Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non–Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study

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ABSTRACT

PURPOSE The randomized, open-label, global phase III TROPION-Lung01 study compared the efficacy and safety of datopotamab deruxtecan (Dato-DXd) versus docetaxel in patients with pretreated advanced/metastatic non–small cell lung cancer (NSCLC).

METHODS Patients received Dato-DXd 6 mg/kg or docetaxel 75 mg/m² once every 3 weeks. Dual primary end points were progression-free survival (PFS) and overall survival (OS). Objective response rate, duration of response, and safety were secondary end points.

RESULTS In total, 299 and 305 patients were randomly assigned to receive Dato-DXd or docetaxel, respectively. The median PFS was 4.4 months (95% CI, 4.2 to 5.6) with Dato-DXd and 3.7 months (95% CI, 2.9 to 4.2) with docetaxel (hazard ratio [HR], 0.75 [95% CI, 0.62 to 0.91]; $P = .004$). The median OS was 12.9 months (95% CI, 11.0 to 13.9) and 11.8 months (95% CI, 10.1 to 12.8), respectively (HR, 0.94 [95% CI, 0.78 to 1.14]; $P = .530$). In the prespecified nonsquamous histology subgroup, the median PFS was 5.5 versus 3.6 months (HR, 0.63 [95% CI, 0.51 to 0.79]) and the median OS was 14.6 versus 12.3 months (HR, 0.84 [95% CI, 0.68 to 1.05]). In the squamous histology subgroup, the median PFS was 2.8 versus 3.9 months (HR, 1.41 [95% CI, 0.95 to 2.08]) and the median OS was 7.6 versus 9.4 months (HR, 1.32 [95% CI, 0.91 to 1.92]). Grade ≥3 treatment-related adverse events occurred in 25.6% and 42.1% of patients, and any-grade adjudicated drug-related interstitial lung disease/pneumonitis occurred in 8.8% and 4.1% of patients, in the Dato-DXd and docetaxel groups, respectively.

CONCLUSION Dato-DXd significantly improved PFS versus docetaxel in patients with advanced/metastatic NSCLC, driven by patients with nonsquamous histology. OS showed a numerical benefit but did not reach statistical significance. No unexpected safety signals were observed.

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INTRODUCTION

Non–small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer diagnoses and can be broadly subclassified into nonsquamous and squamous histologic types (approximately 75% and 25% prevalence, respectively).[1,2] Historically, the 5-year survival rate among individuals with advanced/metastatic NSCLC has been <10%.[3] First-line immunotherapy and targeted therapies have improved survival and quality-of-life outcomes; however, most patients eventually progress, after which treatment options are limited.[4-7] Docetaxel-based regimens are the current standard of care in the second-line setting and beyond.[7] Unfortunately, survival outcomes remain poor and patients often experience substantial toxicity, underscoring a high unmet need.[8,9] Until now, no new

CONTEXT

Key Objective

Outcomes for patients with advanced/metastatic non–small cell lung cancer (NSCLC) who receive standard docetaxel-based chemotherapy after disease progression remain suboptimal. This global phase III study evaluated datopotamab deruxtecan (Dato-DXd) versus docetaxel in patients with previously treated NSCLC.

Knowledge Generated

Dato-DXd demonstrated a statistically significant improvement in progression-free survival (median, 4.4 *v* 3.7 months; hazard ratio [HR], 0.75; $P = .004$) and numerical improvement in overall survival (OS; median, 12.9 *v* 11.8 months; HR, 0.94; $P = .530$) over docetaxel; superior clinical benefits were observed in patients with nonsquamous histology. Grade ≥3 treatment-related adverse events and treatment discontinuations were less frequent with Dato-DXd than with docetaxel.

Relevance *(T.E. Stinchcombe)*

A prospective trial in patients with NSCLC with nonsquamous histology (with sufficient statistical power to detect a clinically relevant difference in OS) is warranted.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

monotherapies have shown superiority over docetaxel in clinical trials in biomarker-unselected populations after exposure to contemporary first-line agents.[10-12]

Datopotamab deruxtecan (Dato-DXd; DS-1062a) is an antibody–drug conjugate composed of a humanized trophoblast cell surface antigen 2 (TROP2)–directed monoclonal antibody covalently linked to a topoisomerase I inhibitor payload via a plasma-stable, cleavable linker.[13] After TROP2 binding and antibody–drug conjugate internalization, the deruxtecan payload is released within the target cell to induce DNA damage and subsequent cell death; the membrane permeability of deruxtecan also promotes cytotoxic bystander activity.[13]

Early-phase studies demonstrated promising results for Dato-DXd in heavily pretreated patients with NSCLC.[14,15] Here, we report the final analyses from the phase III TROPION-Lung01 clinical trial (ClinicalTrials.gov identifier: NCT04656652), evaluating the efficacy and safety of Dato-DXd compared with those of docetaxel in patients with previously treated advanced/metastatic NSCLC.

METHODS

Patients

Eligible patients had stage IIIB/C or IV NSCLC. Patients without actionable genomic alterations must have only received platinum-based chemotherapy and anti–PD-1/PD-L1 immunotherapy. Patients with protocol-specified actionable genomic alterations (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*) must have received one to two lines of targeted therapy and platinum-based chemotherapy, with or without anti–PD-1/PD-L1. Patients with clinically inactive or treated asymptomatic brain metastases were eligible. Patients were excluded if they had a current or suspected diagnosis or history of interstitial lung disease (ILD) requiring steroids. Full eligibility criteria are provided in the Protocol (online only).

Study Design and Treatment

TROPION-Lung01 is a randomized, open-label, global phase III study comparing the safety and efficacy of Dato-DXd versus docetaxel in patients with advanced/metastatic NSCLC (Appendix Fig A1, online only). Patients were randomly assigned 1:1 (stratified by histology, actionable genomic alteration status, geographic region, and immediate previous therapy with anti–PD-1/PD-L1) to receive Dato-DXd 6 mg/kg or docetaxel 75 mg/m² intravenously once every 3 weeks until disease progression, unacceptable toxicity, or other reasons. Crossover between study groups was not permitted.

This clinical trial was funded, sponsored, and designed by Daiichi Sankyo in collaboration with AstraZeneca, was approved by the institutional review board at each participating site, and was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations regarding the conduct of clinical research. All patients provided written informed consent before participation. Data were analyzed and interpreted by the authors and the funder (Daiichi Sankyo).

End Points and Assessments

The dual primary end points were progression-free survival (PFS) by blinded independent central review per

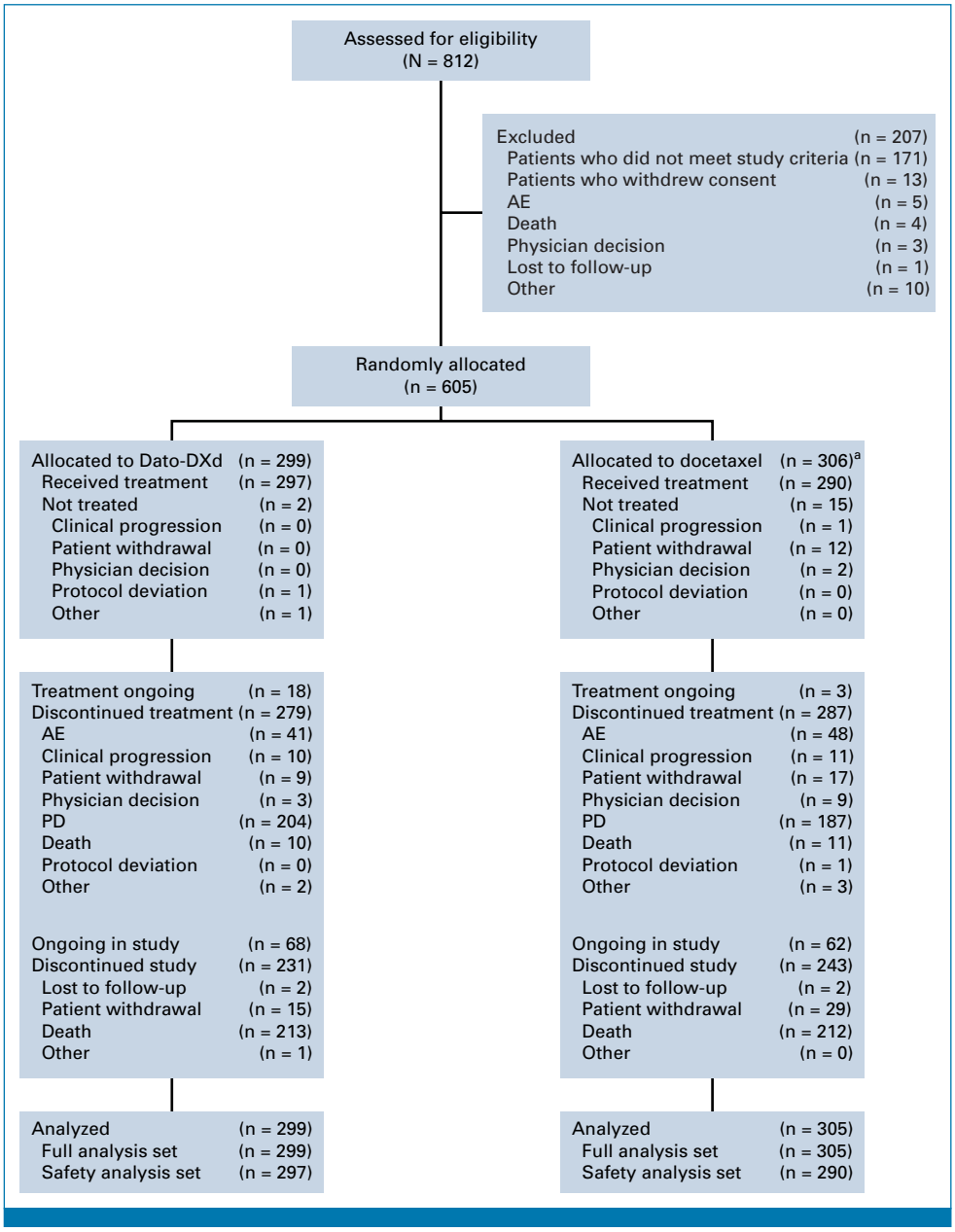

FIG 1. CONSORT diagram. Data cutoff: March 1, 2024. [a]One patient in the docetaxel treatment group was randomly assigned twice; treatment was not initiated under the first patient identifier, and only the second patient identifier was included. A total of 305 unique patients were allocated to docetaxel. AE, adverse event; Dato-DXd, datopotamab deruxtecan; PD, progressive disease.

RECIST version 1.1 and overall survival (OS). Objective response rate (ORR), duration of response (DOR), and safety were secondary end points. The Data Supplement (Table S1, online only) provides data cutoff dates for the analyses.

Treatment-related adverse events (TRAEs) were investigator-determined, coded, and graded per Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 and National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Treatment-emergent adverse events of special interest included oral mucositis/stomatitis, ocular surface events, and adjudicated ILD/pneumonitis; all were grouped terms of predefined MedDRA preferred terms. Treatment management guidelines were implemented and updated during the Dato-DXd clinical development program (Data Supplement, Tables S2 and S3).[16] An independent committee adjudicated any potential cases of ILD/pneumonitis to confirm that events were true cases and, if so, to determine severity and causality.

Tumor response by computed tomography or magnetic resonance imaging was conducted at baseline (within 28 days of random assignment) and then every 6 weeks

TABLE 1. Demographics and Clinical Characteristics of Patients at Baseline

Characteristic	Dato-DXd (n = 299)	Docetaxel (n = 305)
Age, years, median (range)	63.0 (26.0-84.0)	64.0 (24.0-88.0)
Sex, male, No. (%)	183 (61.2)	210 (68.9)
Race, No. (%)		
White	123 (41.1)	126 (41.3)
Asian	119 (39.8)	120 (39.3)
Black or African American	6 (2.0)	4 (1.3)
American Indian or Alaska Native	1 (0.3)	0
Other/missing	50 (16.7)	55 (18.0)
Ethnic group, No. (%)		
Hispanic or Latino	10 (3.3)	8 (2.6)
Not Hispanic or Latino	251 (83.9)	253 (83.0)
Unknown/missing	38 (12.7)	44 (14.4)
Geographic region, No. (%)		
Europe	137 (45.8)	152 (49.8)
Asia	113 (37.8)	118 (38.7)
North America	39 (13.0)	26 (8.5)
Australia	7 (2.3)	8 (2.6)
South America	3 (1.0)	1 (0.3)
Smoking status, No. (%)		
Current	39 (13.0)	42 (13.8)
Former	199 (66.6)	209 (68.5)
Never	61 (20.4)	52 (17.0)
Missing	0	2 (0.7)
ECOG performance status score, No. (%)[a]		
0	89 (29.8)	94 (30.8)
1	210 (70.2)	211 (69.2)
Histology, No. (%)		
Adenocarcinoma	222 (74.2)	223 (73.1)
Large cell	2 (0.7)	1 (0.3)
Squamous	65 (21.7)	71 (23.3)
Other	10 (3.3)	10 (3.3)
Actionable genomic alterations, No. (%)		
Absent	249 (83.3)	254 (83.3)
Present	50 (16.7)	51 (16.7)
PD-L1 expression, No. (%)		
<1%	104 (34.8)	116 (38.0)
≥1%	158 (52.8)	147 (48.2)
Unknown/missing	11 (3.7)	9 (3.0)
Not done	26 (8.7)	33 (10.8)
Brain metastases at baseline, No. (%)	79 (26.4)	91 (29.8)
Previous cancer therapy, No. (%)		
Platinum chemotherapy	297 (99.3)	305 (100)
Nonplatinum chemotherapy	298 (99.7)	304 (99.7)
Anti–PD-L1 therapy	263 (88.0)	268 (87.9)
Targeted therapy	46 (15.4)	50 (16.4)
Other	60 (20.1)	64 (21.0)
Previous lines of systemic therapy for metastatic disease, No. (%)[b]		
1	167 (55.9)	174 (57.0)

(continued on following page)

TABLE 1. Demographics and Clinical Characteristics of Patients at Baseline (continued)

Characteristic	Dato-DXd (n = 299)	Docetaxel (n = 305)
2	108 (36.1)	102 (33.4)
3	17 (5.7)	23 (7.5)
≥4	5 (1.7)	5 (1.6)

NOTE. Percentages are based on the number of patients in the full analysis set. Baseline is defined as the last available assessment before the start of study treatment. If a patient was randomly assigned but not treated, the last available assessment on or before the random assignment date was used as the baseline value.

Abbreviations: Dato-DXd, datopotamab deruxtecan; ECOG, Eastern Cooperative Oncology Group.

[a]Screening score.

[b]Two patients in the Dato-DXd treatment group and one patient in the docetaxel treatment group had no previous lines of systemic therapy in the advanced/metastatic setting. Per investigator reporting, these patients received previous systemic anticancer therapy in settings other than the advanced/metastatic setting.

(plus or minus 7 days) until disease progression. Assessment of response was via RECIST version 1.1 regardless of study treatment discontinuation or start of new anticancer therapy. All randomly assigned patients were followed for survival at least every 3 months after discontinuing the study drug, until the end of the study, or until consent was withdrawn.

Statistical Analysis

The study has dual primary end points, PFS and OS, and was considered positive if the hypothesis test for either one was successful. The planned sample size was approximately 590 patients. The full analysis set included all randomly assigned patients. One patient was randomly assigned twice; only one patient identifier was included in the full analysis set. For the primary analyses, approximately 425 PFS events by blinded independent central review were required to have a 97% power to detect a hazard ratio (HR) of 0.64 at a two-sided significance level of 0.008 and approximately 413 OS events were required to have at least a 90% power to detect an HR of 0.72 at a two-sided significance level of 0.042 (with alpha subject to rollover between PFS and OS).

PFS, OS, and DOR were analyzed using the Kaplan-Meier method, and the corresponding two-sided 95% CIs were determined according to the Brookmeyer and Crowley method. The stratified Cox regression model, stratified by two random assignment factors (histology and region), was used to estimate HRs between groups. Details of the random assignment stratification factors are provided in Appendix 1, Statistical Methods. The Clopper-Pearson method was used to calculate two-sided 95% CIs for ORR and disease control rate. All other end points were summarized descriptively. Safety was evaluated in all patients who received at least one dose of study drug. Data derived from electronic case report forms were used for post hoc analyses of histology and actionable genomic alteration status to account for any discrepancies with interactive response technology at random assignment.

RESULTS

Patients and Treatment

Between February 17, 2021, and November 7, 2022, there were 299 patients randomly assigned to receive Dato-DXd and 305 patients to receive docetaxel (Fig 1). Demographic and baseline characteristics were balanced between groups (Table 1). Most patients had tumors of nonsquamous histology (78.3% and 76.7% for Dato-DXd and docetaxel, respectively) and 16.7% of patients in each group had actionable genomic alterations (Table 1; Data Supplement, Table S4). Baseline characteristics by histologic subgroup are presented in the Data Supplement (Table S5).

The median follow-up for PFS was 10.9 months (95% CI, 9.8 to 12.5) and 9.6 months (95% CI, 8.2 to 11.9) with Dato-DXd and docetaxel, respectively. The median follow-up for OS was 23.1 months (95% CI, 22.0 to 24.8) with Dato-DXd and 23.1 months (95% CI, 21.7 to 24.2) with docetaxel. The median number of treatment cycles was 6.0 with Dato-DXd (range, 1-39) and 4.0 with docetaxel (range, 1-34). A similar proportion of patients treated with Dato-DXd (52.2%) or docetaxel (55.4%) received post-treatment anticancer therapy (Data Supplement, Table S6).

Efficacy

At the primary analysis for PFS, Dato-DXd showed a statistically significant improvement over docetaxel in the full analysis set: the median PFS was 4.4 months (95% CI, 4.2 to 5.6) and 3.7 months (95% CI, 2.9 to 4.2), respectively (HR, 0.75 [95% CI, 0.62 to 0.91]; $P = .004$; Fig 2A). Prespecified subgroup analyses showed benefit in favor of Dato-DXd, except for a differential effect seen with histology (Fig 2B). Among patients with nonsquamous tumors, the median PFS was 5.5 months (95% CI, 4.3 to 6.9) with Dato-DXd and 3.6 months (95% CI, 2.9 to 4.2) with docetaxel (HR, 0.63 [95% CI, 0.51 to 0.79]; Fig 2C). In patients with nonsquamous tumors with actionable genomic alterations, the median PFS was 5.7 months (95% CI, 4.2 to 8.2) with Dato-DXd and

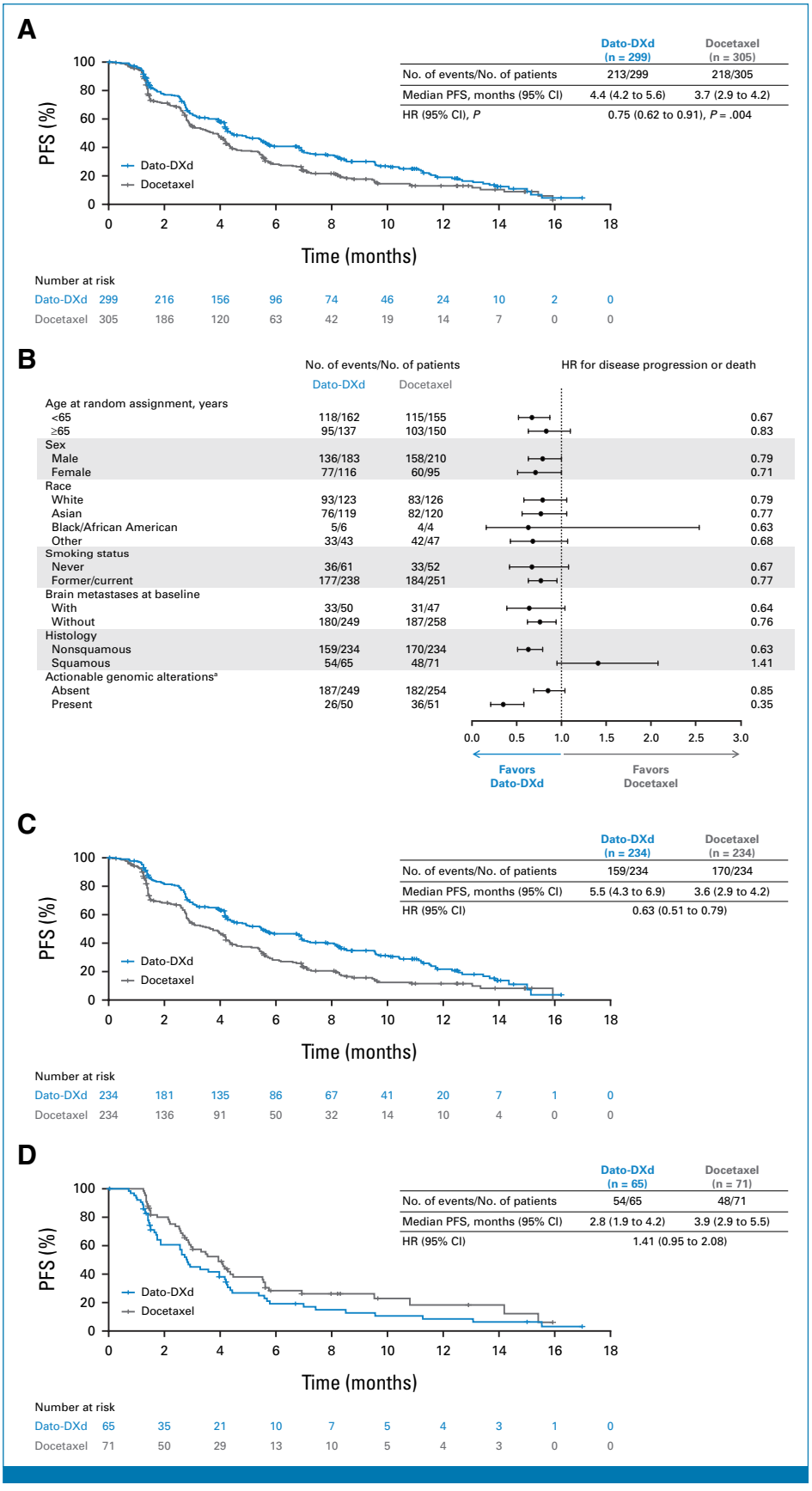

FIG 2. PFS by treatment and key subgroups. Data cutoff: March 29, 2023. (A) Kaplan-Meier curves for PFS in the full analysis set, (B) HRs of PFS in key subgroups, (C) Kaplan-Meier curves for PFS in patients with nonsquamous histology, and (D) Kaplan-Meier curves (continued on following page)

FIG 2. (Continued). for PFS in patients with squamous histology. PFS was assessed by blinded independent central review. Tick marks in the Kaplan-Meier curves represent censored data. HRs and CIs in the forest plot were calculated on the basis of the patient data in the electronic case report forms for the histology and actionable genomic alteration subgroups. [a]Regardless of histology. Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; PFS, progression-free survival.

2.6 months (95% CI, 1.4 to 3.7) with docetaxel (HR, 0.35; 95% CI, 0.21 to 0.60; Data Supplement, Table S7). In patients with squamous tumors, the median PFS was 2.8 months (95% CI, 1.9 to 4.2) and 3.9 months (95% CI, 2.9 to 5.5) for Dato-DXd and docetaxel, respectively (HR, 1.41 [95% CI, 0.95 to 2.08]; Fig 2D). Statistical testing for interaction between treatment and histology provided further support for the PFS findings by histology (Cox regression interaction, P = .0006; Data Supplement, Table S8).

At the final analysis for OS, Dato-DXd showed a numerical, although not statistically significant, improvement over docetaxel in the full analysis set. The median OS was 12.9 months (95% CI, 11.0 to 13.9) with Dato-DXd and 11.8 months (95% CI, 10.1 to 12.8) with docetaxel (HR, 0.94 [95% CI, 0.78 to 1.14]; P = .530; Fig 3A). Most prespecified subgroups tended to numerically favor Dato-DXd or showed no difference, with divergence seen on the basis of histology and in subgroups with small numbers of patients (Fig 3B). Among patients with nonsquamous tumors, the median OS was 14.6 months (95% CI, 12.4 to 16.0) with Dato-DXd and 12.3 months (95% CI, 10.7 to 14.0) with docetaxel (HR, 0.84 [95% CI, 0.68 to 1.05]; Fig 3C). In patients with nonsquamous tumors with actionable genomic alterations, the median OS was 15.6 months (95% CI, 12.0 to 16.9) with Dato-DXd and 9.8 months (95% CI, 6.2 to 14.8) with docetaxel (HR, 0.65 [95% CI, 0.40 to 1.08]; Data Supplement, Table S7). In patients with squamous tumors, the median OS was 7.6 months (95% CI, 5.0 to 11.0) and 9.4 months (95% CI, 7.2 to 12.5) with Dato-DXd and docetaxel, respectively (HR, 1.32 [95% CI, 0.91 to 1.92]; Fig 3D). Interaction testing between treatment and histology also supported the OS histologic findings (Cox regression interaction, P = .0312; Data Supplement, Table S8).

The percentage of patients with a confirmed objective response by blinded independent central review was 26.4% (95% CI, 21.5 to 31.8) with Dato-DXd and 12.8% (95% CI, 9.3 to 17.1) with docetaxel (Table 2). Responses to Dato-DXd (median 7.1 months; 95% CI, 5.6 to 10.9) were more durable than responses to docetaxel (median 5.6 months; 95% CI, 5.4 to 8.1). Consistent with the survival findings, superior secondary efficacy outcomes were observed for Dato-DXd compared with docetaxel in the nonsquamous subgroup (Table 2) and these occurred irrespective of actionable genomic alteration status (Data Supplement, Table S7).

Safety

The safety analysis set included 297 and 290 treated patients in the Dato-DXd and docetaxel groups, respectively. The median treatment durations were 4.2 months (range, 0.7-27.2) with Dato-DXd and 2.8 months (range, 0.7-25.3) with docetaxel. The incidence of any-grade TRAEs was similar in both groups (87.5% and 86.9%, respectively; Table 3). Grade ≥3 TRAEs occurred at rates of 25.6% and 42.1%, serious TRAEs at 11.1% and 12.8%, dose reductions at 20.2% and 29.7%, and treatment discontinuations at 8.1% and 12.1% for Dato-DXd and docetaxel, respectively. No late-onset toxicities were observed for Dato-DXd in this study. Three patients (1.0%) treated with Dato-DXd and 2 (0.7%) with docetaxel had investigator-assessed TRAEs associated with death: two cases of ILD/pneumonitis and one of sepsis (Dato-DXd) and one case of ILD/pneumonitis and one of septic shock (docetaxel).

For Dato-DXd, the most frequently occurring any-grade TRAEs were stomatitis (141 patients [47.5%]) and nausea (101 patients [34.0%]), both of which were more frequent than in the docetaxel group (45 [15.5%] and 48 [16.6%] patients, respectively; Table 4). In patients receiving docetaxel, the most frequent any-grade TRAEs were alopecia (101 patients [34.8%]), neutropenia (76 [26.2%]), and anemia (60 [20.7%]). Febrile neutropenia (any grade) occurred in one patient (0.3%) receiving Dato-DXd and in 20 (6.9%) receiving docetaxel. Twenty patients (6.7%) receiving Dato-DXd experienced grade ≥3 stomatitis, whereas 12 (4.0%) experienced grade ≥3 anemia. With docetaxel, neutropenia (68 patients [23.4%]) and leukopenia (38 [13.1%]) were the most frequent grade ≥3 TRAEs.

Treatment-emergent adverse events of special interest for Dato-DXd are summarized in the Data Supplement (Tables S9 and S10). Oral mucositis/stomatitis occurred in 164 patients (55.2%) receiving Dato-DXd versus 60 (20.7%) receiving docetaxel; most events with Dato-DXd were grade 1 (82 [27.6%]) or 2 (62 [20.9%]). Dose reductions because of oral mucositis/stomatitis occurred in 31 patients (10.4%), and discontinuations occurred in 2 (0.7%) who received Dato-DXd. The median time to onset for stomatitis was 15.0 days with Dato-DXd and 9.0 with docetaxel (assessed by the investigator). The most frequently reported ocular surface events with Dato-DXd were lacrimation increased (23 patients [7.7%]) and dry eye (21 [7.1%]), all of which were mild or moderate; any-grade and grade ≥3 keratitis occurred in 12 (4.0%) and 4 (1.3%) patients, respectively. Adjudicated drug-related ILD occurred in 26 (8.8%) and 12 (4.1%) patients in the Dato-DXd and docetaxel groups, respectively (Table 4). The median time to onset was 52.0 days with Dato-DXd and 42.0 with docetaxel (assessed by adjudication). With Dato-DXd, two (0.7%) events were grade 1. Treatment discontinuations occurred in 15 patients (5.1%); 13 (4.4%)

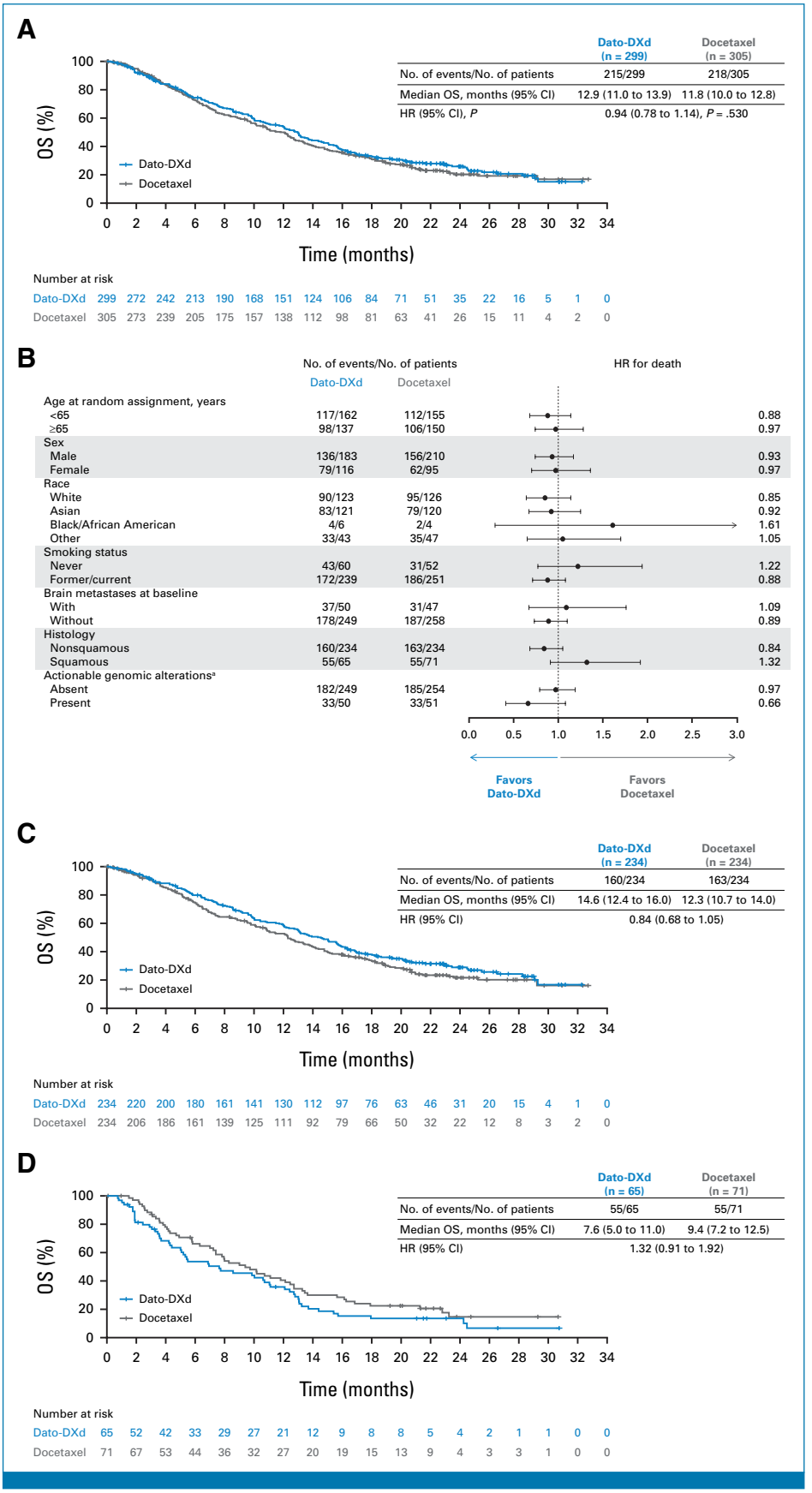

FIG 3. OS by treatment and key subgroups. Data cutoff: March 1, 2024. (A) Kaplan-Meier curves for OS in the full analysis set, (B) HRs of OS in key subgroups, (C) Kaplan-Meier curves for OS in patients with nonsquamous histology, and (D) Kaplan-Meier curves for OS (continued on following page)

FIG 3. (Continued). in patients with squamous histology. Tick marks in the Kaplan-Meier curves represent censored data. HRs and CIs in the forest plot were calculated on the basis of the patient data in the electronic case report forms for the histology and actionable genomic alteration subgroups. [a]Regardless of histology. Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; OS, overall survival.

and 11 patients (3.7%) experienced grade 2 and grade ≥3 events, respectively. Seven patients (2.4%) with adjudicated drug-related ILD died (4 of 232 patients [1.7%] with nonsquamous and 3 of 65 [4.6%] with squamous histologies). Four of these seven cases had the investigator-assessed cause of death attributed to disease progression.

DISCUSSION

TROPION-Lung01 met its dual primary end point of PFS, showing a statistically significant improvement for Dato-DXd over docetaxel in patients with pretreated advanced/metastatic NSCLC. Dato-DXd was also associated with doubling of the ORR and longer DOR compared with docetaxel. Dato-DXd is the first systemic monotherapy to show superior efficacy to docetaxel in a head-to-head, randomized, phase III clinical study of biomarker-unselected patients with NSCLC previously exposed to immuno- or targeted therapies.

A key finding of this study is that the clinical activity of Dato-DXd monotherapy is distinctly different in histologic subgroups of NSCLC. In patients with nonsquamous histology, PFS with Dato-DXd was superior to what was seen with docetaxel and improved efficacy was seen versus docetaxel for all other end points, regardless of actionable genomic alteration status. Histology was a prespecified stratification factor because of the well-known biologic differences and differing sensitivities of histologic subtypes to therapeutic agents[17-19] although the study was not powered to demonstrate statistical significance. These results have been independently supported by findings from ICARUS-Lung01[20] and TROPION-PanTumor02,[21] both of which showed improved ORR and PFS for Dato-DXd in nonsquamous NSCLC. The biologic rationale for the differential efficacy of Dato-DXd by histology is likely to be multifactorial because of its mechanism of action. Dato-DXd activity is dependent on internalization because the linker is cleaved intracellularly.[13] In this regard, precise computational pathology methods may offer insights into the subcellular localization and heterogeneity of TROP2 expression,[22] which could further explain the histologic differences of TROP2 internalization capacity. In addition, lysosomal proteases (which cleave the Dato-DXd linker) and drug efflux pumps are differentially expressed in NSCLC histologic subgroups, potentially affecting Dato-DXd activity.[23-25] Although the benefit of Dato-DXd relative to docetaxel appears to be numerically greater in the actionable genomic alteration subgroup, it is likely that this is driven by limitations of docetaxel. Furthermore, the finding that patients with actionable genomic alterations also tended to respond better to Dato-DXd than those without suggests that histology might not be the only factor that influences Dato-DXd activity in patients with NSCLC.

OS, the second dual primary end point, did not reach statistical significance in the full analysis set. The poorer efficacy identified in patients with squamous histology might have also negatively affected survival outcomes in the overall population. In patients with nonsquamous histology, PFS and OS each showed benefit for Dato-DXd (median improvements of 1.9 months [HR, 0.63] and 2.3 months [HR, 0.84], respectively), suggesting that the delay in disease progression contributed to a clinically meaningful increase in survival (although the study was not powered to show the statistical significance of any improvements in survival in the patient subgroups). Furthermore, in nonsquamous NSCLC, patients with and without actionable genomic alterations had better PFS, OS, and ORR with Dato-DXd. Conversely, with docetaxel, patients with actionable genomic alterations had reduced efficacy outcomes compared with patients without.

Metastatic NSCLC has historically been difficult to treat, especially in patients who progress after immunotherapy or targeted therapies.[4-7] Although not the only option, docetaxel has been the foundation of second-line treatment for metastatic NSCLC for over two decades[26]; however, it is associated with modest clinical benefit at the cost of substantial toxicity.[8,9,26-29] The REVEL trial that evaluated the addition of ramucirumab to docetaxel is the only study to date to show improved combinatorial activity over docetaxel alone (median PFS, 4.5 *v* 3.0 months; ORR, 23% *v* 14% [total population]; median OS, 11.1 *v* 9.7 months in patients with nonsquamous disease).[27] Other studies assessing novel therapeutic approaches have failed to demonstrate benefit over docetaxel, including SAPPHIRE (sitravatinib plus nivolumab),[10] CONTACT-01 (atezolizumab plus cabozantinib),[11] and LEAP-008 (lenvatinib with or without pembrolizumab).[12] More recently, EVOKE-01, evaluating sacituzumab govitecan (a TROP2-directed antibody–drug conjugate with a plasma-labile linker[30]) in a similar NSCLC population, failed to meet its primary end point of improved OS compared with docetaxel, with no improvement in PFS or ORR compared with docetaxel.[31] These results highlight the challenges of treating this patient population and the need for more effective and tolerable treatment options for patients who progress after first-line therapy.

The overall safety profile of Dato-DXd was generally favorable compared with docetaxel. Despite the longer treatment duration, there were fewer grade ≥3 TRAEs, serious adverse events, dose reductions, and discontinuations

TABLE 2. Overall Efficacy for All Patients and by Histology

	All Patients		Nonsquamous Histology		Squamous Histology	
Variable	Dato-DXd (n = 299)	Docetaxel (n = 305)	Dato-DXd (n = 234)	Docetaxel (n = 234)	Dato-DXd (n = 65)	Docetaxel (n = 71)
PFS, months, median (95% CI)[a,b]	4.4 (4.2 to 5.6)	3.7 (2.9 to 4.2)	5.5 (4.3 to 6.9)	3.6 (2.9 to 4.2)	2.8 (1.9 to 4.2)	3.9 (2.9 to 5.5)
HR for disease progression or death (95% CI)	0.75 (0.62 to 0.91)		0.63 (0.51 to 0.79)		1.41 (0.95 to 2.08)	
P	.004		NA		NA	
OS, months, median (95% CI)[c,d]	12.9 (11.0 to 13.9)	11.8 (10.1 to 12.8)	14.6 (12.4 to 16.0)	12.3 (10.7 to 14.0)	7.6 (5.0 to 11.0)	9.4 (7.2 to 12.5)
HR for death (95% CI)	0.94 (0.78 to 1.14)		0.84 (0.68 to 1.05)		1.32 (0.91 to 1.92)	
P	.530		NA		NA	
Confirmed ORR, No.[a,e]	79	39	73	30	6	9
Percent (95% CI)	26.4 (21.5 to 31.8)	12.8 (9.3 to 17.1)	31.2 (25.3 to 37.6)	12.8 (8.8 to 17.8)	9.2 (3.5 to 19.0)	12.7 (6.0 to 22.7)
Best overall response, No. (%)[a]						
CR	4 (1.3)	0	4 (1.7)	0	0	0
PR	75 (25.1)	39 (12.8)	69 (29.5)	30 (12.8)	6 (9.2)	9 (12.7)
SD	149 (49.8)	153 (50.2)	113 (48.3)	110 (47.0)	36 (55.4)	43 (60.6)
Non-CR/non-PD	3 (1.0)	6 (2.0)	2 (0.9)	3 (1.3)	1 (1.5)	3 (4.2)
PD	46 (15.4)	64 (21.0)	31 (13.2)	53 (22.6)	15 (23.1)	11 (15.5)
NE	22 (7.4)	43 (14.1)	15 (6.4)	38 (16.2)	7 (10.8)	5 (7.0)
DCR, No.[a,f]	231	198	188	143	43	55
Percent (95% CI)	77.3 (72.1 to 81.9)	64.9 (59.3 to 70.3)	80.3 (74.7 to 85.2)	61.1 (54.5 to 67.4)	66.2 (53.4 to 77.4)	77.5 (66.0 to 86.5)
DOR, months, median (95% CI)[a,g]	7.1 (5.6 to 10.9)	5.6 (5.4 to 8.1)	7.7 (5.6 to 11.1)	5.6 (5.4 to 6.0)	5.9 (3.2 to NE)	8.1 (2.8 to NE)
TTR, months, median[a]	1.6	2.6	1.6	2.0	1.4	2.7

NOTE. For the overall population, percentages are based on the number of patients in the full analysis set. For patients with nonsquamous and squamous histology, percentages are based on the number of patients in the respective subsets. Values for the nonsquamous and squamous histology subgroups were calculated on the basis of patient data in the electronic case report forms.
Abbreviations: CR, complete response; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; NA, not applicable; NE, not evaluable; Non-CR/non-PD, noncomplete response/nonprogressive disease; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.
[a]Data cutoff: March 29, 2023.
[b]The median follow-up for PFS was 10.9 months (95% CI, 9.8 to 12.5) with Dato-DXd and 9.6 months (95% CI, 8.2 to 11.9) with docetaxel.
[c]Data cutoff: March 1, 2024.
[d]The median follow-up for OS was 23.1 months (95% CI, 22.0 to 24.8) with Dato-DXd and 23.1 months (95% CI, 21.7 to 24.2) with docetaxel.
[e]Confirmed ORR was defined as the sum of CR and PR rates.
[f]DCR was defined as the sum of CR, PR, and SD rates.
[g]Kaplan-Meier estimate.

TABLE 3. Overall Safety Summary

Patients With Events	Dato-DXd (n = 297), No. (%)	Docetaxel (n = 290), No. (%)
TRAEs	260 (87.5)	252 (86.9)
Grade ≥3	76 (25.6)	122 (42.1)
Dose modifications		
Dose reduction	60 (20.2)	86 (29.7)
Treatment interruption	51 (17.2)	35 (12.1)
Treatment discontinuation	24 (8.1)[a]	35 (12.1)[b]
Serious TRAEs	33 (11.1)	37 (12.8)
Grade ≥3	28 (9.4)	34 (11.7)
Associated with death	3 (1.0)	2 (0.7)

NOTE. Data cutoff: March 1, 2024.
Abbreviations: Dato-DXd, datopotamab deruxtecan; ILD, interstitial lung disease; PT, preferred term; TRAE, treatment-related adverse event.
[a]The most common TRAEs leading to discontinuation with Dato-DXd were pneumonitis (PT), with 13 events (4.4%) occurring, and ILD (PT), with three events (1.0%) occurring.
[b]The most common TRAEs leading to discontinuation with docetaxel were asthenia, neuropathy peripheral, and pneumonitis (PT), each with five events (1.7%) occurring.

with Dato-DXd. Treatment interruptions were more frequent with Dato-DXd than with docetaxel. Stomatitis and nausea were more frequent with Dato-DXd than with docetaxel, whereas the incidence of diarrhea and hematologic disorders was more frequent with docetaxel. Stomatitis/oral mucositis and ocular surface events are adverse events of special interest for Dato-DXd.[16] In TROPION-Lung01, prophylaxis for stomatitis and ocular

TABLE 4. TRAEs Observed in ≥15% of Patients and Adjudicated Drug-Related ILD or Pneumonitis

	Dato-DXd (n = 297), No. (%)		Docetaxel (n = 290), No. (%)	
Patients With Events	Any Grade	Grade ≥3	Any Grade	Grade ≥3
GI disorders[a]				
Stomatitis	141 (47.5)	20 (6.7)	45 (15.5)	3 (1.0)
Nausea	101 (34.0)	7 (2.4)	48 (16.6)	3 (1.0)
Diarrhea	30 (10.1)	1 (0.3)	55 (19.0)	4 (1.4)
Hematologic disorders[a]				
Anemia[b]	44 (14.8)	12 (4.0)	60 (20.7)	12 (4.1)
Neutropenia[c]	14 (4.7)	2 (0.7)	76 (26.2)	68 (23.4)
Leukopenia[d]	9 (3.0)	0	45 (15.5)	38 (13.1)
Skin and subcutaneous tissue disorders[a]				
Alopecia	95 (32.0)	0	101 (34.8)	1 (0.3)
Metabolism and nutrition disorders[a]				
Decreased appetite	68 (22.9)	1 (0.3)	46 (15.9)	1 (0.3)
General disorders and administration site conditions[a]				
Asthenia	56 (18.9)	8 (2.7)	56 (19.3)	5 (1.7)
Adjudicated drug-related ILD or pneumonitis[e]	26 (8.8)	11 (3.7)	12 (4.1)	4 (1.4)

NOTE. Data cutoff: March 1, 2024.
Abbreviations: Dato-DXd, datopotamab deruxtecan; ILD, interstitial lung disease; PT, preferred term.
[a]No grade 5 events occurred with Dato-DXd or docetaxel.
[b]Grouped PTs of anemia, hemoglobin decreased, and RBC count decreased.
[c]Grouped PTs of neutropenia and neutrophil count decreased.
[d]Grouped PTs of leukopenia and WBC count decreased.
[e]Among the 26 patients (8.8%) in the Dato-DXd group who had adjudicated drug-related ILD or pneumonitis, two (0.7%) had grade 1 events, 13 (4.4%) had grade 2 events, three (1.0%) had grade 3 events, one (0.3%) had a grade 4 event, and seven (2.4%) had grade 5 events. Among the 12 (4.1%) patients in the docetaxel group who had adjudicated drug-related ILD or pneumonitis, 0 had grade 1 events, eight (2.8%) had grade 2 events, three (1.0%) had grade 3 events, 0 had grade 4 events, and one (0.3%) had a grade 5 event.

surface events was recommended. ILD is a known risk for deruxtecan-containing antibody–drug conjugates,[32] and management guidelines are in place.[16] Most patients who experienced ILD/pneumonitis discontinued treatment per protocol. Some high-grade events and deaths were observed, highlighting the need for continuous education regarding early detection, management, and close monitoring to reduce the risk of serious outcomes. ILD and NSCLC share common risk factors[33]; of note, a higher incidence of fatal ILD events was observed in patients with squamous histology, which might have been driven by the older age, higher burden of smoking history, and comorbidities that are typical of this patient population.[34] Analysis of factors contributing to increased risk of ILD in patients treated with Dato-DXd is ongoing. Overall, the safety profile of Dato-DXd was as expected,[14] with no new safety signals observed.

The open-label study design is a limitation of this trial. While a slight imbalance in pretreatment dropout rates was observed (1% in the Dato-DXd arm *v* 5% in the docetaxel arm), it is unlikely that this affected the overall study outcomes.

In conclusion, Dato-DXd showed statistical superiority over docetaxel in reducing disease progression in patients with NSCLC after first-line therapy; clinically meaningful PFS benefit was observed in patients with nonsquamous disease. OS, the second dual primary end point, was not significantly prolonged with Dato-DXd compared with docetaxel although a numerical improvement was seen. The overall efficacy and tolerability profile supports Dato-DXd as a potential new therapeutic option in patients with nonsquamous NSCLC who are eligible for subsequent therapy.

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Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non–Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study

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Travel, Accommodations, Expenses: MSD, Roche, Janssen, Takeda, AstraZeneca

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Research Funding: IQVIA Services JAPAN K.K (Inst), Syneos Health (Inst), EPS Holdings (Inst), Nippon Kayaku (Inst), Takeda (Inst), MSD K.K (Inst), Amgen (Inst), Taiho Pharmaceutical (Inst), Bristol Myers Squibb Company (Inst), Janssen (Inst), CMIC CO., Ltd (Inst), Pfizer (Inst), Labcorp Drug Development (Inst), Kobayashi Pharmaceutical (Inst), Pfizer (Inst), AbbVie (Inst), A2 Healthcare (Inst), Lilly Japan (Inst), Medpace Japan KK (Inst), Eisai (Inst), EPS Holdings (Inst), Shionogi (Inst), Otsuka (Inst), GSK K.K (Inst), Sanofi (Inst), Chugai Pharma (Inst), Nippon Boehringer Ingelheim (Inst), SRL Medisearch Inc (Inst), PRA Health Sciences Inc (Inst), Astellas Pharma (Inst), Ascent Development Services (Inst), Eisai (Inst), Bayer Yakuhin (Inst), AstraZeneca Japan (Inst), Daiichi Sankyo Co., Ltd (Inst), Novartis (Inst), Merck (Inst), Kyowa Kirin Co., Ltd (Inst)
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Consulting or Advisory Role: AstraZeneca, Merck, Roche, Yuhan
Research Funding: Yuhan

Enriqueta Felip
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Travel, Accommodations, Expenses: AstraZeneca, Janssen, Roche
Other Relationship: GRIFOLS
Uncompensated Relationships: Member of the Scientific Advisory Committee - Hospital Universitari Parc Taulí; SEOM (Sociedad Española de Oncología Médica), President from 2021-2023; "ETOP IBCSG Partners" Member of the Scientific Committee

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Research Funding: Merck Sharp & Dohme (Inst), AstraZeneca/MedImmune (Inst), Mirati Therapeutics (Inst), Lilly (Inst), Daiichi Sankyo/Lilly (Inst), Genentech (Inst), Regeneron (Inst)

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Honoraria: AstraZeneca/MedImmune, Takeda, Janssen, Amgen
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Research Funding: AstraZeneca Spain (Inst)
Travel, Accommodations, Expenses: Takeda, AstraZeneca/MedImmune, Pfizer, Roche/Genentech

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Speakers' Bureau: AstraZeneca, Roche, Hansoh Pharma, Hengrui Therapeutics
Research Funding: AstraZeneca (Inst), Hutchison MediPharma (Inst), BMS (Inst), Hengrui Therapeutics (Inst), BeiGene (Inst), Roche (Inst), Hansoh (Inst), Lilly Suzhou Pharmaceutical Co (Inst)

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Consulting or Advisory Role: Bristol Myers Squibb, MSD, AstraZeneca, Novartis, Takeda, Roche, Sanofi, Celgene, Daiiki Sankyo, Pfizer, Seagen, Lilly, GSK, Bayer, Blueprint Medicines, Janssen, Regeneron, Bayer, AbbVie, Mirati Therapeutics, Merck, Boehringer Ingelheim, Blueprint Medicines, Abion, Gilead Sciences
Speakers' Bureau: AstraZeneca, MSD Oncology, Merck, Mirati Therapeutics, Daiichi Sankyo/AstraZeneca
Research Funding: Bristol Myers Squibb (Inst), MSD (Inst), Roche/Genentech (Inst), AstraZeneca/MedImmune (Inst), AstraZeneca (Inst), Pfizer (Inst), GSK (Inst), Novartis (Inst), Merck (Inst), Incyte (Inst), Takeda (Inst), Spectrum Pharmaceuticals (Inst), Blueprint Medicines (Inst), Lilly (Inst), Ipsen (Inst), Janssen (Inst), Exelixis (Inst), MedImmune (Inst), Sanofi (Inst), Pfizer (Inst), Amgen (Inst)
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Uncompensated Relationships: Merck

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Patents, Royalties, Other Intellectual Property: Pending Patents U.S. Provisional Patent Application No. 63/527,899

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Research Funding: Amgen, Harpoon
Travel, Accommodations, Expenses: AstraZeneca

No other potential conflicts of interest were reported.

APPENDIX 1. SUPPLEMENTAL INFORMATION FOR TROPION-LUNG01 DATO-DXD IN NSCLC

Statistical Methods

This study had four random assignment stratification factors: actionable genomic alteration (present *v* absent), histology (squamous *v* nonsquamous), treatment with PD-1/PD-L1 immunotherapy in the last line (yes *v* no), and geographical region (United States/Japan/Western Europe *v* the rest of the world). Because of the small sample size within some strata, actionable genomic alterations and most immediate previous therapy including with PD-1/PD-L1 were removed from the stratified analyses.

Adjudication Committee

An external, independent interstitial lung disease (ILD) Adjudication Committee has been established for the datopotamab deruxtecan (Dato-DXd) clinical program for the purpose of adjudicating all events of potential ILD/pneumonitis. The ILD adjudication process is always independent of trial investigators and is blinded for randomized controlled trials to avoid any source of bias.

The adjudication committee determined each potential ILD event with regard to whether it was ILD and whether it was related to the study drug (regardless of the determination made by the investigator) and decided grades for the events that the adjudication committee considered to be treatment-related. All patients with a reported preferred term for ILD (defined in the ILD Adjudication Committee Charter) that would trigger adjudication for a potential ILD event were determined in a similar manner. Protocol-defined on-treatment death in any patient who experienced a potential ILD event was also adjudicated as to whether death was due to ILD. Off-treatment deaths in patients who experienced an event of adjudicated drug-related ILD could also be adjudicated if deemed necessary.

As a result of the adjudication process, the ILD Adjudication Committee could potentially identify ILD/pneumonitis cases which differ from the assessment of study investigators.

TABLE A1. List of Investigators

Country, Study Site	Investigator
Argentina	
Sanatorio Parque	Gaston Lucas Martinengo
CER San Juan	Juan Puig
Australia	
Southern Medical Day Care Centre	Daniel Brungs
Blacktown Hospital	Bo Gao
Westmead Hospital	Adnan Nagria
Flinders Medical Centre	Chris Karapetis
Austin Hospital	Sagun Parakh
Macquarie University Hospital	John Park
Belgium	
Centre Hospitalier Jolimont-Lobbes	Gaetan Catala
Centre Hospitalier de l'Ardenne (CHA)	Frederic Forget
CHU UCL Namur	Sebahat Ocak
Canada	
Cross Cancer Institute	Naveen Basappa
University Health Network Princess MArgaret Cancer Centre	Geoffrey Liu
Sunnybrook Health Sciences Centre	Ines Menjak
McGill University Health Centre (MUHC)—Glen Site and MUHC Research Institute	Benjamin Shieh
China	
Shanghai Chest Hospital	Shun Lu
West China Hospital, Sichuan University	Feng Luo
Jiamusi Tuberculosis Hospital (Jiamusi Cancer Hospital)	Hongmei Sun
Fudan University Shanghai Cancer Center	Jialei Wang
The First Affiliated Hospital of Xi'an Jiaotong University	Yu Yao

(continued in next column)

TABLE A1. List of Investigators (continued)

Country, Study Site	Investigator
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France	
Hôpital Foch	Jaafar Bennouna
Institut Curie	Nicolas Girard
APHM—Hôpital Nord	Laurent Greillier
CHU de Poitiers Pôle Régional de Cancérologie	Corinne Lamour
Hôpital Pontchaillou	Herve Lena
Les Hôpitaux Universitaires de Strasbourg	Céline Mascaux
CHU Toulouse Hôpital Larrey	Julien Mazieres
Centre Hospitalier Universitaire de Grenoble	Denis Moro-Sibilot
Centre Léon Bérard	Maurice Pérol
University Hospital of Nantes	Elvire Pons-Tostivint
Hôpital Jean Minjoz	Virginie Westeel
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IKF Krankenhaus Nordwest	Akin Atmaca
Universitätsklinikum Freiburg	Christine Greil
Asklepios Fachkliniken München-Gauting	Niels Reinmuth
Klinikverbund Allgäu	Christian Schumann
Universitätsklinik Giessen und Marburg	Thomas Wehler
Universität zu Köln—Uniklinik Köln	Juergen Wolf
Hong Kong	
Queen Mary Hospital	James Ho
Hungary	
Szent Borbála Kórház	Csaba Bocskei
Italy	
Istituti Fisioterapici Ospitalieri (IFO)—Istituto Regina Elena	Federico Cappuzzo

(continued on following page)

TABLE A1. List of Investigators (continued)

Country, Study Site	Investigator
IRCCS Istituto Europeo di Oncologia	Filippo de Marinis
Fondazione IRCCS Istituto Nazionale dei Tumori	Claudia Proto
ASL 3 Genovese Oncologia Medica Villa Scassi	Manlio Mencoboni
Azienda Ospedaliero-Universitaria San Luigi Gonzaga	Silvia Novello
Azienda Ospedaliero-Universitaria Policlinico S. Orsola-Malpighi	Stefania Salvagni
Azienda Ospedaliero Universitaria Policlinico "G. Rodolico—San Marco"	Hector Soto Parra
Japan	
Osaka City General Hospital	Haruko Daga
National Cancer Center Hospital	Yasushi Goto
Kindai University Hospital	Hidetoshi Hayashi
The Cancer Institute Hospital of JFCR	Satoru Kitazono
National Cancer Center Hospital East	Kiyotaka Yoh
Shizuoka Cancer Center	Ryo Ko
Fujita Health University Hospital	Masashi Kondo
National Hospital Organization Shikoku Cancer Center	Toshiyuki Kozuki
Kansai Medical University Hospital	Takayasu Kurata
Saitama Cancer Center	Hideaki Mizutani
Okayama University Hospital	Kadoaki Ohashi
National Hospital Organization Hokkaido Cancer Center	Satoshi Oizumi
Kyushu University Hospital	Isamu Okamoto
Tokushima University Hospital	Satoshi Sakaguchi
Kyoto University Hospital	Hiroaki Ozasa
Sendai Kousei Hospital	Shunichi Sugawara
Kanazawa University Hospital	Yuichi Tambo
Osaka International Cancer Institute	Motohiro Tamiya
Niigata Cancer Center Hospital	Hiroshi Tanaka
Kyushu University Hospital	Isamu Okamoto
Mexico	
San Peregrino Cancer Center	Froylan Lopez-Lopez
Hospital Civil de Guadalajara Fray Antonio Alcalde	Francisco Javier Ramirez Godinez
Servicios de Oncología Medica Integral, S.A. de C.V. ONCARE	Jeronimo Rafael Rodriguez Cid
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Erasmus MC	Robin Cornelissen
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Szpital Specjalistyczny w Prabutach Sp. Z o.o.	Anna Lowczak

(continued in next column)

TABLE A1. List of Investigators (continued)

Country, Study Site	Investigator
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II Klinika Chorób Płuc i Gruźlicy	Robert Mróz
Med Polonia Sp. Z o.o.	Rodryg Ramlau
Puerto Rico	
FDI Clinical Research	Mirelis Acosta-Rivera
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Samsung Medical Center	Myung-Ju Ahn
Kyungpook National University Chilgok Hospital	Yee Soo Chae
Yonsei University Health System—Severance Hospital	Min Hee Hong
The Catholic University of Korea Seoul St Mary's Hospital	Jin-Hyoung Kang
Asan Medical Center	Sang-We Kim
Seoul National University Boramae Medical Center	Jin-Soo Kim
Seoul National University Bundang Hospital	Se Hyun Kim
Chungbuk National University Hospital	Ki Hyeong Lee
Kangbuk Samsung Hospital	Yun Gyoo Lee
The Catholic University of Korea St Vincent's Hospital	Byoung Yong Shim
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University Headache Clinic LLC	Evgeniy Ledin
VitaMed LLC	Elena Poddubskaya
Singapore	
Icon Cancer Centre Farrer Park	Boon Yeow Daniel Chan
National Cancer Centre Singapore	Amit Jain
OncoCare Cancer Centre (Gleneagles Medical Centre)	Chee Seng Tan
Spain	
Complejo Hospitalario Universitario de Ourense	Maria Carmen Areses
Hospital Regional Universitario de Málaga	Manuel Cobo
Hospital Universitario Fundación Jiménez Díaz	Manuel Domine
Hospital Universitari Vall d'Hebron	Enriqueta Felip
Hospital Universitario de Valme	José Fuentes Pradera
Hospital Clínico Universitario Lozano Blesa	Dolores Isla
Hospital Universitari i Politècnic La Fe	Oscar Juan Vidal
Hospital de la Santa Creu i Sant Pau	Margarita Majem
Hospital Universitario 12 de Octubre	Luis Paz-Ares
Hospital Universitario Puerta de Hierro Majadahonda	Mariano Provencio
Hospital Clínic i Provincial de Barcelona	Noemi Reguart
Hospital Universitario Virgen Macarena	David Vicente Baz

(continued on following page)

TABLE A1. List of Investigators (continued)

Country, Study Site	Investigator
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Kantonsspital St Gallen	Martin Früh
Taiwan	
Chang Gung Medical Foundation Linkou Chang Gung Memorial Hospital	Wen-Cheng Chang
Chung Shan Medical University Hospital	Gee-Chen Chang
Chi Mei Medical Center	Wen-Tsung Huang
National Cheng Kung University Hospital	Chien-Chung Ling
E-Da Hospital	Yu-Feng Wei
Taichung Veterans General Hospital	Tsung-Ying Yang
United Kingdom	
University College Hospital	Tanya Ahmad
The Christie Hospital	Fabio Gomes
The James Cook University Hospital	Talal Mansy
United States	
University Hospitals Cleveland Medical Center	Debora Bruno
Hematology/Oncology Clinic, American Oncology Network	Michael Castine
Astera Cancer Care	Bruno Fang
University of Chicago	Marina Garassino
University of Virginia Health System	Richard Hall
Montefiore Medical Center	Balazs Halmos
Optum Care Cancer Center	Khawaja Jahangir
Sarah Cannon Research Institute	Melissa Johnson
Orlando Health	Tirrell Johnson
Ironwood Cancer & Research Centers	Sujith Kalmadi
St Joseph Heritage Healthcare	William Lawler
University of California, Los Angeles	Aaron Lisberg
Fort Wayne Medical Oncology and Hematology	Ahad Sadiq
Dana-Farber Cancer Institute	Jacob Sands
Avera Cancer Institute	Benjamin Solomon
Northwest Medical Specialties	Andrea Veatch

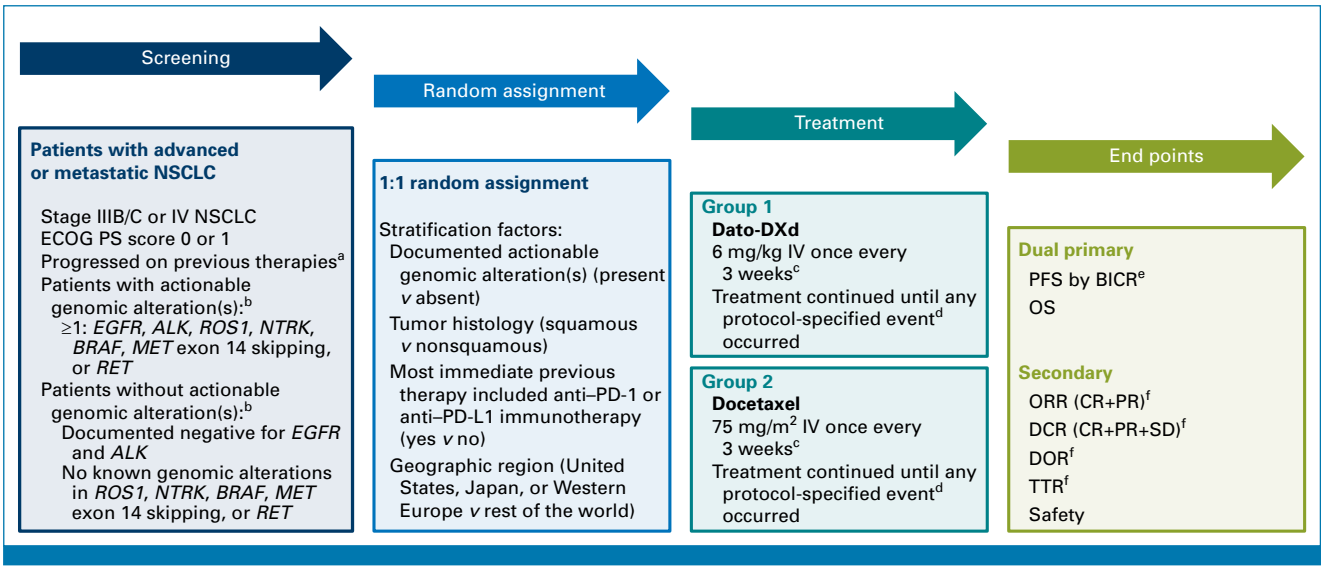

FIG A1. Study design of TROPION-Lung01. Pretreated patients with advanced or metastatic NSCLC received Dato-DXd 6 mg/kg IV once every 3 weeks or docetaxel 75 mg/m^2 IV once every 3 weeks. [a]For patients with actionable genomic alterations, previously treated with one to two lines of approved alteration-targeted therapy, with platinum-based chemotherapy as the only previous line of cytotoxic therapy, with or without not more than one anti–PD-1/PD-L1 monoclonal antibody alone or in combination with a cytotoxic agent. For patients without actionable genomic alterations, previously treated with platinum-based chemotherapy and anti–PD-1/PD-L1 immunotherapy, either in combination as the only previous line of therapy or sequentially as the only two previous lines of therapy. For all patients, no previous docetaxel was permitted. [b]Patients with known *KRAS* mutations, in the absence of any driver genomic alterations, were eligible and had to meet previous therapy requirements for patients without actionable genomic alterations. [c]Day 1 of each 3-week cycle. [d]Radiographic disease progression, clinical progression, death, unacceptable toxicity, loss to follow-up, or withdrawal of patient consent. [e]Per RECIST v1.1. [f]Assessed by BICR and investigator per RECIST v1.1. BICR, blinded independent central review; CR, complete response; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.