



Therapeutic Modality of Datopotamab Deruxtecan: A Comprehensive Overview

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ABSTRACT:

A recently licensed antibody-drug conjugate (ADC) called Datopotamab deruxtecan (Dato-Dxd), or DATROWAY, is used to treat breast cancer that is HER2 negative and has metastasized hormone receptor (HR) positivity. A humanized anti-TROP2 IgG1 monoclonal antibody, a topoisomerase-1 inhibitor payload, and a tetrapeptide-based cleavable linker make up the TROP-2 directed ADC Dato-Dxd. The medication releases the payload and kills cancer cells via binding to the TROP2 surface receptor protein, which is overexpressed in cancer cells. This drug has emerged as a valuable treatment option for the patients with Triple-Negative Breast Cancer (TNBC). The TROPION-Breast01 phase-3 study, which showed a 37% decrease in disease progression or mortality as compared to chemotherapy in patients with HR-positive, HER-2 negative metastatic breast cancer, served as the basis for the FDA's approval of Dato-Dxd. When providing this medication to the elderly and those with co-existing diseases, great care must be given. Pregnant women should not use this medication since it might have negative effects on the foetus and cause adverse effects like alopecia, stomatitis, and interstitial lung disease. Dato-Dxd is a promising new treatment option for individuals with advanced breast cancer, despite its drawback. The use of this medication in combination therapy with PARP inhibitors to treat cancers is being investigated in ongoing clinical trials.

INTRODUCTION

The U.S. Food and Drug Administration just authorized Datopotamab Deruxtecan (Dato-Dxd), commonly known as DATROWAY, on January 17, 2025. Daiichi Sankyo discovered the drug in Tokyo, Japan, on December 27, 2024. Triple Negative Breast Cancer (TNBC) has been

successfully treated with Datopotamab deruxtecan, a TROP-2 directed Antibody Drug Conjugate (ADC) with a very strong Topoisomerase-1 inhibitor Payload [1-2]. DATROWAY is authorized by the FDA to treat metastatic breast cancer that is HER-2 positive or HER-2 negative (IHC0, IHC1 +, or IHC2+/ISH-) [3]. Patients who have had chemotherapy and endocrine-based



treatment and have unresectable or metastatic illness are eligible for this approval. The safety and efficacy of this medication have been assessed in clinical studies in patients with advanced or metastatic non-small cell lung cancer (NSCLC) that has an EGFR mutation [4].

Daiichi Sankyo's Dxd ADC technology was used in the creation of the DATROWAY [3]. The TROPION-Breast01 phase-3 study served as the basis for its clearance. In patients with HR-positive, HER-2 negative metastatic breast cancer, the trial's results showed a 37% decrease in disease progression or mortality when compared to chemotherapy. As the second Dxd antibody-drug conjugate created with an emphasis on enhancing patient outcomes through cutting-edge technology, DATROWAY is a component of Japan's creative approach to cancer patients, which is founded on the technology created by Daiichi Sankyo [5-8].

DERUXTECAN DATOPOTOMAB: A NEARER LOOK

The acquisition of Dato-Dxd by Daiichi Sankyo was made possible by a material transfer agreement. Until it is needed, this medication is kept at minus 80 degrees Celsius. To reach the final concentration of pH 5.5 for in vitro investigations, this medication is formed using a solvent, and its serial dilutions are made using a vehicle (10 mmol/litter acetate buffer and 5% sorbitol). In in vivo experiments, the medication is prepared using a vehicle consisting of polyethylene glycol 400, water, and 100% ethanol. The vehicle is maintained at 4 degrees Celsius, protected from light, to guarantee a dosage of 10 mg/kg in each retroorbital injection[6-8,9].

THERAPEUTIC MECHANISM OF DATOPOTOMAB DERUXTECAN:

Triple-negative breast cancer (TNBC) is associated with increased levels of the transmembrane glycoprotein known as trophoblast cell surface antigen 2 (TROP2), which serves as a surface receptor protein [10]. Through the TACSTD2 gene, it is linked to calcium signaling and protein synthesis, both of which are essential for embryogenesis, placental development, and stem cell proliferation. According to recent studies, TROP2 may encourage the proliferation of cancer cell populations in vitro and in vivo [6,12].

A humanized anti-TROP2 IgG1 monoclonal antibody (mAb), a topoisomerase-1 inhibitor payload that functions

as a therapeutically active medication, and a tetrapeptide-based cleavable linker make up Datopotamab deruxtecan, a TROP-2 directed antibody drug conjugate (ADC)[13].

As an anti-TROP2 monoclonal antibody, Datopotamab acts as a prodrug by binding to the TROP2 surface receptor protein, which is usually overexpressed in cancer cells. Systemic cytotoxicity is decreased by the tetrapeptide-based cleavable linker's stability in the circulation. The topoisomerase 1 inhibitor payload (Deruxtecan-Dxd) is released within cancer cells when it is broken down by enzymes such lysosomes, which are more active inside tumor cells. After being released, this payload attaches itself to the topoisomerase 1 enzyme and inhibits it, damaging DNA, stopping the cell cycle, and eventually killing cancer cells[4,14-15].

By permitting the payload to diffuse into neighboring tumor cells, even those that might not express TROP2, the Datopotamab deruxtecan further increases its anticancer efficacy. The effectiveness against heterogeneous cancers may be enhanced by this method of action, which enables a wider reach inside the tumor microenvironment. Datopotamab deruxtecan's strong antitumor action is also attributed to its high drug-to-antibody ratio, which delivers a significant payload to cancer cells with each antibody binding event. Through a complex method, Datopotamab Deruxtecan's anticancer activity is greatly increased. Because of this action, the payload can spread into neighboring tumor cells, including ones that do not express the target antigen TROP2. This special characteristic makes it possible for the medication to have a wider influence on the tumor microenvironment by causing its cytotoxic effects to extend beyond the cells that were initially targeted. Problems with tumor heterogeneity, in which not all cancer cells inside a tumor express the target antigen evenly, may be resolved by the payload's diffusion to nearby cells[16-17].

In clinical settings, this potential to increase effectiveness against diverse cancers is very beneficial. The efficacy of conventional targeted treatments may be constrained by the fact that tumors frequently have heterogeneous cell populations with differing degrees of target antigen expression. Datopotamab deruxtecan may be able to overcome this difficulty and offer a more thorough therapeutic strategy by permitting the payload to impact neighboring cells irrespective of their TROP2 expression[17-18].



Moreover, one of the main reasons for Datopotamab deruxtecan's strong antitumor action is its high drug-to-antibody ratio (DAR). Each antibody molecule contains many payload units due to its increased DAR, which greatly increases the quantity of cytotoxic chemical that is given to cancer cells with each binding event. A significant payload is delivered by the antibody-drug combination when it attaches to a TROP2-expressing cell, increasing the chance of cell death and boosting therapy effectiveness overall[13,18].

This medication and high DAR work together to provide a synergistic anticancer mechanism. A powerful initial effect on TROP2-expressing cells is ensured by the enhanced payload delivery brought about by the high DAR, and the medication then spreads this effect to nearby cells. This double impact might lead to more efficient destruction of tumor cells and assist stop the emergence of resistance mechanisms that can occur when some cancer cells avoid therapy[14,15].

SIDE EFFECTS OF DATOPOTAMAB DERUXTECAN:

In many nations, this medication is only used to treat individuals with breast cancer. Numerous negative effects of this medication have been found in the meta analysis. Stomatitis, nausea, baldness, exhaustion, and vomiting are some of these side effects. The most frequent side effect linked to drugs is stomatitis. This medication's treatment-emergent side effects include thrombocytopenia, anemia, and pneumonia. Common ocular surface toxicity has been observed in patients with ulcerative keratitis, blepharitis, dry eye, and increased lacrimation. Docetaxel-induced interstitial lung disease is one of the worst drug-related side effects. Neutropenia, stomatitis, anemia, asthenia, nausea, and exhaustion are examples of treatment-related adverse events (TRAE). A meta-analysis of the safety and effectiveness of Datopotamab deruxtecan in patients with non-small cell lung cancer (NSCLC) who had previously received treatment revealed that 5.4% of patients had pneumonia. Adverse Events of Special Interest (AESI) observed in the TROPION-pan tumor01 study include adjudicated drug-related adverse events such as interstitial lung disease/pneumonitis, infusion-related reactions, ocular surface toxicity, oral mucositis/stomatitis, and mucosal inflammation in addition to oral mucositis/stomatitis[19,20–21].

DATOPOTAMAB DERUXTECAN'S POTENCY IN HUMAN BODY

Deruxtecan, also known as Dxd, is a stable exatecan derivative that is covalently bonded to Antibody Drug Conjugate (ADC) by a peptidyl spacer (Gly-Gly-Phe-Gly). Dato-Dxd has a 4:1 drug to antibody ratio (DAR), and its unique linker characteristic makes it extremely stable in the bloodstream. In particular, Dato-Dxd's payload is 10 times more powerful than Sacituzumab govitecan SN38, extending ADC's half-life. Datopotamab deruxtecan (Dato-Dxd) has very little metabolism, such as glucuronidation or oxidation, and is mostly excreted in bile and feces[4].

Similar plasma concentrations for Dato-Dxd and total antibody were found in pharmacokinetic study, although Dxd levels were only weakly found in the plasma shortly after injection. Dato-Dxd has demonstrated anticancer activity in a xenograft mouse model by attaining a 96% tumor growth suppression after a single I/V dosage of 10 mg/kg. Dato-Dxd's plasma concentration, total antibody, and tumor concentration were assessed up to 21 days after an intravenous administration of 6 mg/kg to male cynomolgus monkeys or 10 mg/kg to NCI-N87 xenograft model mice. Dato-Dxd is administered intravenously as an infusion at intervals of three weeks at a dosage of 6 mg/kg. It takes around 90 minutes to administer the medication for the first time. The percentage drug release of Dxd from 100 µg/ml of Dato-Dxd in mouse, rat, monkey, and human plasma was assessed at 37°C for 21 days in order to assess the invitro stability in plasma. Using hydrophobic interaction chromatography, the drug distribution was examined[22].

CLINICAL TRIALS OF DATOPOTAMAB DERUXTECAN

The purpose of the phase 1 clinical study, TROPION-pan tumor01, was to evaluate the efficacy and tolerability of Dato-Dxd in both precancerous and metastatic solid tumors[23]. According to the trial's clinical results, Dato-Dxd has shown good antitumor efficacy and maintained a safety profile in patients with advanced non-small cell lung cancer who had previously received treatment. To determine the effectiveness of Dato-Dxd in Chinese patients with advanced solid tumors, both with and without actionable genetic mutations (AGA), the phase ½ clinical study TROPION-pan tumor02 was created [24]. In a subsequent TROPION-LUNG01 phase 3 clinical



study, the effectiveness of Dato-Dxd and Docetaxel was compared in patients with advanced or metastatic non-small cell lung cancer who had already received treatment. The efficacy of Dato-Dxd was assessed in patients with advanced or metastatic non-small cell lung cancer (NSCLC) with AGA who had progressed during or following at least one AGA-specific treatment or platinum-based chemotherapy in the TROPION-

LUNG05 phase 2 clinical study [25]. Sequential dosage escalation and dose expansion models were employed in the TROPION-LUNG02 phase 1b clinical study to assess the safety, tolerability, and effectiveness of Dato-Dxd in patients with advanced or metastatic non-small cell lung cancer [11,13,21,26–27,28]. Table 1 provides more information on this medication's clinical trials for breast cancer.

Table 1: CLINICAL TRIALS ON DATOPOTOMAB DERUXTECAN FOR BREAST CANCER

Trial Name	Phase	Characteristic	Number of patients	Endpoint
TROPION - Pan Tumor 02	Phase 1/Phase 2 trial	Efficacy, safety, pharmacokinetic and immunogenicity of Dato-Dxd was evaluated in adult Chinese population in locally advanced or metastatic TNBC who have received at least 2 prior Chemotherapy regimens	118	Efficacy and safety
TROPION – Breast 01	Phase 3 trial	Safety and efficacy of Dato-Dxd was Evaluated in patients with inoperable or metastatic HR positive, HER 2 negative breast cancer who have been treated with one or two prior lines of chemotherapy	733	Progression free survival (PFS) and Overall Survival (OS)
TROPION – Breast 02	Phase 3 Trial	Safety and efficacy of Dato-Dxd in TNBC not Candidates for PD-1/PD-L1 inhibitor Therapy	600	Progression free survival (PFS) and Overall Survival (OS)
TROPION – Breast 03	Phase 3 Trial	Demonstrate safety and efficacy of Dato-Dxd in patients with or without durvalumab stage I to III TNBC following neoadjuvant Systemic therapy	1075	Superiority of Dato-Dxd in combination with Duvalumab
TROPION – Breast 04	Phase-3 trials	Evaluate the efficacy and safety neoadjuvant Dato-Dxd plus durvalumab followed by adjuvant durvalumab with or without chemotherapy V/S standard of care in patients with previously untreated early stage TNBC or HR low /HER2 negative breast cancer	1728	Overall survival , disease free survival and safety
TROPION – Breast 05	Phase 3 trials	Evaluate safety of Dato-Dxd plus durvalumab V/S chemotherapy plus pembrolizumab in patients with PD-L1 plus locally recurrent inoperable or metastatic TNBC	~625	Progression free survival, overall survival



MERITS AND DEMERITS OF DATOPOTOMAB DERUXTECAN

Preclinical research on TROP-02 has improved anticancer treatment, triggered apoptosis, and investigated therapeutic potential. By altering the expression of Bax and Bcl 2, the TROP-02 targeting antigen binding fragment has caused apoptosis and disrupted the pro-survival pathway in the triple negative breast cancer TNBC model. There is a about 18.05% decrease in bad effects when this medication is used. Patients with or without brain metastases exhibit systemic effectiveness and safety, indicating that Dato-Dxd is an effective medication that can cross the blood-brain barrier and prevent brain metastases. Dato-Dxd can lessen systemic toxicity and increase the effectiveness of payload delivery into the tumor cell. In trials with cynomolgus monkeys, this medication did not cause any significant hematological alterations, even at the highest practical dosage of 80 mg/kg[22].

In order to increase efficacy, safety, and quality of life, antibody drug conjugate treatments are generally advised for older patients, albeit with caution. Elderly individuals require special attention because of the physiological changes brought on by aging. Changes in hepatic clearance, protein binding, and renal excretion can affect the metabolism of ADC. These changes can lead to toxicities such peripheral neuropathy, interstitial lung disease, and heart malfunction, particularly when HER2 or TROP2 targets ADC. Problems like polypharmacy raise the possibility of negative medication responses. Furthermore, these toxicities may be exacerbated by concomitant conditions such diabetes, smoking, and chronic lung disease. Clinicians must thus take extra care to ensure the safety, effectiveness, and concomitant conditions of older patients as well as their toxicities[29].

TROP2, a protein essential for implantation and placental development, is the target of Datopotamab deruxtecan (Dato-Dxd). Using DATROWAY during pregnancy might result in serious negative fetal outcomes such implantation failure, placental issues, and miscarriage since TROP2 is necessary for embryonic development. Due of these serious dangers to fetal development, DATROWAY is not recommended for use in pregnant women[29].

CURRENT STATUS OF DATOPOTAMAB DERUXTECAN

On January 17, 2025, the US Food and Drug Administration (USFDA) approved Datopotamab deruxtecan (Dato-Dxd) for the treatment of adult patients with HER2 negative and hormone receptor (HR) positive metastatic breast cancer who have already received chemotherapy and endocrine-based therapy.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency released a favorable opinion on January 30, 2025, suggesting that DATROWAY be approved for use in the treatment of HR-positive HER2 negative breast cancer. A new medication application for Datopotamab deruxtecan for pre-treated HR positive HER2 negative advanced breast cancer has been sent to Japan's Ministry of Health, Labor, and Welfare.

Phase 01 to phase 03 scientific studies are now investigating the use of Dato-Dxd in conjunction with immunotherapy and platinum-based chemotherapy. These studies include TROPION LUNG 04, TROPION LUNG 07, TROPION LUNG 08, TROPION LUNG 10, AVANZAR, and NeoCOAST-2. The only authorized ADC for patients with HER2 mutations in NSCLC at the moment is trastuzumab deruxtecan[13,15].

DATOPOTAMAB DERUXTECAN ADMINISTRATION OBSTACLES AND HURDLES

Trophoblast cell surface antigen 2 (TROP2), a glycoprotein expressed by the TACSTD2 gene and essential for implantation, placental development, maternal-fetal immunological tolerance, signaling, and cell control, is the target of Datopotamab deruxtecan (Dato-Dxd). TROP2 plays a dual role in embryonic development as a survival gene and an oncomarker. DATROWAY administration during pregnancy presents a high risk of adverse fetal outcomes, including miscarriage, placental problems, and unsuccessful implantation. Because of its significant and potentially catastrophic effects on fetal development, DATROWAY is therefore prohibited for pregnant women. Through a complex method, the medication Datopotamab deruxtecan dramatically increases its anticancer activity. Because of this action, the payload can spread into neighboring tumor cells, including ones that do not express the target antigen TROP2. This special characteristic makes it possible for the medication to have a wider influence on the tumor microenvironment by causing its cytotoxic effects to extend beyond the cells that were initially targeted. Problems with tumor heterogeneity, in which not all cancer cells inside a tumor express the target antigen



evenly, may be resolved by the payload's diffusion to nearby cells[13].

FUTURE DEVELOPMENT IN DRUG DATOPOTAMAB DERUXTECAN

The US Food and Drug Administration has approved Datopotamab deruxtecan, which is sold under the 'DATROWAY' trademark in several countries to treat HR-positive HER2-negative breast cancer [18]. The use of DATROWAY in the treatment of non-small cell lung cancer (NSCLC), various cancers such as adenocarcinoma and squamous cell carcinoma, as well as in combination chemotherapy, is now being investigated in a number of clinical trials.[11,13,17]

Due to its complex mode of action, Datopotamab deruxtecan and poly (ADP-ribose) polymerase inhibitors (PARPis) work in concert to treat triple negative breast cancer (TNBC). The cytotoxic payload released by antibody drug conjugate (ADC) further damages DNA, making cancer cells dependent on the PARP-dependent repair pathway. By preventing damaged cells from being repaired, PARP inhibition promotes the demise of cancer cells. According to preclinical research, patients with triple negative breast cancer may benefit from a synergistic anticancer impact when ADC and PARPis are used together. PARP inhibition might intensify the DNA damage caused by ADC, rendering TNBC cells irreparable[30].

In the treatment of triple-negative breast cancer (TNBC), the commercialization of antibody drug conjugates such as Datopotamab deruxtecan (Dato-Dxd) has had a significant impact. However, this medication has not yet received approval in a number of countries for the treatment of TNBC, thus many clinicians have little expertise with the medication and its use. In patients with triple negative breast cancer receiving Datopotamab deruxtecan (Dato-Dxd), stomatitis, low grade nausea, and alopecia are among the most common treatment-related side effects, according to data. Several ongoing clinical trials are still determining whether Datopotamab deruxtecan should be used as monotherapy or in combination therapy with other anticancer agents[30].

CONCLUSION:

DATROWAY, also known as Datopotamab deruxtecan (Dato-Dxd), is a newly licensed antibody-drug conjugate (ADC) for the treatment of human epidermal growth factor receptor 2 (HER2) negative and metastatic hormone

receptor (HR) positive breast cancer. This review has covered the drug's pharmacological activity as well as how it works. Clinical studies are looking at the use of Dato-Dxd in conjunction with platinum-based chemotherapy and PARP inhibitors to treat adenocarcinoma and non-small cell lung cancer (NSCLC). This medication's noteworthy adverse effects have been noted. However, as TROP2 is essential for both embryo formation and placental development, Dato-Dxd is contraindicated in pregnant women due to the possible risk of unfavorable fetal outcomes. Despite all of these difficulties, the medication Datopotamab deruxtecan is incredibly successful in treating breast cancer that has spread.

CONFLICT OF INTEREST : The authors declare no conflict of interest in this article.

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