as the issues of acquired resistance and treatment cost. Ongoing research efforts are focused on improving patient selection criteria, developing combination strategies with other targeted or immune-based therapies, and enhancing safety monitoring to mitigate toxicity.

Keywords DXd payload ,Bystander effect, Tumor heterogeneity,Resistance mechanism Interstitial lung disease (ILD)

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1. Introduction

Breast cancer is the most commonly diagnosed cancer among women and the second leading cause of cancer-related death in this population. In the United States alone, over 270,000 new breast cancer cases are diagnosed annually, resulting in approximately 40,000 deaths. While breast cancer in men is rare, around 2,600 cases are reported each year. Among those diagnosed with metastatic breast cancer, about 15% to 20% present with HER2-positive tumors, which are generally more aggressive and occur more frequently in younger patients. The prognosis for these patients varies depending on hormone receptor (HR) status, with a 5-year relative survival rate ranging from 37% to 44%[1].

In the United States, the standard first-line treatment for metastatic HER2-positive breast cancer includes a combination of trastuzumab, pertuzumab, and a taxane. For patients whose disease progresses beyond this initial treatment, ado-trastuzumab emtansine (T-DM1) is the preferred second-line therapy, based on its demonstrated efficacy in clinical trials. However, treatment options become more limited after second-line therapies. Available options in later lines of therapy include lapatinib combined with capecitabine or trastuzumab paired with other chemotherapeutic agents. While patients may initially benefit from these therapies, their effects are often temporary, and relapse is common[2].

The treatment landscape has expanded with the accelerated approval of famtrastuzumab deruxtecan-nxki (T-DXd), offering a new option for patients who have exhausted other antiHER2 therapies. Since this approval, two additional therapies have received regular FDA approval. In February 2020, the combination of neratinib and capecitabine was approved for patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens. Shortly after, in April 2020, the combination of tucatinib, trastuzumab, and capecitabine was approved, including for patients with brain metastases, provided they had received at least one prior anti-HER2 therapy[3].

Despite the notable improvements in outcomes due to anti-HER2 therapies, metastatic HER2 positive breast cancer remains an incurable condition. Consequently, there is a continued and urgent need for the development of more effective treatments, particularly for patients in the later stages of therapy[4]. The article in question highlights the clinical trial results and regulatory review that supported the FDA's decision to grant accelerated approval to T-DXd, representing an important advancement in treatment for this challenging disease[4].

2. Development of Fam-Trastuzumab Deruxtecan-nxki

Fam-trastuzumab deruxtecan-nxki (Enhertu) has emerged as a groundbreaking antibody-drug conjugate (ADC) in the treatment of HER2-positive malignancies. Designed to overcome the shortcomings of earlier HER2-targeted therapies such as trastuzumab and ado-trastuzumab emtansine (T-DM1), this next-generation ADC offers enhanced efficacy, expanded therapeutic reach to HER2-low tumors, and a novel mechanism of action aimed at addressing resistance mechanisms[5].

3. Chemistry

Fam-trastuzumab deruxtecan-nxki (DS-8201a) is a type of antibody-drug conjugate (ADC), an advanced cancer therapy designed to improve the precision and efficacy of chemotherapy. ADCs use monoclonal antibodies to selectively deliver cytotoxic agents directly to cancer cells, enhancing the therapeutic index while minimizing systemic toxicity and side effects[11].

This particular ADC targets HER2-positive tumors and is composed of two main components: a human monoclonal IgG1 antibody—structurally identical to trastuzumab—and a potent chemotherapy drug called DXd (a derivative of exatecan), which works by inhibiting topoisomerase I, a key enzyme required for DNA replication. DXd is linked to the antibody through a cleavable tetrapeptide linker (GGFG: glycineglycinephenylalanine-glycine). Once the drug binds to HER2 receptors on the surface of tumor cells, the entire complex is internalized. Inside the cell, enzymes such as cathepsins B and L—which are often found in higher levels in cancer cells—cleave the linker, releasing DXd. The free DXd then causes DNA damage, leading to apoptosis (programmed cell death). Meanwhile, the antibody component undergoes normal degradation into amino acids through natural metabolic (catabolic) pathways[12]. Preclinical studies (in vitro and in vivo) have shown that the GGFG linker is stable in the bloodstream, even with a high drug-to-antibody ratio (DAR) of 8, which means that each antibody molecule carries approximately eight DXd molecules. This high DAR enables effective drug delivery, potentially enhancing cytotoxic activity even

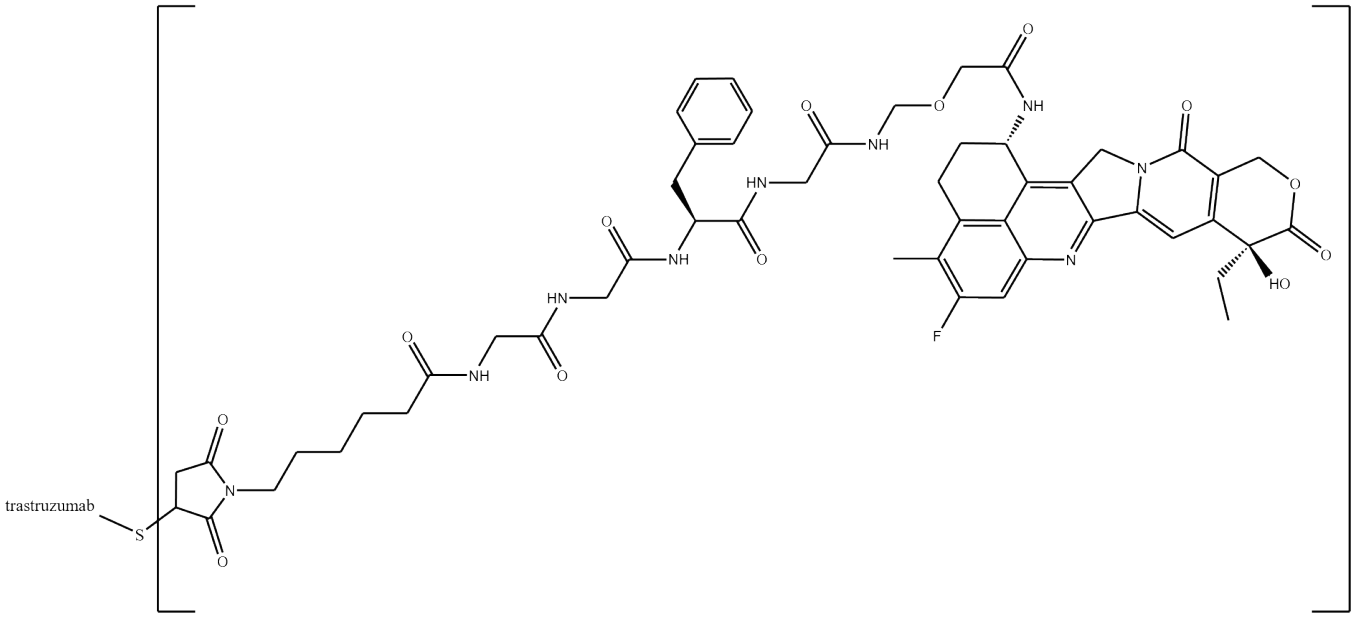

Figure 1: Fam-trastuzumab deruxtecan-nxki

in tumors that express low levels of HER2.

Another critical feature of DXd is its high membrane permeability. After being released into a HER2-expressing tumor cell, DXd can diffuse into neighboring cells, including those with little or no HER2 expression. This results in a bystander effect, allowing the drug to affect a broader range of tumor cells within a heterogeneous tumor environment, where not all cells uniformly express HER2. This property makes fam-trastuzumab deruxtecan-nxki particularly promising for treating HER2-heterogeneous cancers, which are more challenging to treat with conventional HER2-targeted therapies[13].

4. Mechanism of Action

4.1 Non-Small Cell Lung Cancer

Datopotamab deruxtecan (Dato-DXd), commercially known as Datroway, is a novel antibodydrug conjugate (ADC) specifically engineered to target TROP2, a protein often overexpressed in non-small cell lung cancer (NSCLC). This protein plays a key role in tumor progression and resistance to therapies, making it an attractive target for treatment. Datroway integrates a humanized monoclonal antibody targeting TROP2, a cleavable linker, and a highly potent cytotoxic agent derived from exatecan, a topoisomerase I inhibitor[14].

The drug's mechanism begins when the monoclonal antibody binds to TROP2 on the surface of cancer cells, which are commonly found in NSCLC. TROP2 is frequently overexpressed in many cancers, including NSCLC, where it contributes to cancer cell proliferation, survival, and metastasis. Upon binding, Datroway is internalized into the cancer cell through receptormediated endocytosis. The drug complex is then trafficked to the lysosome, where an acidic environment leads to cleavage of the protease-sensitive linker that connects the antibody to the cytotoxic payload[15].

Once the linker is cleaved, the DXd payload, which is a derivative of exatecan, is released inside the cancer cell. DXd acts as a topoisomerase I inhibitor, blocking the enzyme's ability to repair DNA breaks during cell division. This disruption results in accumulation of DNA damage, which leads to cell death, primarily through the activation of apoptosis pathways. Tumor cells, due to their rapid division, are particularly sensitive to this form of DNA damage.

A notable feature of Datroway's mechanism is its bystander killing effect. After the payload is released, DXd is membrane-permeable, meaning it can diffuse into surrounding cells, including those with lower or heterogeneous TROP2 expression. This is particularly beneficial in NSCLC, where tumor cells may exhibit varying levels of TROP2, a challenge for therapies relying on uniform antigen expression. By spreading its cytotoxic effects to neighboring cells, Datroway improves overall treatment efficacy, even in heterogeneous tumor populations. The combined features of targeted delivery, potent DNA-damaging action, and bystander killing provide a multifaceted approach to treating NSCLC. Datroway not only offers precise cytotoxicity to cancer cells but also

minimizes systemic exposure and the risk of damaging healthy tissues, distinguishing it from traditional chemotherapy.

Preliminary clinical trials indicate promising results for Datroway in advanced NSCLC, especially in patients who have previously failed standard therapies like platinum-based chemotherapy and immunotherapy. These studies have shown that Datroway can induce significant tumor shrinkage and progression-free survival with manageable side effects, confirming its potential as a valuable option for treating difficult-to-manage cancers like NSCLC[16].

Datroway's mechanism of action combines targeted antibody binding, precise intracellular drug delivery, DNA damage induction, and a bystander effect to provide a highly effective treatment strategy for advanced NSCLC. As a result, Datroway holds promise for improving outcomes in patients with this challenging and often resistant cancer, providing a more effective and potentially safer alternative to traditional treatment options[17].

4.2 Action of Trastuzumab

Trastuzumab is a recombinant, humanized monoclonal antibody that has significantly changed the therapeutic landscape for HER2-positive breast and gastric cancers. Its mechanism of action is not restricted to a single pathway but involves a combination of direct effects on tumor cell signaling, immune-mediated cytotoxicity, receptor modulation, and synergistic interactions with conventional chemotherapy[18].

At the molecular level, trastuzumab specifically binds to the extracellular domain IV of the HER2 receptor, which is frequently amplified and overexpressed in approximately one-fifth of breast cancers and in a subset of gastric cancers. The binding of trastuzumab prevents HER2 from undergoing heterodimerization with other members of the epidermal growth factor receptor (EGFR) family, particularly HER3 and EGFR itself. This blockade effectively suppresses the activation of downstream intracellular signaling cascades, including the phosphoinositide-3-kinase (PI3K)/AKT and mitogenactivated protein kinase (MAPK) pathways, both of which are critical regulators of cell growth, proliferation, and survival. By attenuating these oncogenic signals, trastuzumab reduces tumor cell proliferation and promotes apoptosis.

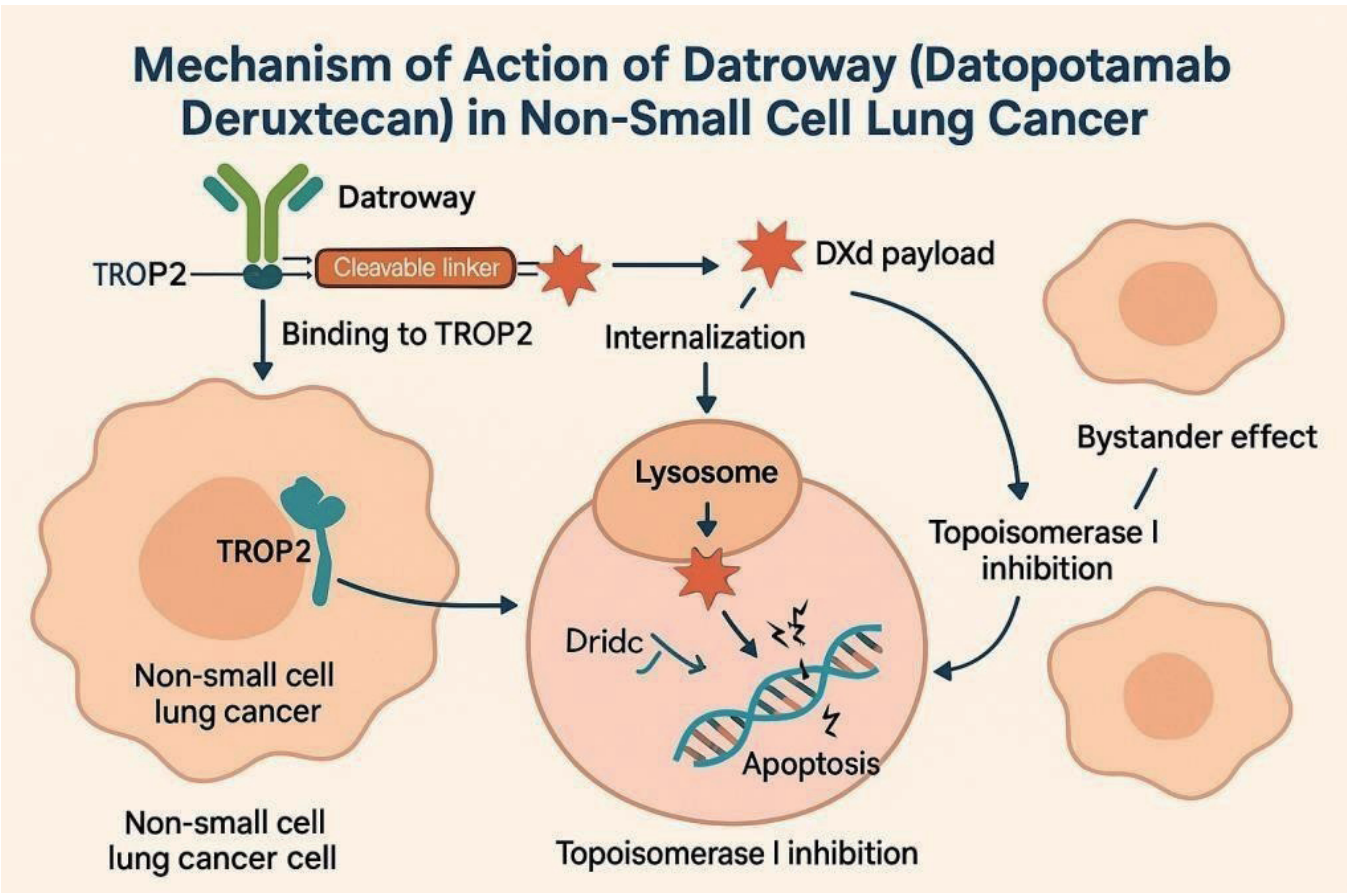

Figure 2: Non-Small Cell Lung Cancer

Beyond this direct signaling inhibition, trastuzumab also exerts profound immunological effects. The Fc portion of the antibody interacts with Fcγ receptors on immune effector cells such as natural killer (NK) cells and macrophages. This interaction activates antibody-dependent cellular cytotoxicity (ADCC), a process in which immune cells recognize and selectively lyse HER2-overexpressing cancer cells. ADCC is considered one of the key mechanisms underlying the clinical efficacy of trastuzumab, linking adaptive immune recognition to innate immune cell function in tumor eradication[19].

Another important mechanism involves receptor modulation. Binding of trastuzumab facilitates internalization and degradation of HER2 receptors, thereby decreasing the number of functional receptors available on the tumor cell surface. This receptor downregulation not only diminishes HER2 signaling capacity but also increases the susceptibility of cancer cells to subsequent therapeutic interventions. Additionally, trastuzumab interferes with tumor angiogenesis by downregulating vascular endothelial growth factor (VEGF) expression, which reduces the formation of new blood vessels required for tumor growth and metastasis[20].

5. Preclinical Studies of Datroway (Datopotamab Deruxtecan) in HR-Positive, HER2 Negative Metastatic Breast Cancer

Hormone receptor (HR)-positive, HER2-negative metastatic breast cancer represents approximately 70% of all breast cancer cases and remains a major clinical challenge due to persistent disease progression despite endocrine and chemotherapy treatments. Datroway (datopotamab deruxtecan), a TROP2-targeted antibody-drug conjugate (ADC) jointly developed by Daiichi Sankyo and AstraZeneca, has emerged as a promising therapeutic agent(35). Approved in 2025 in the U.S. and Europe for patients with previously treated unresectable or metastatic disease, Datroway combines a humanized anti-TROP2 monoclonal antibody with a topoisomerase I inhibitor (DXd) via a cleavable tetrapeptide linker, enabling selective tumor targeting and potent cytotoxic effects. This summary highlights the critical preclinical studies that supported its clinical development[21].

TROP2, a transmembrane glycoprotein highly expressed in epithelial tumors, including HRpositive, HER2-negative breast cancer, offers an ideal therapeutic target given its limited expression in normal tissues and association with poor clinical outcomes. Datroway exploits TROP2's tumor-specific expression by delivering its cytotoxic payload directly into cancer cells, leading to DNA damage and apoptosis. Importantly, the design allows for a "bystander effect," whereby the payload can diffuse into and kill adjacent TROP2-low or -negative tumor cells, addressing the heterogeneity common in metastatic disease. Preclinical rationale for targeting TROP2 also stems from the limitations of current therapies, as resistance to endocrine treatments and suboptimal responses to chemotherapy create significant unmet needs[22].

Extensive in vitro studies demonstrated Datroway' s selective and high-affinity binding to TROP2-positive breast cancer cells such as MCF-7 and T-47D, with minimal crossreactivity to TROP2-negative cells. Upon binding, Datroway was rapidly internalized, ensuring efficient intracellular delivery of DXd. Viability assays confirmed potent, nanomolar-range cytotoxicity, while DNA damage was validated through markers such as γ-H2AX staining[23].

Moreover, co-culture experiments revealed Datroway's ability to kill neighboring TROP2negative cells, reinforcing its therapeutic advantage in heterogeneous tumors. Compared to standard chemotherapy agents like eribulin and capecitabine, Datroway consistently demonstrated superior cytotoxic potency.

In vivo, both patient-derived (PDX) and cell line-derived (CDX) xenograft models recapitulated human disease characteristics, including treatment resistance. Datroway exhibited favorable pharmacokinetics with systemic linker stability and selective tumor accumulation. Administered intravenously at clinically relevant doses (6 mg/kg every 21 days), Datroway significantly inhibited tumor growth, with efficacy correlating to TROP2 expression levels. These findings paralleled subsequent clinical outcomes, where prolonged progressionfree survival (PFS) was observed. Toxicology assessments identified a manageable safety profile; however, pulmonary toxicity, including interstitial lung disease (ILD), was detected, presaging similar safety signals observed later in clinical trials.

Importantly, preclinical combination strategies pairing Datroway with endocrine therapies or CDK4/6 inhibitors such as palbociclib and ribociclib showed synergistic antitumor effects, particularly in models of endocrine resistance. These data provided a strong rationale for clinical trials like TROPION-Breast04 exploring combination regimens[24].

The translational relevance of these findings was validated in the phase 3 TROPIONBreast01 trial, where

Table 1: Preclinical Studies of Datroway

Aspect	Details
Disease Context	HR-positive, HER2-negative metastatic breast cancer (~70% of cases); typically resistant to endocrine therapy and chemotherapy.
Therapeutic Agent	Datroway (Datopotamab Deruxtecan): TROP2-targeted antibody-drug conjugate (ADC) with a topoisomerase I inhibitor (DXd) payload.
Target Rationale	TROP2 is highly expressed in epithelial tumors and minimally in normal tissues, making it an effective and selective target.
Mechanism of Action	Binding to TROP2 leads to internalization; DXd induces DNA damage (via γ-H2AX) and apoptosis. A bystander effect extends activity to adjacent TROP2-negative cells.

Datroway reduced the risk of disease progression or death by 37% compared to chemotherapy and achieved a 36% objective response rate. Nevertheless, consistent with limitations inherent to preclinical models, Datroway did not demonstrate a statistically significant overall survival (OS) benefit, highlighting the complexity of treatment resistance and disease evolution in clinical settings. Preclinical toxicology findings proved invaluable for anticipating and managing adverse events like ILD in the clinical landscape.

Looking forward, ongoing preclinical initiatives aim to extend Datroway's therapeutic reach. Studies are investigating combination strategies with immune checkpoint inhibitors, PI3K inhibitors, and PARP inhibitors to overcome resistance. Efforts to identify predictive biomarkers of TROP2 expression or DXd sensitivity could enable more personalized treatment approaches. In parallel, research into acquired resistance mechanisms, such as TROP2 downregulation and drug efflux, is expected to inform the next generation of ADC therapies.

Datroway's preclinical development provided critical insights into its mechanism, efficacy, and safety, forming the foundation for its successful clinical translation. While challenges remain, continued research is poised to refine Datroway's clinical applications and expand therapeutic options for patients with HR-positive, HER2negative metastatic breast cancer[25].

6. Clinical Trials for Fam-Trastuzumab Deruxtecan-nxki

6.1 Phase I Trial (NCT02564900)

Part 1 Dose Escalation Studies

This open-label, dose-escalation phase I study involved patients with advanced breast cancer and gastric or gastroesophageal tumors. Eligible patients were at least 20 years old, had a life expectancy of at least three months, and had cancer resistant to standard treatments, irrespective of HER2 study.

Participants received fam-trastuzumab deruxtecan-nxki intravenously every three weeks at doses ranging from 0.8 to 8.0 mg/kg. Treatment continued until patients either experienced disease progression, unacceptable side effects, or chose to withdraw consent.

Among the 23 patients included in the analysis, the median follow-up was 6.7 months. The objective response rate (ORR) was 43% (95%CI: 23.2%-65.5%), and the disease control rate (DCR) was 91% (95%CI: 72.0%-98.9%). Response rates varied depending on the type of cancer. In patients with HER2-positive breast cancer, 7 out of 12 patients (58%) achieved an objective response, and all had disease control.

At doses of 5.4 mg/kg or higher, 90% of patients demonstrated partial responses.

The median time to response was 12.1 weeks (95%CI: 3.0–12.4). The median progressionfree survival (PFS) was not reached at the time of reporting because data collection was ongoing and 12 patients were still receiving treatment[26].

Part 2a: Dose Expansion Study

This part targeted patients with HER2-positive, advanced, unresectable, or metastatic breast cancer who had progressed on or could not tolerate standard therapies, including prior treatment with ado-trastuzumab emtansine.

Patients received fam-trastuzumab deruxtecan-nxki at doses of either 5.4 mg/kg or 6.4 mg/kg intravenously every three weeks, following the same treatment continuation criteria as in Part At a median treatment duration of 8.3 months and a median followup of 9.9 months, the confirmed ORR was 59.5% (95%CI: 49.7%-68.7%), and the DCR was 93.7% (95%CI: 87.4%-97.4%).

Patients achieved a median time to response of 1.6 months (95%CI: 1.4–2.8).The median duration of

response was 20.7 months (range: 0–21.8 months). The median PFS was 22.1 months (range: 0.8–27.9 months).At the time of reporting, median overall survival (OS) had not yet been reached, suggesting promising long-term outcomes[43].Phase Ib Study: HER2Low-Expressing Advanced Breast Cancer. This analysis included 54 patients with HER2-low advanced, unresectable, or metastatic breast cancer drawn from parts 1, 2c, and 2e of the phase I trial. Participants received fam-trastuzumab deruxtecan-nxki at 5.4 or 6.4 mg/kg intravenously every three weeks. All patients were either intolerant of, resistant to, or had exhausted all standard treatment options. The confirmed ORR in this HER2-low population was 37% (95%CI: 24.3%-51.3%).The median duration of response was 10.4 months.The median PFS was 11.1 months, and the median OS was 29.4 months (95%CI: 12.9–29.4 months), indicating meaningful clinical benefit even in patients with low HER2 expression[27].

6.2 Phase II Trial: DESTINY-Breast01

DESTINY-Breast01 was a two-part, open-label, single-arm phase II study designed to assess fam-trastuzumab deruxtecan-nxki in adults with HER2-positive, unresectable, or metastatic breast cancer who had previously received ado-trastuzumab emtansine. Part 1 involved a random assignment (1:1:1) of patients to doses of 5.4, 6.4, or 7.4 mg/kg every three weeks, aiming to determine pharmacokinetics and recommend the best dose[28].

Part 2 involved patients treated at the selected dose of 5.4 mg/kg to evaluate drug efficacy and safety[29].

7. Safety and toxicity consideration

Trastuzumab deruxtecan (T-DXd) and datopotamab deruxtecan (Dato-DXd) are advanced antibody–drug conjugates (ADCs) that, while highly effective in targeted breast cancer therapy, present notable safety considerations that require proactive management. The most critical and potentially fatal adverse event linked to both agents is interstitial lung disease (ILD)/pneumonitis, making early detection, immediate treatment interruption, and timely corticosteroid initiation essential components of care[30]. Both drugs can also cause hematologic toxicities such as neutropenia, anemia, and thrombocytopenia, alongside gastrointestinal side effects including nausea, vomiting, diarrhea, stomatitis, and fatigue; these often necessitate supportive care measures and dose modifications to maintain treatment tolerability[31]. Dato-DXd further carries a specific risk of ocular events—such as dry eye, keratitis, and blurred vision—which warrant patient counseling, baseline eye examinations, and prompt ophthalmologic evaluation if symptoms develop[32]. Comprehensive monitoring strategies should include regular complete blood counts, liver function tests, and symptom review at each treatment cycle, with baseline pulmonary assessment and a low threshold for chest imaging in the presence of new respiratory complaints. Adhering closely to label-directed dose adjustment protocols ensures a balance between maximizing therapeutic benefit and minimizing the risk of severe or irreversible toxicity[33].

Conflicts of Interest

The authors declare no conflict of interest.

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