

A Pooled Analysis of Datopotamab Deruxtecan in Patients With *EGFR*-Mutated NSCLC



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ABSTRACT

Background: This exploratory analysis assessed datopotamab deruxtecan (Dato-DXd) in pretreated patients with advanced or metastatic NSCLC and *EGFR* mutations.

Methods: Data were pooled from the phase II TROPION-Lung05 (NCT04484142) and phase III TROPION-Lung01 (NCT04656652) trials. Patients with *EGFR*-mutated advanced or metastatic NSCLC, who had received previous targeted therapies and platinum-based chemotherapy, received Dato-DXd 6 mg/kg (TROPION-Lung05) or were randomized to Dato-DXd 6 mg/kg or docetaxel 75 mg/m² (TROPION-Lung01) once every 3 weeks. End points included objective response rate, duration of response, and progression-free survival, all per blinded independent central review, overall survival, and safety.

Results: In total, 117 patients with *EGFR* mutations who received Dato-DXd were included in the pool. The population was heavily pretreated (median three lines of previous therapies; range, 1–5) and predominantly Asian (69%). The most common mutations were exon 19 deletion (51%), L858R (32%), and T790M (27%); more than one *EGFR* mutation could be present. The confirmed objective response rate was 43% (95% confidence interval [CI]: 34–52), including five complete responses (4%). Median duration of response was 7.0 months (95% CI: 4.2–9.8). Median progression-free survival and overall survival were 5.8 (95% CI: 5.4–8.2) and 15.6 months (95% CI: 13.1–19.0), respectively. The safety profile of Dato-DXd was consistent with the individual studies. No new safety signals were observed. Rates of grade greater than or equal to 3 treatment-related adverse events and serious adverse events were 23% and 6%, respectively.

Conclusion: Dato-DXd demonstrated meaningful clinical activity in patients with *EGFR*-mutated advanced or metastatic NSCLC who had progressed on *EGFR*-directed therapies and chemotherapy, with an acceptable safety profile.

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Keywords: Antibody–drug conjugate; Datopotamab deruxtecan; *EGFR* mutation; NSCLC; Pooled analysis

Introduction

Patients with NSCLC frequently harbor actionable genomic driver mutations, of which *EGFR* is one of the most common, occurring in approximately 50% of Asian and approximately 20% of Western lung cancer populations.^{1,2} The exon 19 deletion and L858R activating mutations are typical of *EGFR*-mutated NSCLC and drive pathogenesis, although other less common driver mutations

can present.^{1,2} Tumors may also bear mutations that confer intrinsic resistance to treatment or acquire others, most frequently T790M, which usually arises during treatment with primary therapies, including first- and second-generation *EGFR* tyrosine kinase inhibitors (TKIs).^{2,3}

Osimertinib, a third-generation TKI, is currently the preferred first-line treatment option for patients with common activating *EGFR* mutations^{4–6}; however, despite good initial responses to therapy, patients inevitably progress owing to the development of heterogeneous resistance mechanisms.^{7–10} Alternatively, patients with these mutations may receive osimertinib with chemotherapy or amivantamab with lazertinib.⁴ Second-line treatment options include amivantamab with platinum-based chemotherapy, atezolizumab–bevacizumab–paclitaxel–carboplatin, or platinum-based chemotherapy alone, depending on the patient's tumor mutation, preferences, and conditions.^{4,5,11,12} Later-line treatment options used as salvage therapy in patients with *EGFR*-mutated NSCLC confer limited benefit and are not defined in treatment guidelines.^{4,5,13} Fourth-generation TKIs are being investigated as a therapeutic option to overcome osimertinib resistance; however, the toxicity of these agents has so far hampered clinical development.¹⁴ Thus, an important unmet need remains for novel, effective, and tolerable treatment options for patients with *EGFR*-mutated NSCLC who have progressed after previous *EGFR*-directed therapies.

Datopotamab deruxtecan (Dato-DXd) is a trophoblast cell-surface antigen-2 (TROP2)-directed antibody–drug conjugate (ADC) recently approved in Japan, the United States, and Europe for the treatment of adult patients with unresectable or metastatic hormone receptor-positive, human *EGFR* 2-negative breast cancer who have received previous endocrine therapy and chemotherapy for unresectable or metastatic disease.^{15–18} In the first-in-human TROPION-PanTumor01 study, Dato-DXd demonstrated promising results in a large cohort of heavily pretreated patients with advanced NSCLC.¹⁹ More recently, Dato-DXd became the first agent to show statistical superiority over standard-of-care docetaxel as monotherapy in reducing disease progression in previously treated patients with advanced or metastatic NSCLC as part of the phase III TROPION-Lung01 trial.²⁰

A key finding from that study, conducted in a TROP2-unselected patient population, was that the clinical benefit for Dato-DXd over docetaxel seemed highest in the subset of patients with actionable genomic alterations (including *EGFR* mutations).²⁰ TROPION-Lung05 is a separate, single-arm, phase II trial that evaluated Dato-DXd in patients with advanced or metastatic NSCLC with actionable genomic alterations who had progressed on or after treatment with targeted therapy and

platinum-based chemotherapy.²¹ In TROPION-Lung05, patients with *EGFR* mutations exhibited numerically improved objective response rates (ORRs) and longer progression-free survival (PFS) compared with the overall and other genomically defined populations.²¹ An independent phase II trial evaluating Dato-DXd as monotherapy, ICARUS-Lung01, has similarly reported improved efficacy outcomes in a subset of patients whose tumors bore genomic alterations (11 of 12 of which were mutations in *EGFR*) relative to the overall population.²² Furthermore, initial findings from the phase II platform study ORCHARD were recently reported, in which it was found that adding Dato-DXd to osimertinib as second-line treatment for patients with *EGFR* mutations who had previously progressed on osimertinib could extend PFS.²³

Here we report exploratory pooled efficacy and safety analyses of Dato-DXd in patients with pretreated advanced or metastatic NSCLC harboring *EGFR* mutations from the TROPION-Lung05 and TROPION-Lung01 clinical trials.

Materials and Methods

Individual Trial Study Designs

Data were pooled from two global clinical trials of Dato-DXd in patients with previously treated advanced or metastatic NSCLC: TROPION-Lung05 and TROPION-Lung01. TROPION-Lung05 is a single-arm, phase II study assessing the safety and efficacy of Dato-DXd in patients with previously treated advanced or metastatic NSCLC with actionable genomic alterations.²¹ TROPION-Lung01 is a randomized, open-label, phase III study comparing the safety and efficacy of Dato-DXd with docetaxel in adults with previously treated advanced or metastatic NSCLC with or without actionable genomic alterations.²⁰ Across both studies, adults had to have stage IIIB or C to IV NSCLC, disease progression on their most recent treatment for advanced or metastatic disease, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with clinically inactive or treated asymptomatic brain metastases were eligible. All patients had previously received one or two *EGFR*-targeted therapies and platinum-based chemotherapy with or without an anti-programmed cell death protein 1/anti-programmed cell death-ligand 1 immunotherapy in the metastatic setting. Patients whose tumors bore exon 20 insertions may have received previous amivantamab. Full eligibility criteria have been published.^{20,21} Dato-DXd dose escalation and expansion were initially performed in the phase I TROPION-PanTumor01 trial, with 6 mg/kg selected for development based on safety, tolerability,

pharmacokinetics, efficacy, and exposure-response modeling and simulation data.¹⁹ In both TROPION-Lung05 and TROPION-Lung01, patients were treated with Dato-DXd 6 mg/kg once every 3 weeks. Patients in the comparator arm of TROPION-Lung01 received docetaxel 75 mg/m² once every 3 weeks.

Ethics Approval

The parent study protocols were approved by the institutional review board at each participating site. Both studies were conducted in accordance with the International Council for Harmonisation consolidated Guideline E6 for Good Clinical Practice, the Declaration of Helsinki, and applicable local and regional regulations. All patients provided a written informed consent before enrollment. Individual trial designs and full eligibility criteria have been published previously.^{20,21}

Assessment of *EGFR* Mutational Status

EGFR mutational status was tested locally at participating clinical sites using blood or tumor tissue and documented in the electronic case report form by the investigator. Documentation of genomic alterations, including *EGFR*, was performed locally, before enrollment, if genomic alteration results were not available.

Exploratory Pooled Analysis Plan

For this analysis, data were retrospectively pooled from patients with at least one common or uncommon mutation in *EGFR* who had received at least one dose of Dato-DXd in TROPION-Lung05 and TROPION-Lung01. An additional safety analysis was performed that included eight patients with *EGFR*-mutated NSCLC from the phase I TROPION-PanTumor01 study (NCT03401385).

Exploratory Efficacy End Points

ORR, defined as the proportion of patients who achieved a confirmed complete response (CR) or partial response (PR) as assessed by blinded independent central review (BICR) per RECIST version 1.1, was the primary end point of TROPION-Lung05 and a secondary end point of TROPION-Lung01. Disease control rate (DCR) was the proportion of patients with confirmed CR, PR, or stable disease, and duration of response (DOR) was the time from the first objective response to the first documentation of disease progression or death. Time to response (TTR) was measured from the start of treatment (TROPION-Lung05) or randomization (TROPION-Lung01) to the first documentation of objective response. PFS was defined as the time from the start of treatment (TROPION-Lung05) or randomization (TROPION-Lung01) to the first documentation of disease progression or death from any cause, whichever came

first. Overall survival (OS) was defined as the time from the start of treatment (TROPION-Lung05) or randomization (TROPION-Lung01) to death. Best overall response, DCR, DOR, TTR, and PFS were assessed by BICR per RECIST version 1.1. Study duration was defined as the time between the start of treatment (TROPION-Lung05) or randomization (TROPION-Lung01) and data cutoff.

Safety

Adverse events (AEs) were investigator determined and coded and graded per the Medical Dictionary for Regulatory Activities version 26.0 and the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, respectively. Treatment-emergent AEs of special interest (AESIs) included oral mucositis or stomatitis, ocular surface events, and adjudicated drug-related interstitial lung disease (ILD) or pneumonitis. All AESIs were grouped in terms of predefined Medical Dictionary for Regulatory Activities preferred terms. An independent adjudication committee reviewed all potential ILD or pneumonitis events to determine diagnosis, causality, and severity grading.

Statistical Analysis

Baseline demographic and clinical characteristic data were reported for the pooled population and the individual studies. Efficacy and safety end points were reported for both the pooled and individual trial populations.

The two-sided 95% confidence intervals (CIs) for ORR and DCR were calculated using the Clopper-Pearson exact binomial method. Median DOR, PFS, and

OS were estimated using the Kaplan-Meier method and the corresponding two-sided 95% CIs were computed using the Brookmeyer-Crowley method. Safety end points were summarized using descriptive statistics. Statistical analyses were performed using SAS version 9.4 (or newer; SAS Institute Inc., Cary, NC).

Results

Patients

The retrospective pooled schema is presented in Figure 1. A total of 117 patients with *EGFR* mutations (TROPION-Lung05, n = 78; TROPION-Lung01, n = 39) comprised the overall pooled population. Data cutoff for TROPION-Lung05 was December 14, 2022. For TROPION-Lung01, the data cutoff for ORR, DCR, DOR, TTR, and PFS was March 29, 2023, and the data cutoff for OS and safety was March 1, 2024.

Baseline Characteristics and Previous Therapies

Baseline characteristics for the *EGFR*-mutated pooled and individual parent-trial populations are presented in Table 1. In the pooled population, the median age was 63 years (range, 36–81) and most patients were of Asian descent (69%). Overall, 98% of patients had tumors of nonsquamous histologic type and 31% had clinically inactive or treated asymptomatic brain metastases. The most frequent mutations present were the classical activating mutations exon 19 deletion (51%) and L858R (32%). The uncommon activating mutations G719X and L861G were seen in 5% and 4% of patients, respectively. The *EGFR* TKI-resistance mutation T790M occurred as a comutation in 27% of patients, and 4% bore a unique

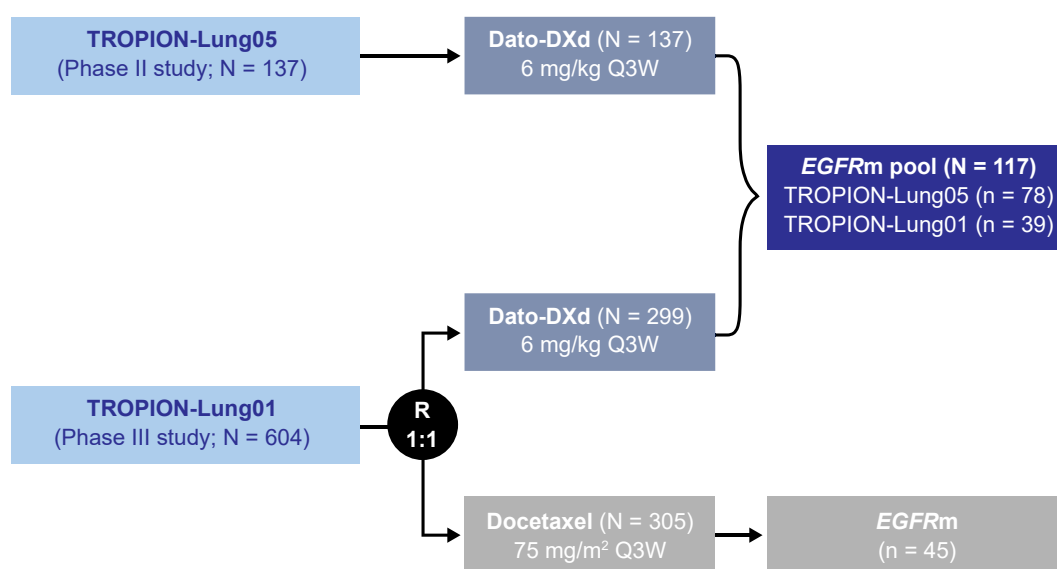


Figure 1. Pooled analysis schema. Dato-DXd, datopotamab deruxtecan; *EGFRm*, epidermal growth factor receptor mutated; Q3W, every 3 weeks; R, randomized.

Table 1. Baseline Characteristics and Previous Therapies

Characteristic	EGFRm Pool (N = 117)	TROPION-Lung05 (n = 78)	TROPION-Lung01 (n = 39)
Age, median (range), y	63 (36-81)	63 (36-77)	62 (39-81)
Female	73 (62)	52 (67)	21 (54)
Race			
Asian	81 (69)	55 (71)	26 (67)
White	27 (23)	20 (26)	7 (18)
Black or African American	1 (1)	0	1 (3)
Other or missing	8 (7)	3 (4)	5 (13)
ECOG PS			
0	39 (33)	24 (31)	15 (38)
1	78 (67)	54 (69)	24 (62)
Smoking history			
Current	1 (1)	0	1 (3)
Former	54 (46)	34 (44)	20 (51)
Never	62 (53)	44 (56)	18 (46)
Histology			
Nonsquamous ^a	115 (98)	77 (99)	38 (97)
Squamous	2 (2)	1 (1)	1 (3)
Brain metastases at study entry	36 (31)	21 (27)	15 (38)
Summary of <i>EGFR</i> mutation types ^b			
Ex19del	60 (51)	41 (53)	19 (49)
L858R	37 (32)	25 (32)	12 (31)
T790M	32 (27)	26 (33)	6 (15)
G719X	6 (5)	5 (6)	1 (3)
L861G	5 (4)	3 (4)	2 (5)
Ex20ins	5 (4)	2 (3)	3 (8)
C797S	1 (1)	0	1 (3)
Other <i>EGFR</i> mutation	7 (6)	5 (6)	2 (5)
Unknown <i>EGFR</i> mutation	3 (3)	3 (4)	0
Previous lines of systemic therapies for advanced or metastatic disease			
Median (range)	3 (1-5)	3 (1-5)	2 (1-5)
1-2	51 (44)	28 (36)	23 (59)
3	36 (31)	23 (29)	13 (33)
≥4	30 (26)	27 (35)	3 (8)
Previous cytotoxic systemic therapy ^c			
Platinum-based chemotherapy	116 (99)	78 (100)	38 (97)
Nonplatinum chemotherapy	116 (99)	77 (99)	39 (100)
Anti-PD-1/anti-PD-L1 immunotherapy	34 (29)	25 (32)	9 (23)
Other	40 (34)	28 (36)	12 (31)
Previous <i>EGFR</i> -directed therapy			
First- or second-generation TKI ^d			
As first line	52 (44)	37 (47)	15 (38)
As second line	9 (8)	7 (9)	2 (5)
Osimertinib			
As first line	47 (40)	27 (35)	20 (51)
As second line	34 (29)	20 (26)	14 (36)
Any line	96 (82)	61 (78)	35 (90)

Note: Data are n (%) unless otherwise indicated.

^aIncludes adenocarcinoma and other subtypes; no patients had large- or small-cell carcinomas.

^bPatients may have had at least one *EGFR* mutation with or without a non-*EGFR* mutation.

^cPatients may have received more than one type of cytotoxic systemic therapy.

^dAfatinib, erlotinib, or gefitinib.

Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*m, epidermal growth factor receptor mutated; Ex19del, exon 19 deletion; Ex20ins, exon 20 insertion; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; TKI, tyrosine kinase inhibitor.

exon 20 insertion mutation (Fig. 2A). Patients may have had tumors with more than one *EGFR* mutation with or without a non-*EGFR* mutation. Other mutation types

identified alongside *EGFR* are presented in Supplementary Table 1. The median study duration for the two pooled studies was 16.9 months (range, 10.9–23.1).

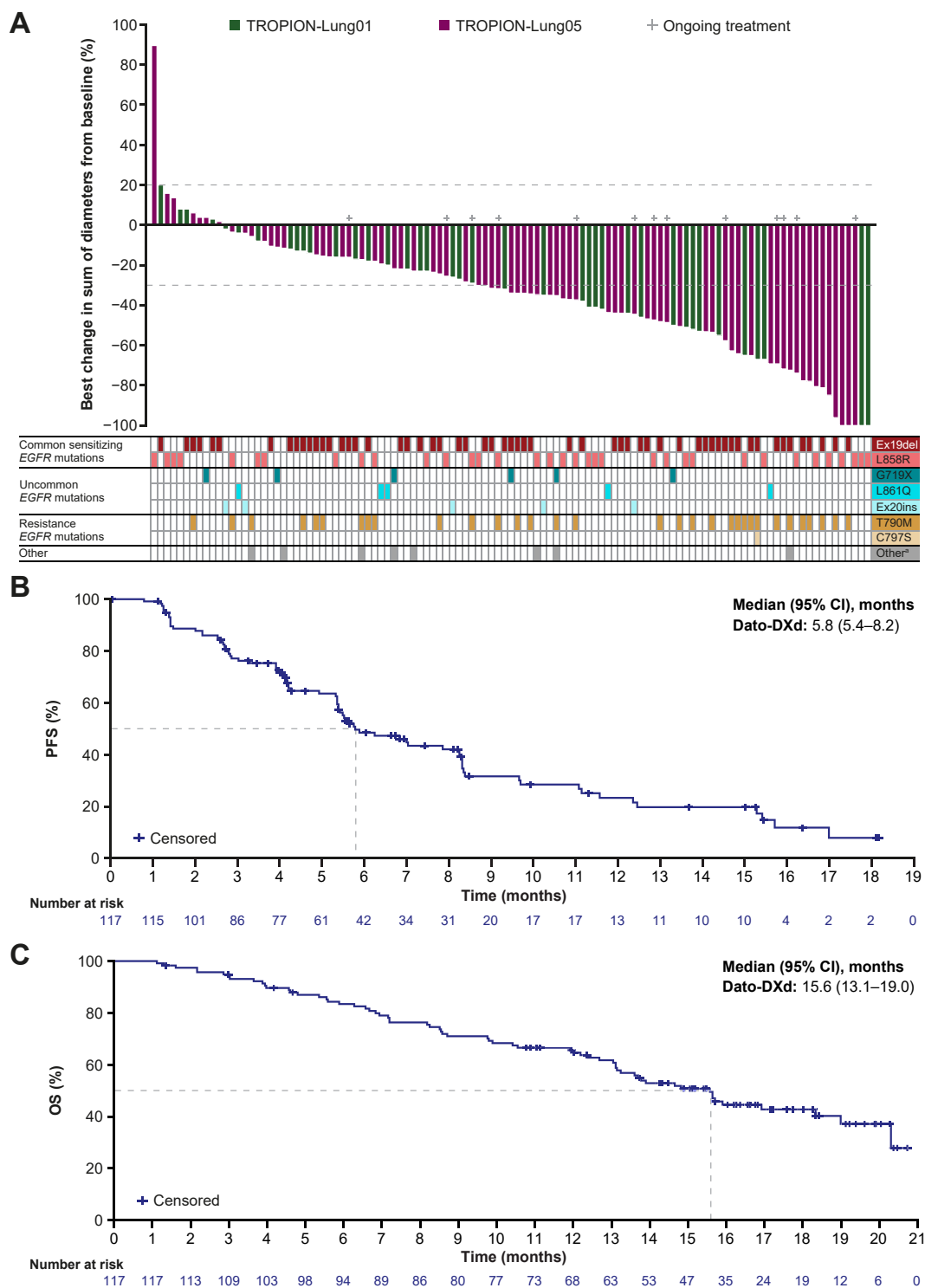


Figure 2. Tumor response and survival with Dato-DXd. (A) Best percentage change from baseline in the SOD and EGFR mutation status. Kaplan-Meier curve of (B) exploratory PFS by BICR and (C) exploratory OS. T790M mutations were included as an EGFR-dependent TKI-resistance mechanism to first- and second-generation TKI therapy. ^aIncludes S768I, Ex19ins, V323I p.1759M, G724S, and unknown. BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; Ex19ins, exon 19 insertion; OS, overall survival; PFS, progression-free survival; SOD, sum of diameters; TKI, tyrosine kinase inhibitor.

The median number of previous treatment regimens in the advanced or metastatic disease setting was 3 (range, 1–5), with one-quarter of patients having

received at least four lines. All but one patient (99%) in the pool had previously received platinum-based chemotherapy, and 29% of patients had received anti-

programmed cell death protein 1/anti-programmed cell death-ligand 1 immunotherapy. With respect to previous EGFR-directed therapy, 44% of patients received a first- or second-generation TKI as their initial line of treatment. Overall, 82% of patients had received previous osimertinib, including 40% as first-line therapy (Table 1).

Efficacy

The confirmed ORR in the pooled population was 43% (95% CI: 34%–52%), including five CRs (4%) and 45 PRs (38%) (Table 2). Best percentage change from baseline in target lesion size is presented in Figure 2A. Activity was observed across a range of *EGFR* mutation types and in patients whose tumors harbored multiple mutations within this receptor (Fig. 2A). The overall DCR was 86% (95% CI: 79%–92%) and the median TTR was 1.9 months (range, 1.2–11.3 mo). Responses were durable, with a median DOR of 7.0 months (95% CI: 4.2–9.8 mo). The median PFS for the pooled population was 5.8 months (95% CI: 5.4–8.2 mo) (Fig. 2B), and the median OS was 15.6 months (95% CI: 13.1–19.0 mo) (Fig. 2C).

An additional ad hoc analysis of the subset of patients within the pool who had received previous osimertinib treatment reported comparable outcomes to the overall population, with a confirmed ORR of 45% (95% CI: 35%–55%), median DOR of 6.9 months (95% CI: 4.2–9.8 mo), and a median DCR of 85% (95% CI: 77%–92%) (Supplementary Table 2).

Safety

All 117 pooled patients were included in the safety analysis, and the overall safety summary is presented in

Table 3. The median Dato-DXd treatment duration was 6.1 months (range, 0.7–20.6). Treatment-related AEs (TRAEs) of any grade occurred in 95% of patients, with grade greater than or equal to 3 TRAEs seen in 23% of patients. The most common TRAEs included stomatitis (any grade, 60%; grade ≥ 3 , 9%), alopecia (49%), and nausea (46%; grade ≥ 3 , 0%) (Supplementary Table 3). Serious TRAEs were infrequent (any grade, 8%; grade ≥ 3 , 6%) and no treatment-related deaths occurred (Table 3). TRAEs led to dose delays in 23% of patients, dose reductions in 22%, and treatment discontinuations in 5%. Outcomes for patients with pretreated advanced or metastatic NSCLC in the TROPION-PanTumor01 study have previously been reported¹⁹; the overall safety profile remained consistent when additional patients with *EGFR* mutations from that study were included in the current pool (Supplementary Table 4).

Treatment-emergent AESIs for Dato-DXd are presented in Table 4. The most common AESI was oral mucositis or stomatitis. Overall, 81 patients (69%) experienced an any-grade event of oral mucositis or stomatitis, with grade greater than or equal to 3 events seen in 9% of patients. Dose reductions or delays occurred in 14% and 8% of patients, respectively, and no patient discontinued treatment owing to oral mucositis or stomatitis. Grade 1 events occurred in 36% of patients in the pool and 33% experienced clinically symptomatic grade greater than or equal to 2 events. The median time to onset of grade greater than or equal to 2 events was 29 days (range, 4–412), and the median time to resolution from the first grade greater than or equal to 2 event to asymptomatic (grade 1 or resolved) was 50 days (range, 8–240). Overall, 82% of cases recovered in this

Table 2. Exploratory Efficacy Outcomes in *EGFR*-Mutated Patient Subsets From TROPION-Lung05 and TROPION-Lung01

Efficacy Outcome	<i>EGFR</i> m Pool	TROPION-Lung05	TROPION-Lung01	
	Dato-DXd (N = 117)	Dato-DXd (n = 78)	Dato-DXd (n = 39)	Docetaxel (n = 45)
Confirmed ORR, ^{a,b} % (95% CI)	43 (34–52)	44 (32–55)	41 (26–58)	9 (3–21)
Best overall response, n (%)				
CR	5 (4)	4 (5)	1 (3)	0
PR	45 (38)	30 (38)	15 (38)	4 (9)
SD	48 (41)	27 (35)	21 (54)	18 (40)
Non-CR or non-PD	3 (3)	3 (4)	0	0
PD	12 (10)	10 (13)	2 (5)	10 (22)
NE	4 (3)	4 (5)	0	13 (29)
Median DOR, ^a mo (95% CI)	7.0 (4.2–9.8)	7.0 (4.2–10.2)	6.9 (2.9–NE)	NE (3.6–NE)
DCR, ^{a,c} % (95% CI)	86 (79–92)	82 (72–90)	95 (83–99)	49 (34–64)
Median PFS, ^a mo (95% CI)	5.8 (5.4–8.2)	5.8 (5.4–8.3)	6.8 (4.2–8.2)	2.7 (1.5–4.4)
Median OS, mo (95% CI)	15.6 (13.1–19.0)	18.3 (12.4–NE)	15.6 (12.0–16.9)	12.8 (6.9–17.2)

^aAssessed by BICR per RECIST version 1.1.

^bCR + PR.

^cCR + PR + SD or non-CR or non-PD.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; *EGFR*m, epidermal growth factor receptor mutated; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Table 3. Overall Safety Summary

Patients With Events	EGFRm Pool (N = 117)
TRAEs	
Any	111 (95)
Grade ≥ 3	27 (23)
Serious TRAEs	
Any	9 (8)
Grade ≥ 3	7 (6)
TRAEs leading to:	
Dose delay	27 (23)
Dose reduction	26 (22)
Treatment discontinuation	6 (5)
Death	0 (0)

Note: Data are n (%).

EGFRm, epidermal growth factor receptor mutated; TRAE, treatment-related adverse event.

time frame. Ocular surface events of any grade were observed in 32% of all patients, with a median time to onset of 120 days (range, 16–353). The most common events were grade less than or equal to 2 cases of dry eye (12%), blurred vision (7%), and keratitis (7%). Three grade 3 events (3%) were seen: one case each of corneal disorder (1%), punctate keratitis (1%), and cornea verticillata (1%). Adjudicated drug-related ILD or pneumonitis occurred in 4% of patients (grade 1, n = 1; grade 2, n = 3; grade 3, n = 1), and no grade 4 or fatal events occurred.

Discussion

Previous clinical findings for Dato-DXd in pretreated patients with advanced or metastatic NSCLC have

Table 4. Adverse Events of Special Interest

Patients With Events ^a	EGFRm Pool (N = 117)
Oral mucositis or stomatitis	
Any grade	81 (69)
Grade 1	42 (36)
Grade 2	28 (24)
Grade 3	11 (9)
Ocular surface events	
Any grade	38 (32)
Grade 1	24 (21)
Grade 2	11 (9)
Grade 3	3 (3)
Adjudicated drug-related ILD or pneumonitis	
Any grade	5 (4)
Grade 1	1 (1)
Grade 2	3 (3)
Grade 3	1 (1)

Note: Data are n (%).

^aNo grade 4 or 5 AESIs occurred.

AESI, adverse event of special interest; EGFRm, epidermal growth factor receptor mutated; ILD, interstitial lung disease.

suggested that those with actionable genomic alterations may experience greater clinical benefit than those without.^{19,20} This pooled analysis aimed to describe the efficacy and safety profile of Dato-DXd in a defined subset of patients with *EGFR* mutations enrolled across one phase II and one phase III Dato-DXd trial. The study population consisted of 117 heavily pretreated patients who had received a median of three previous lines of therapy in the advanced or metastatic setting, including *EGFR*-directed therapy and platinum-based chemotherapy. This exploratory analysis revealed that Dato-DXd elicited robust and durable clinical efficacy, as evidenced by a confirmed ORR of 43% (95% CI: 34%–52%) and median DOR of 7.0 months (95% CI: 4.2–9.8 mo) and supported by a median PFS and OS of 5.8 (95% CI: 5.4–8.2 mo) and 15.6 months (95% CI: 13.1–19.0 mo), respectively. These pooled outcomes highlight the consistency in Dato-DXd activity in this patient population across the two individual trials. The safety profile was also consistent with the overall populations from TROPION-Lung05 and TROPION-Lung01,^{20,21} and no new safety signals were identified.

For patients with *EGFR*-mutated NSCLC, there is an important unmet need for effective and tolerable treatment options after progression on first- and second-line therapies. Approximately half of patients with activating *EGFR* mutations acquire the secondary T790M mutation when treated with first- and second-generation TKIs, leading to subsequent disease progression.^{24–26} Osimertinib targets the acquired T790M mutation in addition to the classical activating mutations³; the FLAURA trial (NCT02296125) reported superior survival with osimertinib as a first-line therapy compared with first-generation TKIs.^{7,27} However, despite initial disease control, resistance to osimertinib develops for most patients.⁹ Potential second-line treatment options after progression on *EGFR*-directed therapies include platinum-based chemotherapy, amivantamab with chemotherapy, or atezolizumab–bevacizumab–paclitaxel–carboplatin.^{4,5} However, current guidelines do not address treatment recommendations for patients in the post-*EGFR*-directed and post-platinum therapeutic setting.^{4,5} A recent real-world study has reported that, after progression on osimertinib and platinum-based chemotherapy, patients are treated with docetaxel with or without ramucirumab, immune checkpoint inhibitors alone or in combination, first- or second-generation TKIs, osimertinib rechallenge, or platinum rechallenge. In that report, the median OS with these therapies ranged from 9.6 to 12.3 months.¹³ Overall, these currently used treatments after progression on *EGFR*-directed therapies and chemotherapy seem to confer limited clinical benefit.

A key finding of the current pooled analysis was that Dato-DXd had broad activity across a range of *EGFR*

mutation types, encompassing both common and uncommon sensitizing and resistance mutations and regardless of the presence or absence of secondary alterations. This activity was observed in a heavily pretreated population, with a median of three previous lines of therapy including both EGFR-directed therapy and chemotherapy. In addition, previous osimertinib treatment seemed to have little effect on responsiveness to Dato-DXd, with comparable efficacy outcomes observed in patients with previous osimertinib exposure and the overall population. Taken together, these data suggest that Dato-DXd could be a potential treatment option for patients with *EGFR*-mutated disease after progression on EGFR-directed therapy and chemotherapy. The underlying biological rationale for the consistently enhanced activity of Dato-DXd observed across multiple clinical studies in *EGFR*-mutated NSCLC is under investigation and likely related to both the complex mechanism of action of Dato-DXd itself and the known pathophysiology of *EGFR*-mutated tumor cells. Accordingly, several nonclinical assessments are ongoing, evaluating hypotheses derived from three key areas involving TROP2 expression and expression patterns, enhanced ADC internalization, and *EGFR*-mutated tumor cell susceptibility to the Dato-DXd payload.

Since the initiation of the TROPION-Lung05 and TROPION-Lung01 studies, the treatment landscape for patients with *EGFR*-mutated advanced or metastatic NSCLC has evolved rapidly.²⁸ Findings from pivotal studies such as MARIPOSA, FLAURA, and FLAURA2 have been practice changing in the first- and second-line settings, and the combination of osimertinib plus chemotherapy is now indicated for use as first-line therapy. The observed activity of Dato-DXd in the post-EGFR-directed and post-platinum therapy setting remains of clear relevance, and based on the results described here, further clinical evaluation of Dato-DXd is underway. The randomized phase III TROPION-Lung15 trial (NCT06417814) is investigating Dato-DXd both as monotherapy and in combination with osimertinib versus platinum-based chemotherapy in patients with *EGFR*-mutated advanced or metastatic NSCLC whose disease has progressed on previous osimertinib treatment.²⁹ Another randomized phase III study, TROPION-Lung14 (NCT06350097), evaluating Dato-DXd plus osimertinib versus osimertinib alone as first-line treatment for *EGFR*-mutated advanced or metastatic nonsquamous NSCLC has recently been initiated.³⁰ The findings of these and other studies will be informative as to the clinical application of Dato-DXd within this dynamic treatment landscape.

A limited number of other novel agents are presently under clinical investigation in patients who have progressed on EGFR-directed therapy and platinum-based chemotherapy. The phase II HERTHENA-Lung01 trial

(NCT04619004) of patritumab deruxtecan, a human EGFR 3-directed ADC bearing the same payload as Dato-DXd, reported an ORR of 30% and a median PFS of 5.5 months in patients who had received previous EGFR TKI therapy and platinum-based chemotherapy.³¹ BL-B01D1, a bispecific ADC targeting EGFR and human EGFR 3, has shown promise in a phase I trial (NCT05194982), with an ORR of 63% in patients from China with *EGFR*-mutated locally advanced or metastatic NSCLC, most of whom had been treated with a third-generation EGFR TKI and platinum-based chemotherapy.³²

No new or unexpected safety signals were observed in this pooled analysis of patients with *EGFR*-mutated NSCLC, and the safety profile of Dato-DXd was consistent with the original findings from TROPION-Lung05 and TROPION-Lung01.^{20,21} Oral mucositis or stomatitis, an AESI for Dato-DXd, occurred in 69% of patients, one-third of whom required dose adjustments owing to grade greater than or equal to 2 events, but did not lead to any treatment discontinuations. Similar incidences of oral mucositis or stomatitis have been reported in other studies of Dato-DXd in both breast and lung cancer; events were generally low grade and resulted in few discontinuations ($\leq 2\%$ of patients across trials).^{33–35} Recommendations for prophylaxis and management of Dato-DXd-induced oral mucositis or stomatitis are in place and were implemented during the studies.³⁵ ILD is an identified risk factor for DXd-containing ADCs,^{31,36} including Dato-DXd^{17,35}; the importance of early detection and monitoring is recognized in current management guidelines.³⁵ ILD is the most frequent cause of drug-related mortality from EGFR TKIs and is an important consideration for clinical rechallenge with osimertinib.^{37,38} Although most patients (82%) included in this pooled analysis had received at least one previous line of osimertinib therapy, the overall incidence of adjudicated drug-related ILD was low (4%) and no grade 4 or fatal events were seen. Together with the encouraging antitumor activity observed, the safety findings provide further support for a favorable benefit-risk profile of Dato-DXd in patients with *EGFR*-mutated advanced or metastatic NSCLC.

A strength of pooled analyses is that the increased sample size enables the detection of effects that individual studies might miss. This is particularly useful when analyzing potentially small subgroups of patients with specific actionable genomic alterations. Despite similarities in the trial eligibility criteria between the two studies and consistency in the outcomes of Dato-DXd across studies reported here, a general limitation of pooled analyses is variability among study designs, primary end points, patient populations, and treatment durations. In addition, both TROPION-Lung05 and TROPION-Lung01 were open-label studies with a

potential risk to introduce bias. In this regard, tumor assessments for ORR and PFS efficacy outcomes were evaluated using BICR across both trials, and the resulting data sets were consistent. The pooled population was also predominantly Asian (69%), not unexpected given the high prevalence of *EGFR* mutations seen in this population.² Clinical evidence supports that no notable differences exist between Asian and Western patient populations in terms of responsiveness to *EGFR*-targeted agents. Furthermore, subset analyses of Asian patients who received Dato-DXd in TROPION-Lung05, including those with *EGFR*-mutated disease (n = 47), reported consistent results with the global trial population.³⁹

In summary, the results of this pooled analysis support Dato-DXd as a potential new treatment option for patients with advanced or metastatic NSCLC harboring a range of *EGFR* mutations who have progressed on *EGFR*-directed therapy and platinum-based chemotherapy.

CReDiT Authorship Contribution Statement

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Data Sharing Statement

Deidentified individual participant data and applicable supporting clinical trial documents may be available on request at Vivli – Center for Global Clinical Research Data. In cases in which trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc., will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found online at <https://vivli.org/ourmember/daiichi-sankyo/>.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <https://doi.org/10.1016/j.jtho.2025.06.002>.

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