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REVIEW

Therapeutic Potential of Datopotamab Deruxtecan in the Treatment of Advanced Non-Small Cell Lung Cancer: Evidence to Date

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Abstract: Lung cancer is the leading cause of global cancer mortality, accounting for an estimated 2 million diagnoses and 1.8 million deaths annually. Treatment choices for non-small cell lung cancer include surgery, radiation therapy, chemotherapy, immunotherapy, or molecularly targeted therapy. Antibody-drug conjugates (ADCs), often likened to "biological missiles", are rapidly evolving as a targeted therapeutic approach. Trophoblast cell surface antigen 2 (Trop 2) is a 36-kDa cell surface glycoprotein, which is expressed in various cancers. This fuels oncogenic signaling pathways, driving tumor advancement, invasion, and spread. Its limited expression in healthy human tissues underscores its potential as a target for cancer treatment. Datopotamab Deruxtecan (Dato-Dxd) is an investigational ADC that targets Trop-2. This review discusses the current treatment landscape involving therapy with Dato-Dxd for advanced NSCLC. Dato-DXd was first used in metastatic solid tumors in the Phase I TROPION-PanTumor 01 trial, which showed promising antitumor activity in the previously pretreated NSCLC cohort and a manageable safety outline. In TROPION-Lung01, Dato-DXD was studied in metastatic NSCLC patients who were previously treated and showed an objective response rate of 26.4% (Dato-DXd). Other trials, including TROPION PanTumor 02, ICARUS – Lung 01, and TROPION Lung 05, showed comparable results. Dato-DXd used along with pembrolizumab, with or without systemic chemotherapy, in TROPION Lung 02 with promising efficacy results. The most common any-grade treatment-emergent adverse events were stomatitis, nausea, and hair loss, mostly grade 1–2. There are several clinical trials in the pipeline using Dato-DXd in the front-line metastatic setting and resectable NSCLC patients. Dato-DXd is currently pending approval from the US Food and Drug Administration (FDA). If approved, datopotamab deruxtecan will be the first TROP2-directed antibody–drug conjugate for non-small cell lung cancer.

Keywords: TROPION-Lung01, datopotamab deruxtecan, Dato-Dxd, non-small cell lung cancer, antibody–drug conjugate

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with approximately 2 million new cases and 1.8 million deaths annually. It is the second most frequently diagnosed cancer in both men and women, following prostate cancer in men and breast cancer in women.[1] In 2024, the American Cancer Society projected that of the 611,720 cancer-related deaths in the United States, roughly 340 people would die daily from lung cancer—almost 2.5 times the daily deaths caused by colorectal cancer, the second leading cause of cancer deaths.[2]

Non-small cell lung cancer (NSCLC) makes up about 85% of all lung cancer cases and includes several histological subtypes, with squamous cell carcinoma (SQ), adenocarcinoma, and large cell carcinoma being the most common.[3,4] Treatment options for NSCLC typically depend on the stage of the cancer and may include chemotherapy, radiation therapy, immunotherapy, surgery or molecular targeted therapy.[5] Progress in targeted therapy and immunotherapy has greatly

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improved outcomes for NSCLC patients, especially those with identifiable genetic mutations or biomarkers.[6] Early detection and personalized treatment strategies have become increasingly important in managing NSCLC effectively.

Antibody-drug conjugates (ADCs), often likened to "biological missiles", are rapidly evolving as a therapeutic approach.[7] ADCs represent an innovative class of targeted cancer therapies that combine the specificity of monoclonal antibodies with the potent cytotoxic effects of chemotherapeutic agents. By linking a cytotoxic payload to an antibody targeting a tumor-specific antigen, ADCs enable selective delivery of the drug to cancer cells, minimizing damage to healthy tissues.[7] The design of ADCs involves three critical components: the monoclonal antibody, the cytotoxic payload, and a chemical linker that ensures stability in circulation and efficient release within the tumor microenvironment. These unique features underscore the role of ADCs as a promising therapeutic modality in oncology.

Trophoblast cell surface antigen 2 (Trop 2), also known as tumor-associated calcium signal transducer 2, is a 36-kDa glycoprotein encoded by the TACSTD2 gene. Trop 2 is overexpressed in various cancers, driving oncogenic signaling pathways that promote tumor progression, invasion, and metastasis. At the same time, its limited presence in healthy human tissues highlights its potential as a tumor-specific target for cancer treatment, particularly for ADC development.[8] Elevated Trop2 expression has been observed in a significant proportion of patients with adenocarcinoma (64%) and squamous cell carcinoma (75%), further reinforcing its relevance as a therapeutic target in non-small cell lung cancer (NSCLC).[9]

Trop2 is closely associated with tumor aggressiveness and poor prognosis. For example, a study demonstrated that elevated Trop2 expression is correlated with increased lung cancer-specific mortality in adenocarcinoma patients (univariable hazard ratio [HR] = 1.60; 95% CI, 1.07–2.44; P = 0.022). Conversely, no significant association was observed in squamous cell carcinoma (HR = 0.79; 95% CI, 0.35–1.94; P = 0.79).[10] These findings underscore Trop2's role in tumor biology and its value as a therapeutic target for NSCLC. Datopotamab Deruxtecan (Dato-Dxd) is an experimental antibody–drug conjugate (ADC) that specifically targets Trop-2.[11] This review discusses the current treatment landscape involving therapy with Dato-Dxd for advanced NSCLC.

Role of TROP MUTATIONS in Tumor Biology

Based on its success in breast cancer, researchers have explored Dato-Dxd in other types of tumors, including NSCLC.[12–14] Research in early breast cancer has revealed that elevated Trop-2 levels are associated with lower pathological complete response rates to neoadjuvant chemotherapy. This indicates that Trop-2 could be a marker of resistance and a potential target for developing new treatment approaches.[15] Beyond its tumor-specific upregulation, Trop2 plays a functional role in cancer biology through its involvement in various signaling pathways. As a calcium signal transducer, Trop2 activates pathways such as ERK1/2-MAPK, cyclin D1, and NF-κB, which are critical for cell cycle progression and evasion of apoptosis.[16–18] These tumorigenic pathways enable Trop2 to drive cancer cell proliferation and survival.

Preclinical studies have also explored Trop2's potential in inducing apoptosis and enhancing anti-cancer therapy. In a triple-negative breast cancer (TNBC) model, Trop2-targeting antigen-binding fragments (Fabs) disrupted pro-survival pathways and induced apoptosis by modulating Bax and Bcl-2 expression.[9] These findings suggest Trop2's dual role in oncogenesis and tumor suppression, depending on its molecular context.

Pharmacology of Datopotamab Deruxtecan

ADCs are a cutting-edge class of cancer therapies that combine the targeted precision of biologics with the potent effects of cytotoxic chemotherapy.[10,19] Datopotamab (Dato), a human IgG1 monoclonal antibody, was derived by humanizing a muse antibody against human Trop-2.[20]

Deruxtecan (Dxd) is a DNA topoisomerase I inhibitor, a class of drugs crucial for stabilizing DNA supercoiling and resolving DNA entanglements.[21] For the past 20 years, topoisomerase inhibitors have been a mainstay in cancer treatment. However, their clinical effectiveness has been limited by chemical instability and short plasma half-lives, leading to side effects. To address these challenges, tumor-targeted drug delivery systems, such as antibody-drug conjugates (ADCs), have been developed to enhance efficacy and reduce adverse effects.[22,23]

Dato-Dxd is an ADC that pairs a humanized anti-Trop-2 IgG1 monoclonal antibody (datopotamab) with a potent topoisomerase I inhibitor (deruxtecan). The antibody and the cytotoxic payload are linked together by a tetrapeptide-based linker engineered to minimize cysteine residues in datopotamab. This linker is stable in plasma and is designed to

release Dxd upon proteolytic cleavage by lysosomal enzymes, thereby reducing systemic exposure and limiting adverse effects.[24] Stability tests revealed low levels of Dxd in plasma, indicating Dato-Dxd's stability both in vitro and in vivo. The primary target for Dato-Dxd binding is Trop-2.[11] Once bound, Dato-Dxd undergoes internalization into tumor cells, where the payload is released in lysosomal compartments due to the proteolytic cleavage of the linker.[25] Subsequently, the deruxtecan diffuses into the cytoplasm, inducing DNA damage and triggering cellular apoptosis.[26]

Pharmacokinetics and Pharmacodynamics

In a xenograft mouse model, Dato-Dxd had remarkable antitumor efficacy, achieving a tumor growth inhibition of 96% following a single intravenous dose of 10mg/kg.[11] Pharmacokinetic analysis revealed similar plasma concentrations for both Dato-Dxd and the total antibody, while Dxd levels were minimally detectable in the plasma soon after administration. However, Dxd accumulation was observed within tumors. This accumulation coincided with the induction of DNA damage markers, persisting up to day 7 in Dato-Dxd treated animals.[11] These findings underscore Dato-Dxd's mechanism of action, involving tumor-specific Dxd accumulation and subsequent induction of DNA damage, resulting in potent tumor growth inhibition.

In patient-derived xenograft (PDX) models of NSCLC, Dato-Dxd consistently demonstrated substantial tumor growth inhibition in tumors with high Trop-2 expression, achieving reductions ranging from 77% to 98% in models, such as CTG-0163, CTG-0838, and CTG-1014.[11] Notably, Dato-Dxd did not produce any significant side effects or weight loss in the mice across all models. These findings underscore Dato-Dxd's potential as an effective treatment for NSCLC tumors with Trop-2 expression.

Dato-Dxd did not produce severe toxicity at doses up to 200 mg/kg in rats and showed low rates of severe pulmonary toxicity at doses of 30 mg/kg or higher in monkeys. Dato-Dxd caused only mild gastrointestinal and hematological toxicities in both animal models. Higher doses led to some dermatological and ocular adverse effects, which were generally resolved after the treatment was stopped.[11]

Clinical Trials Data in All Metastatic Solid Tumors (NSCLC Cohort)

TROPION-PanTumor01, was a Phase 1 trial designed to assess the tolerability and effect of Dato-Dxd in advanced and metastatic solid tumors. In the NSCLC cohort, patients received escalating doses of Dato-Dxd. The objective response rate (ORR) was 26% (95% CI, 14.6 to 40.3), median progression-free survival (PFS) was 6.9 months (95% CI, 2.7 to 8.8 months), and overall survival (OS) was 11.4 months (95% CI, 7.1 to 20.6 months). The median duration of response (DOR) was 10.5 months. Responses were noted irrespective of the levels of TROP2 expression. The findings suggest that Dato-Dxd demonstrates effective antitumor activity and maintains a safety profile similar to that observed in heavily pretreated patients with advanced NSCLC.[27]

The Phase 1/2 clinical trial, TROPION-PanTumor02 was designed to assess the efficacy of Dato-DXd (6 mg/kg IV Q3W) in Chinese patients with advanced solid tumors (NSCLC-40) with or without actionable genetic mutations (AGA). In the NSCLC cohort, 57.5% had tumors with non-squamous (NSQ) histology, 42.5% had squamous (SQ) histology, and 10% had sensitizing EGFR mutations. The ORR was 45.0% in the overall cohort, 56.5% in NSQ subgroup, 29.4% in the SQ subgroup and 75.0% in patients with EGFR mutations. The median PFS was 7.4 months (95% CI: 5.7–not calculable [NC]) for the overall cohort, 9.6 months (95% CI: 7.1–NC) in the NSQ subgroup, and 5.5 months (95% CI: 1.4–NC) in the SQ subgroup.[28]

Early Clinical Trial Data in NSCLC (Table 1)

Dato-DXD as a Single Agent

The Phase 3 clinical trial TROPION-LUNG01 was designed to compare the efficacy of Dato-Dxd (6 mg/kg Q3W) against docetaxel (75 mg//m² Q3W) in patients with previously treated advanced or metastatic NSCLC. The results showed that for the overall group, the median PFS was 4.4 months (95% CI, 4.2 to 5.6) with Dato-Dxd, compared to 3.7 months (95% CI, 2.9 to 4.2) with docetaxel. In the NSQ subgroup, Dato-Dxd demonstrated a significantly longer median PFS of 5.5 months (95% CI, 4.3 to 6.9) compared to 3.6 months (95% CI, 2.9 to 4.2) for docetaxel. However, Dato-Dxd had a median PFS of 2.8 months in the SQ subgroup, compared to 3.9 months with docetaxel. While the median OS was numerically higher for Dato-Dxd compared to docetaxel (12.9 vs 11.8 months) in the overall group and the NSQ

Table 1 Early Clinical Trial Data in NSCLC

Name	Phase	N	Population	Intervention	PFS (months)	OS (months)	ORR%
TROPION PanTumor 01 NSCLC cohort[27] NCT03401385	I	890	a/m Solid Tumors	0.27–10 mg/kg Dato-DXd Q3w during escalation or 4, 6, or 8 mg/kg Dato-DXd Q3q during expansion.	6.9 (2.7–8.8)	11.4 (7.1–20.6)	26(14.6–40.3)
TROPION PanTumor 02 NSCLC Cohort[28] NCT05460273	I/2	119	Chinese patients with a/m solid cancers	6 mg/kg Dato-Dxd every 3 weeks NSQ histology SQ histology	7.4 (5.7-NC) 9.6 (7.1-NC) 5.5 (1.4 - NC)		45 56.5 29.4
TROPION LUNG 01[29] NCT04656652	3	590	a/m NSCLC with AGA	6 mg/kg Dato-DXd every 3 weeks 75 mg/m^2 docetaxel every 3 weeks	4.4 (4.2–5.6) 3.7 (2.9–4.2)	12.4(10.8–14.8) 11 (9.8–12.5)	26.4(21.5–31.8) 11.0 (9.8–12.5)
TROPION LUNG 02[31] NCT04526691	Ib	145	a/m NSCLC	Dato-DXd (4 or 6 mg/kg) + pembrolizumab without PCT Dato-DXd (4 or 6 mg/kg) + pembrolizumab with PCT	8.3 (6.8–11.8) 7.8 (5.6–11.1)		60(36–81) 55 (39–70)
TROPION LUNG 05[32] NCT04484142	2	137	a/m NSCLC with AGA and previously treated	Dato-Dxd 6 mg/kg	5.4		35.8
ICARUS-LUNG01[33] NCT04940325	2	100	a/m NSCLC progressed on 1–3 lines of therapies	6 mg/kg Dato-Dxd every 3 weeks NSQ histology SQ histology	3.6 (2.6–6.0) 4.8 (2.6–6.1) 2.9 (1.9–3.5)	11.9 (7.5–14.6) 12.6 (9.5–15.4) 6.3 (3.5–9.1)	28 32.9 5

Abbreviations: a/m, advanced/metastatic; NSCLC, non-small cell lung cancer; Dato-DXd, Datopotamab Deruxtecan; Q3w, every 3 weeks; NSQ, non-squamous histology of NSCLC; SQ, squamous histology of NSCLC; AGA, actionable genomic alterations; NC, not calculable; PCT, platinum-based chemotherapy.

subgroup (14.6 months vs 12.3 months), the differences were not statistically significant. Additionally, the ORR% was higher for Dato-Dxd compared to docetaxel in both the overall and NSQ subgroups (Table 1). [29,30]

The Phase 2 clinical trial TROPION-LUNG05 was designed to assess the effectiveness of Dato-Dxd (6 mg/kg Q3W) in patients with advanced or metastatic NSCLC with AGAs who experienced progression on or after receiving at least one AGA-specific therapy and platinum-based chemotherapy. This trial enrolled 137 patients with a median age of 61 years. Of these, 71.5% had undergone 3 or more prior treatments, and 56.9% had EGFR mutations. The results showed ORR of 35.8%, a median DOR of 7 months, and a DCR of 78.8%. Responses in patients with EGFR mutations were similar with ORR of 34%.[32]

The phase 2 clinical trial, ICARUS-LUNG01, aimed to assess the efficacy of Dato-Dxd administered at 6 mg/kg Q3W in patient with advanced or metastatic NSCLC who have AGAs and have experienced progression on 1–3 lines of therapies (median of 2 therapies), including AGA-specific treatment. This study enrolled 100 patients, 23% with AGA and 82% with NSQ histology. The median age of this cohort was 63 years (26–83 years). The majority were males (62%) and smokers (89%). The median duration of treatment was 2.8 months (95% CI 2.1–4.8), with a median follow-up period of 19.4 months (95% CI 18.2–20.4). The results showed the highest benefits in the NSQ sub-group with ORR of 32.9% (28% - overall and 5% - SQ subgroup), the median PFS of 4.8 months (3.6 months – overall and 2.9 months – SQ) and the median OS of 12.6 months (11.9 months – overall and 6.3 months– SQ).[33]

Dato-DXD in Combination with Immunotherapy

The Phase 1b clinical trial, TROPION-LUNG02, was designed in a sequential dose-escalation and dose-expansion model to assess the safety, tolerability, and efficacy of Dato-Dxd in patients with advanced/metastatic NSCLC. The patients received a combination of Dato-Dxd (4 or 6 mg/kg) and pembrolizumab 200 mg with (doublet) or without (triplet) platinum-based chemotherapy (cisplatin 75 mg/m2 or carboplatin AUC 5) every 3 weeks as the first-line treatment. Participants in the dose expansion phase did not receive any prior treatment, while those in dose escalation had received ≤2 previous treatments. The median age of the patient population was 66 years, and the median duration of treatment was 6.6 months in doublet and 5.8 months in triplet subgroups. This treatment regimen showed stable anti-cancer activity with efficacy demonstrated in the overall population and the subgroups. The details of ORR% and the median PFS across the overall population and subgroups are provided in Table 1. This study is the largest to date examining the combination of antibody-drug conjugate and an anti-PD1/L1 agent as the first-line treatment for patients with advanced/metastatic NSCLC.[31,34]

Several ongoing clinical trials, from the early phase to phase 3, are investigating the Dato-Dxd in combination with immunotherapies and platinum-based chemotherapy. These trials include AVANZAR, NeoCOAST-2, TROPION-LUNG 04, TROPION-LUNG 07, TROPION-LUNG 08, and TROPION-LUNG 10. Table 2 outlines the key aspects of each trial. The experimental medications, Oleclumab, monalizumab, and volrustomig are being used in these trials. Oleclumab is a monoclonal antibody against the ectoenzyme CD73 (cluster of differentiation 73), also known as 5′-nucleotidase (5′-NT; ecto-5′-nucleotidase) with potential antineoplastic activity.[35] Monalizumab (IPH2201) targets NKG2A receptors expressed on tumor infiltrating cytotoxic CD8+ T cells and NK cells, while NKG2A is an inhibitory checkpoint receptor for HLA-E.[36] Volrustomig is an engineered fragment crystallizable (Fc) domain bispecific human immunoglobulin G1 (IgG1) monoclonal antibody directed against PD-1 and CTLA-4.[37]

Table 2 Ongoing Clinical Trials

Name	Phase	N	Population	Intervention	Primary Endpoints	Secondary Endpoints
AVANZAR[38] **NCT05687266**	3	1280	a/m NSCLC without AGAs with no prior chemotherapy or systemic therapy	***Group 1*** Dato-DXd + Durvalumab + Carboplatin Vs ***Group 2*** Pembrolizumab + histology specific PCT	PFS and OS in the TROP-2 positive population.	PFS and OS in TROP-2 negative population DOR and time to second progression or death (PFS2) in the TROP-2 negative population Pharmacokinetics Immunogenicity Safety
NeoCOAST-2[39] **NCT05061550**	2	490	Resectable, Early-stage (II to IIIB) NSCLC	***Arm 1:*** Oleclumab + Durvalumab ***Arm 2:*** Monalizumab + Durvalumab + CTX ***Arm 3:*** Volrustomig + CTX ***Arm 4:*** Dato-DXd + durvalumab ***Arm5***: AZD0171 + durvalumab + CTX	pCR rate Safety & tolerability	Investigator assessed event free survival Disease-free survival OS Feasibility to surgery Major pCR ORR Pharmacokinetics Immunogenicity Changes in the circulatory tumor DNA

(*Continued*)

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Table 2 (Continued).

Name	Phase	N	Population	Intervention	Primary Endpoints	Secondary Endpoints
TROPION LUNG 04[40] **NCT04612751**	1b	321	a/m NSCLC without AGA	11 study cohorts. **Cohorts 1–4**: Dato-Dxd + durvalumab ± carboplatin **Cohorts 5–8** Dato-Dxd + AZD2936 ± carboplatin **Cohorts 9–11** Dato-Dxd + MEDI15752 ± carboplatin	Safety	ORR, DOR, DCR, PFS, OS, TTR Best percentage change in the sum of diameters of target lesions Pharmacokinetics Immunogenicity (anti-drug antibodies)
TROPION LUNG 07[41] **NCT05555732**	3	975	a/m PD-L1 TPS <50% NSCLC without AGAs	***Experimental Arm 1:*** Dato-DXd + Pembrolizumab ± PCT ***Experimental Arm2***: Dato-Dxd+ pembrolizumab ***Active Comparator***: Pembrolizumab + pemetrexed + PCT	PFS OS	ORR, DOR, DCR, TTR, PFS2 Time to Deterioration (TTD) Number of participants with TEAEs Proportion of Participants who have Anti-Drug Antibody (ADA) and proportion of participants who have treatment emergent ADA.
TROPION LUNG 08[42] **NCT05215340**	3	740	a/m PD-L1 High (TPS ≥50%) NSCLC without AGAs	***Experimental arm***: Pembrolizumab + Dato-DXd ***Active Comparator***: Pembrolizumab	PFS & OS	ORR, PFS2, DOR, TTR, DCR, TTD Number of participants with TEAE Proportion of Participants who are ADA Positive and proportion of participants who have treatment emergent ADA.
TROPION LUNG 10[43] **NCT06357533**	3	675	a/m NSQ NSCLC with high PD-L1 expression (TC ≥ 50%) and without AGAs	***Arm1***: Dato-DXd + Rilvegostomig Q3W ***Arm2***: Rilvegostomig Q3W ***Active Comparator***: Pembrolizumab Q3W	PFS & OS in TROP2 + biomarker patients	ORR, DOR, PFS2 Safety, Pharmacokinetics, Immunogenicity

Abbreviations: a/m, advanced/metastatic; AGA, actionable genomic alterations; Dato-DXd, Datopotamab Deruxtecan; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; DOR, Duration of response; PFS2, time to second progression or death; pCR, pathological complete response; DCR, disease control rate; TTR, time to response; ORR, objective response rate; CTX, platinum based chemotherapy; TEAEs, treatment emergent adverse events; TTD, time to deterioration; ADA, Anti-Drug Antibody.

Intracranial Activity

In an exploratory analysis of intracranial efficacy in the phase 2 TROPION-Lung05 trial, Dato-Dxd demonstrated encouraging intracranial activity. Out of the 137 patients, 53 had baseline brain metastases; 55% had an EGFR mutation. Of the patients with baseline intracranial metastases, 34% had measurable lesions (3 untreated), while 66% had only non-target lesions. In 18 patients with target lesions, the intracranial response rate was 22% (95% CI, 6–48); disease control rate was 72% (95% CI, 47–90); and the clinical benefit rate (CBR) was 44% (95% CI, 22–69). Reduction in the size of brain lesions was seen in 56% of patients. The median time to intracranial response was 1.5 (range, 1.3–5.4) months and the median duration of intracranial response was 5.5 (95% CI, 3.4–NE) months. Systemic efficacy and safety were similar in patients with and without brain metastases, suggesting that Dato-Dxd can penetrate the blood-brain barrier and is active against brain metastases.[44]

Safety

Dato-DXd has been studied extensively in breast cancer patients. In a meta-analysis, the incidence of any grade treatment-related adverse events was 94.44% (95% CI 72.62–100.0). The most observed adverse events were stomatitis (45.9%), nausea (58.3%), alopecia (47.2%), fatigue (34.7%) and vomiting (23.6%). The pooled incidence rate of grade 3–4 treatment-related adverse events was 31.9%, stomatitis was the most common (13.8%), followed by fatigue (4.1%) and vomiting (1.3%). The incidence of Dato-DXd dose reduction due to AEs was 18.05%, and serious adverse events were observed in 13.88% (Table 3). [45]

In TROPION-PanTumor01 – NSCLC cohort, the most frequent any-grade TEAEs were nausea (64%), stomatitis (60%), and alopecia (42%). Grade ≥3 TEAEs and treatment-related AEs occurred in 54% and 26% of patients, respectively. Across dose escalation and expansion, any-grade TEAEs were observed in 98% of patients receiving Dato-DXd 4 (30.0% grade ≥ 3) or 6 mg/kg (54.0% grade ≥ 3) and 100% of patients receiving 8 mg/kg (58.8% grade ≥ 3). Serious TEAEs occurred in 20.0%, 48.0%, and 48.8% of patients receiving Dato-DXd 4, 6, or 8 mg/kg, respectively. TEAEs associated with discontinuation occurred in 16.0%, 14.0%, and 23.8% of patients receiving Dato-DXd 4, 6, or 8 mg/kg, respectively; TEAEs associated with dose reduction occurred in 2.0%, 10.0%, and 27.5% of patients, respectively. Infusion-related reactions (IRRs) occurred in 24%, 20%, and 25% of patients receiving Dato-DXd 4, 6, or 8 mg/kg, respectively. The most common grade ≥3 TEAEs were pneumonia, anemia, and decreased lymphocyte count. Ocular surface toxicities (OSTs) occurred in 13 patients (any grade, 26.0%; grade ≥3, 0%) receiving 4 mg/kg, 12 (any grade, 24.0%; grade 3, 2%) receiving 6 mg/kg, and 33 (any grade, 41.3%; grade 3, 2.5%) receiving 8 mg/kg. Common OSTs were dry eye, increased lacrimation, and blepharitis. Grade 3 OSTs included keratitis (one in Dato-DXd 8 mg/kg) and ulcerative keratitis (one in 6 and one in 8 mg/kg; both considered serious TEAEs). Stomatitis events were predominately grade 1–28.3% or 2–21.7%. Grade 3 stomatitis occurred in one patient receiving Dato-DXd 6 mg/kg and three receiving 8 mg/kg; grade 4 stomatitis was observed in one patient receiving 8 mg/kg. Alopecia had 24.4% - grade 1, and 15.6% - grade 2 AEs. Adjudicated ILD as drug-related occurred in five patients (10.0%) receiving Dato-

Table 3 Treatment-Emergent Adverse Events of Dato-DXd

Trial	Treatment		Grade ≥ 3 TEAEs %		Stomatitis % (Any, Grade ≥3)		Nausea % (Any, Grade ≥3)		ILD % (Any, Grade ≥3)
TROPION PanTumor01 (NSCLC cohort)[27]	Single Agent		54		60		64		1.4, 0.5
TROPION PanTumor 02 (NSCLC Cohort)[28]	Single Agent		57.5		57.5		62.5		0,-
TROPION- Lung01[29,30]	Single Agent		25		49.2, 6		37, 1		3.4,-
TROPION-Lung05[32]	Single agent		25		-, 9.5		-		3.6, 1
TROPION-Lung02[31]	+ ICI	+ ICI and PCT	57	76	57	33	40	46	7.5, 2.5

Abbreviations: TEAEs, treatment emergent adverse events; ILD, interstitial lung disease; ICI, immunotherapy; PCT, platinum-based chemotherapy.

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DXd 4 mg/kg, three (6.0%) receiving 6 mg/kg, and 11 (13.8%) receiving 8 mg/kg. These events were primarily grade 1 or 2 (n = 13 [7.2%]). Grade ≥3 events occurred in six patients (two grade 3, one grade 4, and three grade 5). All grade 5 events occurred in the 8-mg/kg cohort.[27]

In TROPION-PanTumor02 – NSCLC cohort, TEAEs occurred in 95.0% of patients; grade ≥3 TEAEs occurred in 57.5%, and there were no fatal TEAEs. The most common AEs included nausea (62.5%), stomatitis (57.5%) and anemia (57.5%). Dose reduction/discontinuation was necessary in 20.0%/10.0% of patients. No drug-related interstitial lung disease was reported.[28]

In TROPION-Lung01, the most common adverse events (AE) seen with Dato-DXd were stomatitis (49.2%, mostly grade 1–2) and nausea (37%). Adjudicated drug-related grade ≥3 interstitial lung disease (ILD) occurred in 3.4% of patients with Dato-DXd compared to 1.4% with docetaxel. Grade ≥3 TRAEs occurred in 25% of patients in the Dato-DXd arm. The most common grade ≥3 TRAEs were neutropenia (1%), stomatitis (6%), anemia (4%), asthenia (3%), nausea (2%) and fatigue (1%). Grade 3 or higher drug-related interstitial lung disease (ILD) events occurred in 3% of patients, including 7 grade 5 events (2%). Of the 7 grade 5 ILD events, four (1.7%) were in patients with non-sq NSCLC, while 3 (4.6%) were in patients with squamous cell lung cancer.[29,30]

In the TROPION-LUNG05 study, the most common grade ≥3 treatment-related AEs were stomatitis (9.5%), anemia (5.8%), and increased amylase (5.8%). Grade 3 treatment related AEs were 25%, most common being stomatitis and nausea. TEAEs associated with dose reduction 21.9% and drug discontinuation 9.5%.[32] In the ICARUS-LUNG01 trial, 25% had grade ≥3 AEs. Most common AEs were again stomatitis (Grade 1–2 = 49%, Grade ≥3 = 10%) and nausea (Grade 1–2 = 45%). There was 1 confirmed case of ILD.[33]

In TROPION-Lung02, across doublet and triplet treatment arms, the most common treatment-related AEs were stomatitis (57%, 33%) and nausea (40%, 46%), respectively. The majority were grade 1–2. Grade ≥3 treatment-related AEs were seen in 57% and 76% of patients respectively, of which 38% and 44%, respectively, were serious AEs. AEs associated with Dato-DXd discontinuation occurred in 29% and 39% of patients receiving doublet or triplet treatment, respectively. AEs associated with death were seen in 2% and 9%, but none was considered related to Dato-DXd.[31]

Conclusions

Clinical Implications

Dato-DXd has shown positive antitumor activity and was reasonably well tolerated in heavily pretreated patients with metastatic NSCLC, most of whom had been treated with at least 2 lines of therapy including platinum combination chemotherapy, immunotherapy, and when indicated, targeted therapy. Responses were seen regardless of TROP2 expression level, PDL1 status or AGA. The association of high TROP2 expression with prognosis varied based on the lung cancer subtype. In adenocarcinoma, high TROP2 expression was associated with higher patient mortality. In SCC, high TROP2 expression was not associated with mortality.[18] Most frequent any-grade treatment-emergent adverse events were stomatitis, nausea, and alopecia, mostly grade 1–2. Any grade ILD varied from 0 to 7.5% in trials, with ≥grade 3 ILD in 0.5–2.5% in those trials. The most commonly used dose was 6 mg/kg every 3 weeks; however, the maximum tolerated dose was established as 8 mg/kg once every 3 weeks in TROPION-PanTumor01. In an exploratory analysis of TROPION-Lung05, Dato-DXd showed encouraging intracranial activity consistent with systemic responses in patients with advanced/metastatic NSCLC with AGAs.

Future Directions

Based on TROPION-LUNG01 Phase III study results, Dato-DXd has passed biological license approval and is pending the Food and Drug Administration (FDA) regulatory decision in the fourth quarter of 2024. If accepted, datopotamab deruxtecan will be the first TROP2-directed antibody–drug conjugate for patients with NSCLC.[46] Keen attention to the occurrence of ILD, particularly grade ≥3 as more data on Dato-DXd are published. There are numerous ongoing trials where Dato-DXd is being used in 1st line setting in metastatic NSCLC patients, in combination with immunotherapy and/or chemotherapy. The results of these trials will establish the role of Dato-DXd in NSCLC.

Disclosure

Maya Gogtay, Nikhila Aimalla, Ram Prakash Thirugnanasambandam report no conflicts of interest in this work. Apar Kishor Ganti – Consultant: Genentech, AstraZeneca, G1 Therapeutics, Jazz Pharmaceuticals, Flagship Biosciences, Sanofi-Genzyme, Regeneron, Catalyst Pharmaceuticals; Research Support: Takeda; DSMC: Y-mAbs Therapeutics; Personal fees: Blueprint Medicines, Cardinal Health, Beigene Ltd, Mirati, Pfizer, Zai Labs, Bayer, Amgen, Chimerix; Institutional PI on sponsored clinical trial: Merck, Mirati, IOVANCE Therapeutics, POSEIDA Inc.

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