



Original Article

Datopotamab Deruxtecan: Expanding the Horizons of Trop2-Directed Antibody–Drug Conjugates

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ABSTRACT

Antibody–drug conjugates (ADCs) have emerged as one of the fastest expanding therapeutic platforms in oncology, driven by advances in antibody engineering, linker chemistry and payload design that have substantially improved their therapeutic index. Among the newest additions to this class is datopotamab deruxtecan (Dato-DXd), a trophoblast cell-surface antigen 2 (TROP2)-directed ADC comprising a humanized anti-TROP2 monoclonal antibody linked through a tumour-selective cleavable tetrapeptide linker to an exatecan-derived topoisomerase I inhibitor payload. Building upon the clinical success of earlier ADCs, Dato-DXd has demonstrated encouraging efficacy across multiple epithelial malignancies while exhibiting a toxicity profile distinct from both conventional chemotherapy and other TROP2-directed ADCs. The global TROPION clinical development programme has established clinically meaningful activity in hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer and advanced non-small cell lung cancer (NSCLC), resulting in regulatory approvals and incorporation into contemporary treatment algorithms. Unlike traditional cytotoxic agents, Dato-DXd delivers targeted intracellular chemotherapy while maintaining relatively limited systemic payload exposure, thereby improving treatment selectivity. Characteristic toxicities, including stomatitis, ocular adverse events and interstitial lung disease, require proactive monitoring but are generally manageable with early recognition and multidisciplinary supportive care. Ongoing studies are evaluating Dato-DXd in earlier disease settings, combination regimens and additional tumour types, with the potential to further expand its therapeutic indications. This review summarizes the biological rationale, molecular design, pharmacology, pivotal clinical evidence, toxicity profile, current clinical positioning and future directions of Dato-DXd, highlighting how advances in ADC engineering have established this agent as an important milestone in the evolution of TROP2-directed cancer therapy.

Keywords: Antibody–drug conjugate; Datopotamab deruxtecan; Dato-DXd; Non-small cell lung cancer; Breast cancer; TROP2.

INTRODUCTION

Antibody–drug conjugates (ADCs) have transformed systemic therapy for solid tumours by combining the specificity of monoclonal antibodies with the potency of cytotoxic chemotherapy. Improvements in antibody engineering, linker chemistry and payload design have substantially enhanced tumour-selective drug delivery while reducing systemic toxicity, establishing ADCs as a major therapeutic platform in oncology.[1,2]

Among the emerging ADC targets, trophoblast cell-surface antigen 2 (TROP2) has gained considerable attention because of its broad expression in epithelial malignancies including breast, non-small cell lung (NSCLC), urothelial, ovarian, pancreatic and gastrointestinal cancers. Besides serving as a surface marker, TROP2 promotes tumour proliferation, invasion and epithelial–mesenchymal transition, and its overexpression is consistently associated with adverse prognosis.[3,4]

Clinical validation of TROP2 was achieved with Sacituzumab Govitecan, while continued advances in ADC technology have led to the development of next-generation agents with improved linker stability, payload delivery and therapeutic index. Datopotamab deruxtecan (Dato-DXd; DS-1062a), jointly developed by Daiichi Sankyo and AstraZeneca, comprises a humanized anti-TROP2 IgG1 monoclonal antibody linked via a protease-cleavable tetrapeptide linker to the exatecan-derived topoisomerase I inhibitor DXd. Its optimized drug-to-antibody ratio and stable linker minimize premature payload release while enhancing intracellular drug delivery.[5–7]

Clinical development through the TROPION programme has demonstrated encouraging efficacy in metastatic breast cancer and advanced NSCLC, leading to regulatory approvals and rapid incorporation into clinical practice.[8–12] Beyond its individual clinical activity, Dato-DXd exemplifies the evolution of ADC engineering and highlights how refinement of antibody, linker and payload components can improve therapeutic outcomes. This review summarizes the biological rationale, molecular design, clinical evidence, toxicity profile and future role of Dato-DXd in contemporary oncology.

EVOLUTION OF ANTIBODY–DRUG CONJUGATES AND THE EMERGENCE OF TROP2 AS A THERAPEUTIC TARGET

The concept of antibody–drug conjugates (ADCs) was introduced more than four decades ago with the aim of combining the tumour specificity of monoclonal antibodies with the cytotoxic activity of chemotherapy. Early ADCs achieved limited success because of unstable linkers, inadequate payload potency and inefficient intracellular drug release. Advances in antibody engineering, linker chemistry and conjugation technology have since transformed ADCs into one of the fastest-growing therapeutic classes in oncology, with agents targeting HER2, nectin-4, tissue factor and TROP2 demonstrating significant survival benefits across multiple solid tumours.[1,2]

An effective ADC target should be highly expressed on tumour cells, minimally expressed in normal tissues, capable of efficient receptor-mediated internalization and remain expressed throughout disease progression. TROP2 fulfils many of these characteristics, making it an attractive therapeutic target.[2]

TROP2 is a 36-kDa transmembrane glycoprotein encoded by the TACSTD2 gene. Although present in several normal epithelial tissues, it is markedly overexpressed in numerous epithelial malignancies, including breast, NSCLC, urothelial, colorectal, pancreatic, gastric, ovarian and endometrial cancers.[3] Increased expression correlates with higher tumour grade, metastatic potential and poorer survival, supporting its role as both a prognostic biomarker and therapeutic target.[3,4]

Functionally, TROP2 promotes tumour progression through activation of multiple signalling pathways, including MAPK/ERK, PI3K/AKT, β -catenin and NF- κ B, resulting in enhanced proliferation, invasion, migration and epithelial–mesenchymal transition.[3,4] Importantly, the TROP2–antibody complex undergoes rapid receptor-mediated internalization after ligand binding, facilitating efficient lysosomal delivery and intracellular release of ADC payloads.[5] The therapeutic relevance of TROP2 was established with Sacituzumab Govitecan, the first TROP2-directed ADC to improve survival in metastatic triple-negative breast cancer and later in hormone receptor-positive breast cancer and urothelial carcinoma.[6] Its success confirmed TROP2 as a clinically actionable target while highlighting opportunities to improve linker stability, payload pharmacology and pharmacokinetics.

Datopotamab Deruxtecan (Dato-DXd) was developed as a next-generation TROP2-directed ADC using the DXd platform. Compared with earlier ADCs, it incorporates a highly stable protease-cleavable tetrapeptide linker, an optimized drug-to-antibody ratio of approximately four and a membrane-permeable exatecan-derived payload, designed to maximise intracellular drug delivery while minimizing premature systemic payload release.[7]

These advances illustrate the evolution of ADC development from simply identifying a suitable antigen to optimizing every component of the conjugate. Consequently, ADCs directed against the same target may demonstrate markedly different efficacy and toxicity profiles, emphasizing that molecular engineering is now as important as antigen selection.

MOLECULAR DESIGN, PHARMACOLOGY AND MECHANISM OF ACTION OF DATOPOTAMAB DERUXTECAN

The clinical performance of an antibody–drug conjugate (ADC) depends on the coordinated function of its antibody, linker, payload and conjugation chemistry. Datopotamab Deruxtecan (Dato-DXd; DS-1062a) represents a next-generation TROP2-directed ADC developed using Daiichi Sankyo's DXd platform, with each component optimized to improve tumour-selective drug delivery while maintaining favourable pharmacokinetic stability.[7]

• MOLECULAR ARCHITECTURE

Dato-DXd comprises a humanized anti-TROP2 IgG1 monoclonal antibody linked through a protease-cleavable tetrapeptide linker to DXd, an exatecan-derived topoisomerase I inhibitor.[7] Following binding to TROP2, the ADC undergoes receptor-mediated endocytosis and lysosomal trafficking. Intracellular proteases cleave the linker, releasing free

DXd, which inhibits topoisomerase I, stabilizes DNA cleavage complexes and induces irreversible DNA damage, culminating in apoptotic cell death.[7,8]

The tetrapeptide linker remains highly stable in the circulation, minimizing premature payload release while allowing efficient intracellular cleavage after lysosomal internalization. The released DXd payload is membrane permeable and can diffuse into neighbouring tumour cells, producing a bystander effect that may overcome heterogeneous TROP2 expression within solid tumours.[7]

DRUG-TO-ANTIBODY RATIO AND CONJUGATION STRATEGY

Dato-DXd has an average drug-to-antibody ratio (DAR) of approximately four, balancing payload potency with pharmacokinetic stability.[7] Clinical pharmacokinetic studies demonstrated dose-proportional exposure with minimal accumulation during repeated administration. The recommended dose of 6 mg/kg every three weeks was selected based on integrated pharmacokinetic, pharmacodynamic and exposure–response analyses.[10]

A notable feature of Dato-DXd is the very low circulating concentration of free DXd, reflecting the stability of the linker and predominantly intracellular payload release. The antibody component undergoes catabolic degradation with minimal cytochrome P450 involvement, suggesting a low potential for clinically significant pharmacokinetic drug–drug interactions.[7,9]

COMPARISON WITH OTHER TROP2-DIRECTED ADCS

Although both Dato-DXd and Sacituzumab Govitecan target TROP2, they differ substantially in molecular design. Dato-DXd incorporates a stable tetrapeptide linker, a DAR of approximately four and the highly potent DXd payload, whereas Sacituzumab Govitecan uses a hydrolysable CL2A linker, a higher DAR and the SN-38 payload.[6,7] These structural differences contribute to distinct toxicity profiles. Dato-DXd is more frequently associated with stomatitis, ocular adverse events and occasional interstitial lung disease, whereas Sacituzumab Govitecan is characterized predominantly by neutropenia and diarrhoea.[6]

Direct comparative studies are unavailable, and the two agents should currently be regarded as complementary rather than interchangeable. Their optimal sequencing will likely depend on tumour type, previous therapy, patient characteristics and emerging evidence from ongoing clinical trials.

CLINICAL DEVELOPMENT OF DATOPOTAMAB DERUXTECAN

The clinical development of Datopotamab Deruxtecan (Dato-DXd) has been conducted through the global TROPION programme, encompassing early-phase dose-escalation studies and randomized phase III trials across multiple epithelial malignancies. Initial basket studies established proof of concept, while subsequent disease-specific trials [Table 1] defined its role in metastatic breast cancer and non-small cell lung cancer (NSCLC).[10]

TROPION-PANTUMOR01: ESTABLISHING PROOF-OF-CONCEPT

TROPION-PanTumor01 was the first-in-human phase I study evaluating Dato-DXd in patients with advanced solid tumours refractory to standard therapy. The trial included dose-escalation and dose-expansion cohorts to determine safety, pharmacokinetics and preliminary efficacy.[10]

TABLE 1. MAJOR COMPLETED CLINICAL TRIALS OF DATOPOTAMAB DERUXTECAN

TRIAL	PHASE	POPULATION	COMPARATOR	KEY FINDING
TROPION-PanTumor01 NSCLC [10]	I	Advanced NSCLC	None	Established RP2D; activity
TROPION-PanTumor01 Breast [11]	I	Breast cancer	None	Promising efficacy
TROPION-Breast01 [12]	III	HR+/HER2– mBC	Chemotherapy	Improved PFS
TROPION-Breast02 [13]	III	TNBC	Chemotherapy	Improved PFS/OS
TROPION-Lung01 [14]	III	NSCLC	Docetaxel	Improved PFS
TROPION-Lung05 [15]	II	Driver-positive NSCLC	Single arm	Meaningful activity

The study established 6 mg/kg every three weeks as the recommended phase II dose, with dose-proportional pharmacokinetics and minimal systemic release of free DXd, confirming the stability of the tetrapeptide linker.[10]

Clinically meaningful responses were observed across multiple tumour types, particularly hormone receptor-positive (HR+)/HER2-negative breast cancer, triple-negative breast cancer (TNBC) and NSCLC, supporting further disease-specific development.[10,11]

The study also defined the characteristic safety profile of Dato-DXd. Stomatitis emerged as the most common adverse event, while ocular toxicity and interstitial lung disease (ILD) were recognized as important toxicities requiring prospective monitoring. Severe haematological toxicity was comparatively infrequent, reflecting reduced systemic payload exposure.[10]

TROPION-BREAST01: FIRST PHASE III SUCCESS

TROPION-Breast01 was a global phase III trial comparing Dato-DXd with investigator's-choice chemotherapy in patients with unresectable or metastatic HR+/HER2-negative breast cancer previously treated with endocrine therapy and at least one line of chemotherapy for advanced disease.[12]

The trial met its primary endpoint by significantly improving progression-free survival compared with chemotherapy while reducing grade ≥ 3 treatment-related adverse events. Objective response rates were also higher with Dato-DXd, confirming the benefit of targeted intracellular delivery of the DXd payload.[12]

Importantly, the comparator arm reflected contemporary clinical practice, including Capecitabine, Eribulin, Vinorelbine and Gemcitabine, thereby supporting the applicability of the results to routine oncology care. The favourable balance between efficacy and tolerability positions Dato-DXd as a valuable chemotherapy-sparing option after endocrine resistance.

TROPION-BREAST02: EXPANDING THE ROLE OF DATO-DXD IN TRIPLE-NEGATIVE BREAST CANCER

Following the encouraging activity observed in the triple-negative breast cancer (TNBC) expansion cohort of TROPION-PanTumor01, the global TROPION-Breast02 trial was designed to evaluate whether Dato-DXd could improve outcomes in one of the most aggressive breast cancer subtypes. Patients with metastatic TNBC frequently experience rapid disease progression after first-line therapy, and although immune checkpoint inhibitors and PARP inhibitors have expanded therapeutic options for selected populations, chemotherapy remains the standard of care for many patients. The development of an effective TROP2-directed ADC with an acceptable toxicity profile therefore represented an important unmet clinical need.[13]

TROPION-Breast02 was an international, randomized phase III study comparing Dato-DXd with investigator's-choice chemotherapy in patients with unresectable or metastatic TNBC who had received prior systemic therapy. The study enrolled a heavily pretreated population representative of routine clinical practice, in whom therapeutic options are limited and durable disease control is uncommon. Consistent with earlier studies, Dato-DXd demonstrated superior progression-free survival compared with standard chemotherapy while maintaining a manageable safety profile. Objective response rates and duration of response also favoured Dato-DXd, confirming that the antitumour activity observed during early-phase development could be reproduced in a randomized phase III setting.[13]

The significance of TROPION-Breast02 extends beyond the numerical improvement in efficacy. The trial reinforces the concept that optimization of ADC engineering can produce clinically meaningful benefits even in biologically aggressive tumours such as TNBC. Unlike conventional chemotherapy, which exposes both malignant and normal proliferating tissues to cytotoxic agents, Dato-DXd achieves selective intracellular delivery of a highly potent topoisomerase I inhibitor, thereby improving the therapeutic index. This distinction is particularly relevant in patients requiring prolonged treatment, where cumulative toxicity often limits continued chemotherapy.[7,13]

Another important implication of TROPION-Breast02 concerns treatment sequencing. Sacituzumab Govitecan has already established TROP2-directed therapy as a standard option in metastatic TNBC; however, Dato-DXd differs substantially in linker chemistry, payload characteristics and toxicity profile. Although direct comparative studies are lacking, these structural differences suggest that the two ADCs should not be regarded as interchangeable. Instead, future clinical practice is likely to focus on identifying the optimal sequence of TROP2-directed ADCs based on disease biology, prior therapies, patient comorbidities and toxicity considerations.

TROPION-LUNG01: DEFINING THE ROLE OF DATO-DXD IN ADVANCED NSCLC

Building on the encouraging activity observed in the NSCLC cohort of TROPION-PanTumor01, TROPION-Lung01 became the first randomized phase III trial evaluating Dato-DXd in previously treated advanced or metastatic NSCLC. Patients had experienced disease progression after platinum-based chemotherapy and, where appropriate, immune checkpoint inhibitors or targeted therapies. The study compared Dato-DXd with Docetaxel, the long-standing standard second-line chemotherapy in advanced NSCLC.[14]

The trial demonstrated a statistically significant improvement in progression-free survival with Dato-DXd compared with Docetaxel, confirming clinically meaningful antitumour activity in previously treated NSCLC. However, the magnitude of benefit was more modest than that observed in TROPION-Breast01, prompting considerable discussion regarding the biological factors influencing ADC efficacy in lung cancer. Subsequent subgroup analyses demonstrated that patients with nonsquamous histology derived greater benefit than those with squamous tumours, suggesting that tumour biology rather than TROP2 expression alone may influence therapeutic response.[14]

Several explanations have been proposed for these observations. NSCLC exhibits substantial molecular heterogeneity, with marked differences in genomic alterations, tumour microenvironment and prior treatment exposure that may influence ADC internalization and payload sensitivity. Furthermore, previous platinum chemotherapy and immune checkpoint inhibition may alter tumour biology in ways that affect susceptibility to topoisomerase I inhibitor-based ADCs. Collectively, these factors may account for the more heterogeneous efficacy observed in NSCLC compared with breast cancer.

Despite the relatively modest overall improvement in progression-free survival, TROPION-Lung01 remains clinically important because it establishes Dato-DXd as an effective alternative to docetaxel, a treatment associated with considerable myelosuppression, neuropathy and impairment in quality of life. The distinct toxicity profile of Dato-DXd, characterized primarily by stomatitis and ocular adverse events rather than severe haematological toxicity, offers clinicians an additional therapeutic option for appropriately selected patients.[14]

TROPION-LUNG05 AND ONGOING CLINICAL DEVELOPMENT

TROPION-Lung05 evaluated Dato-DXd in patients with advanced NSCLC harbouring actionable genomic alterations following progression on targeted therapy and platinum chemotherapy.[15] Encouraging response rates and durable disease control suggest that Dato-DXd may address an important unmet need after tyrosine kinase inhibitor resistance.

The TROPION programme has subsequently expanded into earlier disease settings and combination strategies, including studies with immune checkpoint inhibitors, endocrine therapy and other targeted agents.[16,17] These ongoing trials will determine whether the efficacy observed in metastatic disease can be translated into earlier treatment settings.

SAFETY PROFILE AND PRACTICAL TOXICITY MANAGEMENT

Datopotamab Deruxtecan (Dato-DXd) has a safety profile distinct from conventional chemotherapy and other TROP2-directed antibody–drug conjugates (ADCs). Most treatment-related adverse events are grade 1–2 and can be managed with early recognition, supportive care and appropriate dose modification. Characteristic toxicities include stomatitis, ocular adverse events and interstitial lung disease (ILD)/pneumonitis, whereas severe neutropenia and diarrhoea are less frequent than with SN-38-based ADCs.[17]

Across the TROPION programme, permanent treatment discontinuation due to toxicity was uncommon, and most patients were able to continue treatment after temporary interruption or dose reduction, highlighting the importance of proactive toxicity management rather than reactive intervention.

STOMATITIS AND ORAL MUCOSAL TOXICITY

Stomatitis is the most frequently reported adverse event with Dato-DXd and typically occurs during the first two treatment cycles.[17] Although predominantly grade 1–2, it may affect nutrition, quality of life and treatment adherence if inadequately managed.

Preventive strategies include baseline dental assessment, meticulous oral hygiene, avoidance of alcohol-containing mouthwashes and initiation of prophylactic steroid mouthwash from the first treatment cycle.[17,18] Persistent grade 2 or grade ≥ 3 stomatitis should prompt temporary treatment interruption followed by dose reduction according to prescribing recommendations.

OCULAR ADVERSE EVENTS

Common ocular toxicities include dry eye, keratitis, conjunctivitis and blurred vision.[17] Routine use of preservative-free lubricating eye drops, prompt ophthalmological assessment for persistent symptoms and temporary treatment interruption when clinically indicated are generally sufficient to achieve symptom resolution.

INTERSTITIAL LUNG DISEASE AND PNEUMONITIS

Among all treatment-related toxicities, ILD or pneumonitis remains the most clinically significant because of its potential severity. Similar events have been reported with several DXd-based ADCs, suggesting that this toxicity represents a platform-related rather than target-specific phenomenon. Fortunately, the overall incidence of severe ILD with Dato-DXd appears lower than that reported with Trasutuzumab Deruxtecan, although continued vigilance remains essential.[18]

Patients should undergo baseline thoracic imaging before treatment initiation and be educated regarding the importance of reporting new cough, dyspnoea, fever or unexplained fatigue without delay. New pulmonary infiltrates require prompt

evaluation to exclude infection, tumour progression and drug-induced pneumonitis. Early multidisciplinary assessment involving oncologists, pulmonologists and radiologists is recommended whenever ILD is suspected.

Management depends upon severity. Grade 1 pneumonitis generally requires temporary treatment interruption with close radiological follow-up and consideration of corticosteroid therapy. Grade 2 or higher ILD warrants immediate discontinuation of Dato-DXd and prompt initiation of systemic corticosteroids according to established institutional protocols. Early diagnosis remains the most important determinant of favourable clinical outcome.[18]

GASTROINTESTINAL AND HAEMATOLOGICAL TOXICITY

Nausea is common but usually manageable with standard antiemetic prophylaxis. Fatigue, decreased appetite and constipation are generally mild and respond to supportive care.[17]

Clinically significant neutropenia and diarrhoea occur less frequently than with Sacituzumab Govitecan, reflecting reduced systemic exposure to free payload. Routine prophylactic granulocyte colony-stimulating factor is therefore not routinely indicated and should be individualized according to patient-specific risk factors.[19,20]

DOSE MODIFICATION AND SUPPORTIVE CARE

Appropriate dose modification remains central to safe administration of Dato-DXd. Temporary treatment interruption is recommended for clinically significant stomatitis, ocular toxicity or suspected ILD, with subsequent dose reduction after recovery depending on toxicity grade. Permanent discontinuation is generally reserved for recurrent severe toxicity or confirmed grade ≥ 2 ILD.

Successful administration of Dato-DXd therefore requires a proactive multidisciplinary approach involving oncologists, specialist nurses, dentists, ophthalmologists and pulmonologists. Patient education before treatment initiation is equally important, as early reporting of symptoms frequently prevents progression to more severe toxicity and allows continuation of effective therapy.

CURRENT CLINICAL POSITIONING, CHALLENGES AND FUTURE DIRECTIONS

Datopotamab Deruxtecan (Dato-DXd) represents an important advance in antibody–drug conjugate (ADC) therapy and reflects the evolution of ADC engineering from proof-of-concept to clinically meaningful precision oncology. Rather than introducing a new therapeutic target, Dato-DXd demonstrates how optimization of antibody design, linker stability and payload delivery can improve efficacy while maintaining an acceptable safety profile.[19]

CURRENT CLINICAL POSITIONING

Current evidence supports the use of Dato-DXd primarily in patients with previously treated HR-positive/HER2-negative metastatic breast cancer, where it offers an effective alternative to conventional chemotherapy following endocrine resistance.[12] Its favourable balance between efficacy and tolerability provides an opportunity to delay prolonged exposure to sequential cytotoxic chemotherapy while maintaining disease control.

The role of Dato-DXd in triple-negative breast cancer (TNBC) continues to evolve. With both Dato-DXd and Sacituzumab Govitecan targeting TROP2, treatment selection will depend on patient characteristics, prior therapies, toxicity profile and drug availability. At present, there is insufficient evidence to recommend one agent over the other, and prospective sequencing studies are awaited.

In advanced NSCLC, Dato-DXd offers an additional therapeutic option after platinum-based chemotherapy and appropriate targeted or immunotherapy. The greatest benefit has been observed in nonsquamous disease and in selected patients with actionable genomic alterations, suggesting that careful patient selection will be essential for maximizing clinical benefit.[14,15]

REMAINING CHALLENGES

Despite encouraging clinical outcomes, several questions remain unresolved. TROP2 expression alone has not consistently predicted response, and routine assessment of TROP2 by immunohistochemistry is not currently recommended for patient selection.[3,4] Future biomarker research should evaluate quantitative antigen expression, receptor internalization, tumour microenvironment and circulating tumour DNA to improve prediction of treatment benefit.

Acquired resistance also remains incompletely understood. Proposed mechanisms include reduced TROP2 expression, impaired intracellular trafficking, altered lysosomal processing, increased drug efflux and resistance to topoisomerase I inhibition. Better understanding of these mechanisms may inform future treatment sequencing and combination strategies.

FUTURE DIRECTIONS

The next phase of Dato-DXd development is likely to focus on earlier disease settings and rational combination therapy. Ongoing studies are evaluating combinations with immune checkpoint inhibitors, endocrine therapy and other targeted

agents [Table 2] based on evidence that topoisomerase I inhibitor-based ADCs may enhance antitumour immunity through immunogenic cell death.[16,17]

TABLE 2. SELECTED ONGOING/EXPANDING DEVELOPMENT PROGRAMME

TRIAL	DISEASE	STRATEGY	RATIONALE
TROPION-Breast04 [16]	Early breast cancer	Dato-DXd + durvalumab	Earlier-stage evaluation
TROPION-Lung02 [17]	Advanced NSCLC	Dato-DXd + pembrolizumab	Combination strategy
Additional TROPION studies	Multiple	Combination regimens	Expand indications

In addition, incorporation into neoadjuvant and adjuvant treatment strategies may further expand its clinical role. As experience with ADCs grows, optimization of patient selection, sequencing with other ADCs and biomarker-guided treatment will become increasingly important.

From an Indian perspective, wider adoption of Dato-DXd will depend not only on clinical efficacy but also on availability, cost and infrastructure for toxicity monitoring. Development of standardized supportive care pathways and generation of real-world data from Indian oncology centres will be important to define its role in routine practice.

CONCLUSION

Datopotamab Deruxtecan (Dato-DXd) represents a major advance in the evolution of antibody–drug conjugates (ADCs), demonstrating how optimization of antibody design, linker chemistry and payload selection can translate into meaningful clinical benefit. Although TROP2 had already been established as a therapeutic target, Dato-DXd highlights that refinement of ADC engineering can improve efficacy while maintaining a favourable therapeutic index.[7,19] Evidence from the TROPION clinical programme has established Dato-DXd as an effective treatment option for patients with previously treated HR-positive/HER2-negative metastatic breast cancer and selected patients with advanced non-small cell lung cancer, with emerging data supporting its role in triple-negative breast cancer.[12–15] Its characteristic toxicities—stomatitis, ocular adverse events and interstitial lung disease—are generally predictable and manageable with proactive monitoring, patient education and timely dose modification.[17,18]

Important challenges remain, including identification of predictive biomarkers, understanding mechanisms of resistance and defining the optimal sequencing of Dato-DXd with other ADCs. Ongoing studies evaluating combination regimens and earlier disease settings are expected to further refine its clinical role and may expand its indications beyond metastatic disease.[16,17]

In conclusion, Dato-DXd is more than another TROP2-directed therapy; it represents the maturation of next-generation ADC technology. As clinical experience and biomarker development continue to evolve, Dato-DXd is likely to become an increasingly important component of precision oncology and a benchmark for future ADC development.

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CONFLICTS OF INTEREST

Nothing to disclose.

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