ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Osimertinib plus datopotamab deruxtecan in patients with *EGFR*-mutated advanced NSCLC after progression on first-line osimertinib: ORCHARD

J. W. Riess[1*], H. A. Yu[2,3], X. Le[4], A. J. de Langen[5], B. C. Cho[6], Z. Piotrowska[7], L. E. L. Hendriks[8], A. Morabito[9], L. Bonanno[10,11], O. T. Brustugun[12], T. O. Halvorsen[13], Y. J. Kim[14], K. A. Marrone[15], Y. Shiraishi[16], J. W. Goldman[17], H. Ambrose[18], P. E. Smith[19], P. G. Fraenkel[20], K. H. Tang[21], J. M. Lehman[22] & S. B. Goldberg[23]

[1]Internal Medicine — Hematology/Oncology, University of California Davis Comprehensive Cancer Center, Sacramento; [2]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York; [3]Weill Cornell Medical College, New York; [4]Department of Thoracic and Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston, USA; [5]Department of Thoracic Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [6]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [7]Department of Medicine, Massachusetts General Hospital, Boston, USA; [8]Department of Pulmonary Diseases, GROW Research Institute for Oncology and Reproduction, Maastricht University Medical Centre, Maastricht, The Netherlands; [9]Thoracic Department, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Naples; [10]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova; [11]Medical Oncology 2, Istituto Oncologico Veneto, IOV IRCCS, Padova, Italy; [12]Department of Oncology, Drammen Hospital, Vestre Viken Health Trust, Drammen; [13]Department of Oncology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [14]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [15]Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, USA; [16]Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [17]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, USA; [18]Early Clinical Development, Oncology R&D, AstraZeneca, Cambridge; [19]On behalf of Oncology Biometrics, Oncology R&D, AstraZeneca, Cambridge, UK; [20]Oncology R&D, AstraZeneca, Waltham; [21]Translational Medicine, Research and Early Development, Oncology R&D, AstraZeneca, Boston; [22]Early Global Development, Research and Early Development, Oncology R&D, AstraZeneca, Gaithersburg; [23]Medical Oncology, Yale School of Medicine, New Haven, USA

Available online 2 March 2026

Background: ORCHARD (NCT03944772) was a phase II platform study conducted to characterize resistance mechanisms and evaluate novel treatment combinations following progressive disease (PD) on first-line osimertinib. Datopotamab deruxtecan (Dato-DXd) is an anti-TROP2 antibody—drug conjugate approved as monotherapy in *EGFR*-mutated advanced non-small-cell lung cancer (NSCLC). We report final data from the osimertinib plus Dato-DXd module.

Methods: Eligible patients had *EGFR*-mutated advanced NSCLC and PD on first-line osimertinib. Patients received oral osimertinib (80 mg once daily) plus intravenous Dato-DXd (4 or 6 mg/kg every 3 weeks). The primary endpoint was investigator-assessed confirmed objective response rate (ORR) per RECIST v1.1. Secondary endpoints were progression-free survival (PFS), duration of response (DoR), overall survival (OS), and safety.

Results: Sixty-nine patients received study treatment. Among patients in the 4 mg/kg ($N = 35$) and 6 mg/kg ($N = 34$) cohorts, respectively, confirmed ORR was 43% [80% confidence interval (CI) 32% to 55%] and 36% (80% CI 25% to 49%); median PFS was 9.5 months (95% CI 7.2-9.8 months) and 11.7 months (95% CI 8.3-21.7 months); median DoR was 6.3 months (95% CI 3.8-8.1 months) and 20.5 months [95% CI 6.2 months-not calculable (NC); estimated median of at least 16 months]; and median OS was 19.8 months (95% CI 13.5-23.3 months) and 26.2 months (95% CI 14.8 months-NC; estimated median greater than or equal to the 4 mg/kg cohort). In the 4 mg/kg and 6 mg/kg cohorts, respectively, grade $\geq$3 adverse events (AEs) were reported in 49% and 76% of patients; AEs leading to Dato-DXd dose reduction in 23% and 59%; and adjudicated interstitial lung disease/pneumonitis in 3% and 15%.

Conclusions: Osimertinib plus Dato-DXd demonstrated clinical benefit in patients with *EGFR*-mutated advanced NSCLC who progressed on first-line osimertinib. AEs in the 6 mg/kg cohort were of higher frequency and severity but could be managed with prophylaxis, careful monitoring, and dose reduction. The safety profile was consistent with the known profiles of the individual drugs. Considering the overall benefit—risk profile, 6 mg/kg is suggested as the preferred Dato-DXd starting dose for combining with osimertinib 80 mg.

Clinical trial number: ClinicalTrials.gov NCT03944772.

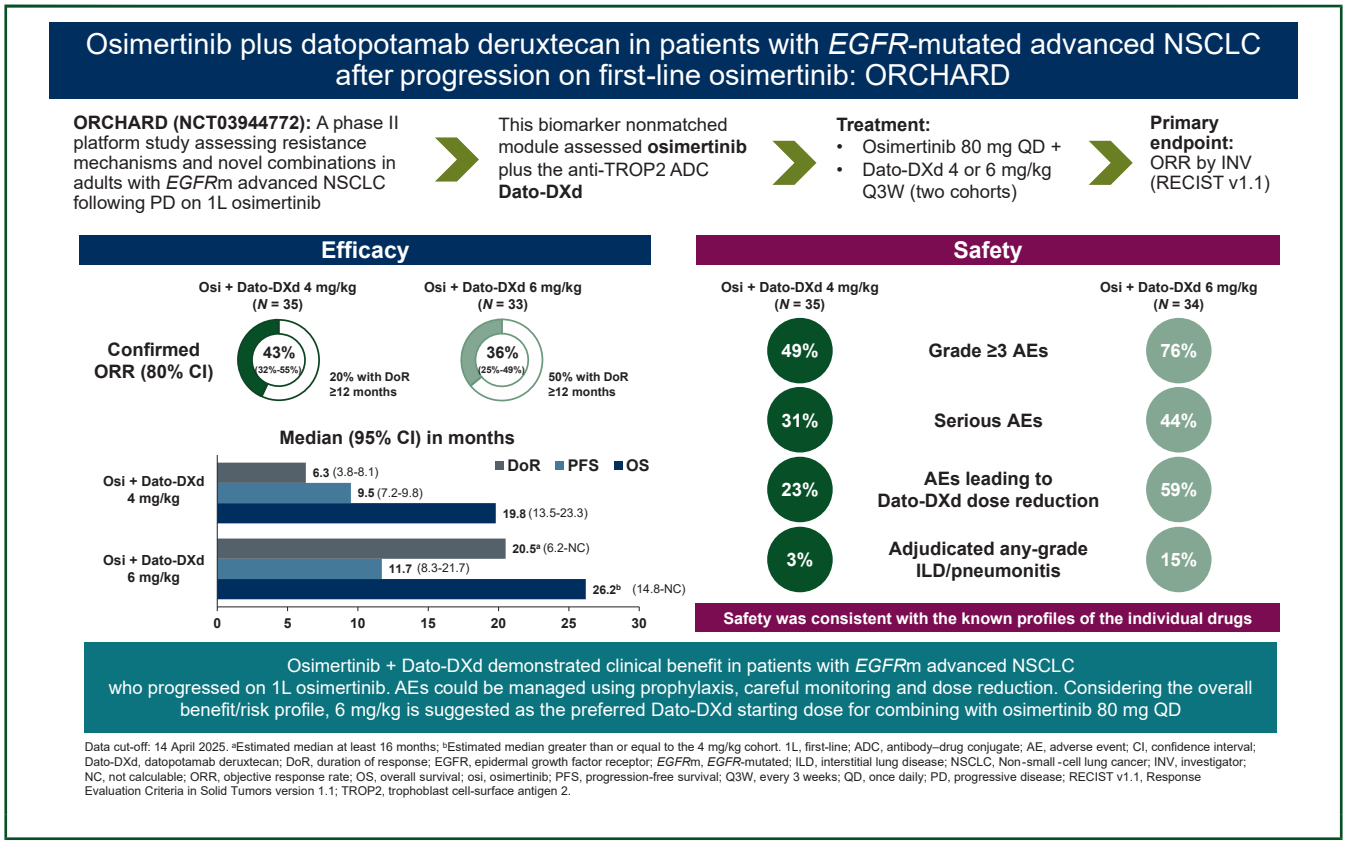
Key words: osimertinib, datopotamab deruxtecan, EGFR, NSCLC, ctDNA clearance, molecular alteration

*Correspondence to: Dr Jonathan W. Riess, Internal Medicine — Hematology/Oncology, University of California Davis Comprehensive Cancer Center, 4501 X Street, Suite 3016, 95817, Sacramento, CA, USA. Tel: +1-916-734-3772
E-mail: jwriess@health.ucdavis.edu (J. W. Riess).

INTRODUCTION

Osimertinib, a third-generation, irreversible, oral epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), has demonstrated efficacy in *EGFR*-mutated non-small-cell

GRAPHICAL ABSTRACT



lung cancer (NSCLC), including central nervous system (CNS) metastases.[1-11] Based on the phase III FLAURA study,[4,5] osimertinib monotherapy was established as a standard-of-care option for first-line treatment.[12] However, acquired resistance to osimertinib eventually leads to disease progression in most patients.[13]

Options for patients with *EGFR*-mutated advanced NSCLC who progress on first-line osimertinib include platinum-based chemotherapy with or without amivantamab (after osimertinib monotherapy), and datopotamab deruxtecan (Dato-DXd) monotherapy (after osimertinib and platinum-based chemotherapy).[12,14-17] As EGFR-TKI-sensitizing mutations often persist beyond progression and second-line options only offer modest benefit,[12,14-19] there is a rationale for continuing osimertinib alongside other treatments in subsequent lines. In cases where actionable biomarkers are not identified at progression, combining osimertinib with more general, biomarker-agnostic cytotoxic strategies may be appropriate.

Dato-DXd is an antibody—drug conjugate consisting of a humanized anti-trophoblast cell-surface antigen 2 (anti-TROP2) monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload (DXd) via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker.[20] DXd is released after internalization, leading to DNA damage and apoptosis of tumor cells.[20] In a pooled analysis of 117 patients with *EGFR*-mutated advanced/metastatic NSCLC from the TROPION-Lung05 and TROPION-Lung01 trials, Dato-DXd treatment led to a meaningful clinical response [median progression-free survival (PFS), 5.8 months; median overall survival (OS), 15.6 months].[21] Based on data from these trials, Dato-DXd 6 mg/kg was approved in the United States as monotherapy to treat adults with *EGFR*-mutated advanced NSCLC who have received prior EGFR-directed therapy and platinum-based chemotherapy.[15] Whether continued osimertinib in combination with Dato-DXd can provide meaningful clinical outcomes in *EGFR*-mutated NSCLC postprogression on first-line osimertinib remains an important unanswered question. Continued use of osimertinib may help to control *EGFR*-mutated disease and prevent progression/development of CNS metastases.[8-11]

ORCHARD (NCT03944772) was an open-label, multicenter, multidrug, phase II, biomarker-directed platform study in patients with *EGFR*-mutated advanced NSCLC whose disease had progressed on first-line osimertinib. The study aimed to characterize resistance mechanisms among patients treated with first-line osimertinib and evaluate novel post-osimertinib monotherapy treatment combinations in patients without intervening treatment. Here, results from the biomarker nonmatched module evaluating osimertinib plus Dato-DXd are reported.

MATERIALS AND METHODS

Trial design and patients

Details of the ORCHARD trial design have previously been published.[22] Eligible patients were aged ≥18 years (≥20 years in Japan), had locally advanced or metastatic, histologically or cytologically confirmed NSCLC (predominant adenocarcinoma histology) harboring an EGFR-TKI-sensitizing mutation (including non-Ex19del/L858R EGFR-TKI-sensitizing mutations) at diagnosis, with measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and World Health Organization performance status of 0 or 1. All patients had progressed ≥3 months after initiation of first-line osimertinib (i.e. patients with primary osimertinib resistance were excluded) without intervening treatment and were able to have a mandatory biopsy. Patients with stable, asymptomatic CNS metastases were eligible, with or without prior local therapy. If definitive therapy was administered, then patients needed to have had stable neurologic status for ≥2 weeks after completion of definitive therapy and steroids. Additional details of the study design, key exclusion criteria, and additional eligibility criteria for the osimertinib plus Dato-DXd module can be found in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.02.014.

Following progression on first-line osimertinib monotherapy, tumor biopsies were analyzed using next-generation sequencing [NGS; (FoundationOne®CDx, Foundation Medicine Inc., Boston, MA)] and patients were allocated to treatment groups based on these results or detection of small cell/neuroendocrine transformation. Patients without an available biomarker match were allocated to group B, which included the osimertinib plus Dato-DXd module (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2026.02.014).

The trial was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice guidelines, and applicable laws/regulations. Patients provided written informed consent.

Treatments

Patients received oral osimertinib 80 mg once daily plus intravenous Dato-DXd 4 or 6 mg/kg every 3 weeks, as determined by the Safety Review Committee following the safety run-in, carried out to confirm the tolerability of osimertinib plus Dato-DXd (see Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.02.014). Dato-DXd was administered on day 1 of every 3-week cycle. Premedication was required before any dose of Dato-DXd (see Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.02.014 for details). Treatment continued until RECIST v1.1-defined progressive disease (PD), unacceptable tolerability, patient/investigator decision, or another discontinuation criterion was met. Treatment beyond PD was permitted if the patient was obtaining clinical benefit in the opinion of the investigator.

Endpoints and assessments

The primary endpoint was confirmed objective response rate (ORR) per investigator assessment using RECIST v1.1. Secondary endpoints included PFS and duration of response (DoR) per investigator assessment using RECIST v1.1, and OS (see Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.02.014 for definitions). See Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.02.014 for details of tumor assessments and CNS imaging assessments. Safety was assessed throughout, including physical examinations, vital signs, laboratory assessments, and adverse events (AEs). AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. An external, independent interstitial lung disease (ILD) Adjudication Committee was responsible for reviewing all cases of potential ILD/pneumonitis to confirm the diagnosis and assess drug-relatedness.

Exploratory endpoints included correlation of baseline molecular alterations with response, with plasma samples evaluated using NGS (GuardantOMNI™, Guardant Health. Redwood City, CA). We also evaluated circulating tumor DNA (ctDNA) for common EGFR-TKI sensitizing mutations (Ex19del and L858R) at baseline and on-treatment by droplet digital PCR (ddPCR; Biodesix, Boulder, CO). Additionally, acquired molecular alterations were detected by NGS (GuardantOMNI™) of plasma ctDNA from paired samples before osimertinib plus Dato-DXd and after PD on study treatment.

Statistical methods

Analyses were carried out by cohort based upon initial Dato-DXd dose (4 or 6 mg/kg). Safety was analyzed in all patients who received one or more doses of study treatment. ORR, DoR, PFS, and OS were analyzed in all efficacy eligible patients who received one or more doses of study treatment.

ORR was summarized with two-sided exact binomial 80% CIs (Clopper—Pearson) in order to determine whether to continue further clinical development per a decision framework and to gain a preliminary understanding of efficacy. See Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.02.014 for the sample size rationale and decision framework. PFS, DoR, and OS were analyzed using the Kaplan—Meier method. Data cut-off for the final analysis was 14 April 2025 (all endpoints).

RESULTS

Patients

Between 21 July 2022 and 12 October 2023, 69 patients from 33 centers in 8 countries (Italy, Japan, Netherlands, Norway, Republic of Korea, Spain, Sweden, and the United States) were enrolled and started treatment. A safety run-

in was carried out to evaluate the safety of the combination at the two different Dato-DXd doses (Supplementary Results, available at https://doi.org/10.1016/j.annonc.2026.02.014). An interim analysis of 19 evaluable patients in each cohort supported continuation of recruitment (Supplementary Results, available at https://doi.org/10.1016/j.annonc.2026.02.014).

All patients received one or more doses of study treatment; 35 patients received osimertinib plus Dato-DXd 4 mg/kg and 34 received osimertinib plus Dato-DXd 6 mg/kg (Supplementary Figure S2 and Supplementary Results, available at https://doi.org/10.1016/j.annonc.2026.02.014). In the 4 and 6 mg/kg cohorts, respectively, 8 (23%) and 16 (47%) patients completed the study. The most common reason for study discontinuation was death [26 (74%) and 17 (50%) patients in the 4 and 6 mg/kg cohorts, respectively; see Supplementary Results, available at https://doi.org/10.1016/j.annonc.2026.02.014 for details].

Patient demographics and disease characteristics are summarized in Table 1. In the 4 and 6 mg/kg cohorts, respectively, median age was 62.0 years [minimum (min)-maximum (max) 37-76 years] and 63.5 years (min-max 42-78 years), with 63% and 53% of patients aged <65 years. Most patients were female (69% and 65%), white (63% and 65%), and had never used tobacco (54% and 71%). Stable CNS metastases, as permitted in the protocol, were present in 46% (4 mg/kg) and 32% (6 mg/kg) of patients at baseline. PD on first-line osimertinib occurred within 12 months for 51% (4 mg/kg) and 9% (6 mg/kg) of patients, and ≥12 to ≤18 months for 6% (4 mg/kg) and 35% (6 mg/kg) of patients.

While this was a non-biomarker-matched module, some patients with an identified predefined biomarker (e.g. *MET* alterations, *EGFR* C797X mutation, or *BRAF* alterations) were allocated to this module due to the respective biomarker-matched modules being completed/closed at the time these patients were enrolled in the ORCHARD study (see Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2026.02.014 for details of ORCHARD study design and treatment modules).

Table 1. Patient demographics and disease characteristics

Characteristic	Osimertinib plus Dato-DXd 4 mg/kg (*N* = 35)	Osimertinib plus Dato-DXd 6 mg/kg (*N* = 34)
Age, years		
Median (min-max)	62.0 (37-76)	63.5 (42-78)
Age group, *n* (%)		
≥18 to <65 years	22 (63)	18 (53)
≥65 years	13 (37)	16 (47)
Sex, *n* (%)		
Female	24 (69)	22 (65)
Male	11 (31)	12 (35)
Race, *n* (%)		
White	22 (63)	22 (65)
Asian	12 (34)	10 (29)
Black or African American	1 (3)	0
Other	0	2 (6)
Region, *n* (%)		
North America	13 (37)	13 (38)
Europe	14 (40)	16 (47)
Asia	8 (23)	5 (15)
Tobacco use, *n* (%)		
Never	19 (54)	24 (71)
Former	0	1 (3)
Current	16 (46)	9 (26)
WHO performance status, *n* (%)		
0	18 (51)	15 (44)
1	17 (49)	19 (56)
Sites of disease, *n* (%)[a]		
Sites of locally extensive disease	22 (63)	18 (53)
Sites of metastasis	35 (100)	34 (100)
Patients with CNS/liver/skeletal metastases at baseline, *n* (%)	16 (46)/13 (37)/16 (46)	11 (32)/4 (12)/14 (41)
Time to progression on first-line osimertinib, *n* (%)		
<12 months	18 (51)	3 (9)
≥12 to ≤18 months	2 (6)	12 (35)
>18 months	15 (43)	19 (56)

CNS, central nervous system; Dato-DXd, datopotamab deruxtecan; max, maximum; min, minimum; WHO, World Health Organization.
[a]Sites of disease classification did not denote TNM (tumor—node—metastasis) staging but was based on evaluation of individual disease sites in individual patients. For example, an individual patient could have both locally extensive sites of disease (such as bulky lymph nodal or primary disease) and metastatic sites of disease.

Treatment exposure

Median (min-max) treatment durations in the osimertinib plus Dato-DXd 4 and 6 mg/kg cohorts, respectively, were 9.0 months (1.4-28.2 months) and 9.8 months (0.7-22.8 months). Osimertinib relative dose intensity (RDI) was ≥75% for 30 (86%) and 34 (100%) patients in the 4 and 6 mg/kg cohorts, respectively, while Dato-DXd RDI was ≥75% for 30 (86%) and 20 (59%) patients, respectively. Osimertinib dose reductions occurred in six (17%) patients in the 4 mg/kg cohort; there were no osimertinib dose reductions in the 6 mg/kg cohort. Dato-DXd dose reductions occurred in 8 (23%) and 21 (62%) patients, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2026.02.014). See Supplementary Results and Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2026.02.014 for details of actual Dato-DXd dose received by cycle number.

Osimertinib dose interruption occurred in 40% (4 mg/kg) and 41% (6 mg/kg) of patients, and Dato-DXd interruptions in 34% (4 mg/kg) and 35% (6 mg/kg) of patients (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2026.02.014).

Efficacy

In the 4 and 6 mg/kg cohorts, respectively, there were 35 and 33 patients evaluable for efficacy. One patient in the 6 mg/kg cohort was excluded from the efficacy analysis as they had received osimertinib monotherapy as second-line rather than first-line treatment. Confirmed responses were reported in 15 and 12 patients in the 4 and 6 mg/kg cohorts, respectively [all partial responses (PRs)], corresponding to an ORR of 43% [80% confidence interval (CI) 32% to 55%] and 36% (80% CI 25% to 49%) (Table 2). Median (Q1-Q3) time to onset of response from first dose was 2.7 months (1.5-4.1 months) (4 mg/kg) and 1.4 months (1.2-2.1 months) (6 mg/kg). Most patients had a reduction

Table 2. Objective response summary

Best objective response	Osimertinib plus Dato-DXd 4 mg/kg (*N* = 35)	Osimertinib plus Dato-DXd 6 mg/kg (*N* = 33)
Objective response rate, % (80% CI)	43 (32-55)	36 (25-49)
Responders, *n* (%)[a]	15 (43)	12 (36)
PR	15 (43)	12 (36)
Nonresponders, *n* (%)		
Stable disease ≥6 weeks[b]	17 (49)	18 (55)
Unconfirmed CR or PR[c]	1 (3)	3 (9)
Stable disease	16 (46)	15 (45)
Progression		
RECIST progression	3 (9)	1 (3)
Death in the absence of progression	0	0
Not evaluable		
Stable disease <6 weeks	0	1 (3)
Incomplete postbaseline assessments	0	1 (3)
Time to onset of response (months), median (Q1-Q3)	2.7 (1.5-4.1)	1.4 (1.2-2.1)

CI, confidence interval; CR, complete response; Dato-DXd, datopotamab deruxtecan; PR, partial response.

[a]Response required confirmation after at least 4 weeks.

[b]Stable disease could be recorded at 6 weeks minus 1 week to allow for an early assessment within the assessment window.

[c]PR or CR achieved but either no confirmation assessment carried out, or a confirmation assessment carried out but response not confirmed.

in tumor size, more frequently in the 6 mg/kg cohort (Figure 1), and often noted at the first RECIST assessment visit (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2026.02.014). In the 6 mg/kg cohort, there were more PRs at the first RECIST follow-up visit than in the 4 mg/kg cohort. Additionally, responses were deeper and longer, and there were fewer progressions (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2026.02.014). Of the patients with a confirmed response, 13/15 (87%) and 6/12 (50%) in the 4 and 6 mg/kg cohorts, respectively, subsequently died or had PD, while 2/15 (13%) and 5/12 (42%) had an ongoing response at data cut-off (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2026.02.014). Median (95% CI) DoR was 6.3 months (3.8-8.1 months) (4 mg/kg) and 20.5 months [6.2 months-not calculable (NC)] (6 mg/kg); a stable median was not reached for the 6 mg/kg cohort, although it was at least 16 months. There were 3/15 (20%; 4 mg/kg) and 6/12 (50%; 6 mg/kg) patients with a DoR ≥12 months; 4 patients in the 6 mg/kg cohort were in response for >18 months.

Thirty-one (89%) and 21 (64%) patients in the 4 and 6 mg/kg cohorts, respectively, had a PFS event, with 29 and 20 having progressed, and 2 and 1 having died in the absence of progression. Median (95% CI) PFS was 9.5 months (7.2-9.8 months) (4 mg/kg) and 11.7 months (8.3-21.7 months) (6 mg/kg) (Figure 2A). Progression-free rate at 12 months was 21% and 40%, and at 18 months was 12% and 33%, respectively, in the 4 and 6 mg/kg cohorts. PFS by presence of CNS metastases at baseline and by time to progression on first-line osimertinib are described in Supplementary Results and shown in Supplementary Figures S6 and S7, available at https://doi.org/10.1016/j.annonc.2026.02.014. In a *post hoc* analysis, most patients with baseline RECIST-evaluable CNS metastases in the 4 mg/kg [*N* = 16 (46%)] and 6 mg/kg [*N* = 11 (33%)] cohorts had PD outside of the CNS; 3/16 (19%) and 6/11 (55%) patients, respectively, had first on-study progression in the CNS (noting that interpretation is limited due to CNS imaging limitations; see Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.02.014 for details). Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2026.02.014 presents a further breakdown of outcomes among patients with baseline CNS metastases, and initial CNS progression in patients with and without CNS metastases at baseline.

Twenty-six (74%) and 16 (48%) patients in the 4 and 6 mg/kg cohorts, respectively, had died by the data cut-off. Median (95% CI) OS was 19.8 months (13.5-23.3 months) (4 mg/kg) and 26.2 months (14.8 months-NC) (6 mg/kg) (Figure 2B). There was similar follow-up (median ∼19 months) across cohorts, but more deaths in the 4 mg/kg cohort, which meant that the survival curve was less affected by censored patients than the 6 mg/kg cohort, for which a stable median was not reached (although it was at least the same or longer than that in the 4 mg/kg cohort). Survival rates at 18 months were 57% and 59% in the 4 and 6 mg/kg cohorts, respectively.

Safety

All patients had one or more treatment-emergent adverse events (TEAEs) (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2026.02.014). The most common any-grade TEAEs by preferred term in the 4 and 6 mg/kg cohorts, respectively, were stomatitis (66% and 76%), nausea (57% and 74%), and alopecia (51% and 68%) (Table 3). Several AEs were reported more frequently in the 6 mg/kg cohort, including cough (4 mg/kg versus 6 mg/kg: 26% versus 53%), vomiting (17% versus 50%), asthenia (11% versus 29%), rash (9% versus 24%), malaise (9% versus 21%), gastroesophageal reflux disease (3% versus 21%), dysgeusia (6% versus 18%), and lacrimation increased (0% versus 15%). Grade ≥3 TEAEs were reported in 17 (49%) and 26 (76%) patients in the 4 and 6 mg/kg cohorts, respectively, including 12 (34%) and 19 (56%) that were considered possibly related to any treatment. There were two (6%) grade 4 events in the 4 mg/kg cohort (amylase increased and pneumonitis) and none in the 6 mg/kg cohort. Serious AEs (SAEs) were reported in 11 (31%) (4 mg/kg) and 15 (44%) (6 mg/kg) patients. The most common SAEs by system organ class and preferred term are shown in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2026.02.014. One patient in each cohort died due to an SAE of pneumonia, and one additional patient in the 6 mg/kg cohort died due to sudden death (neither were considered as possibly related to any treatment).

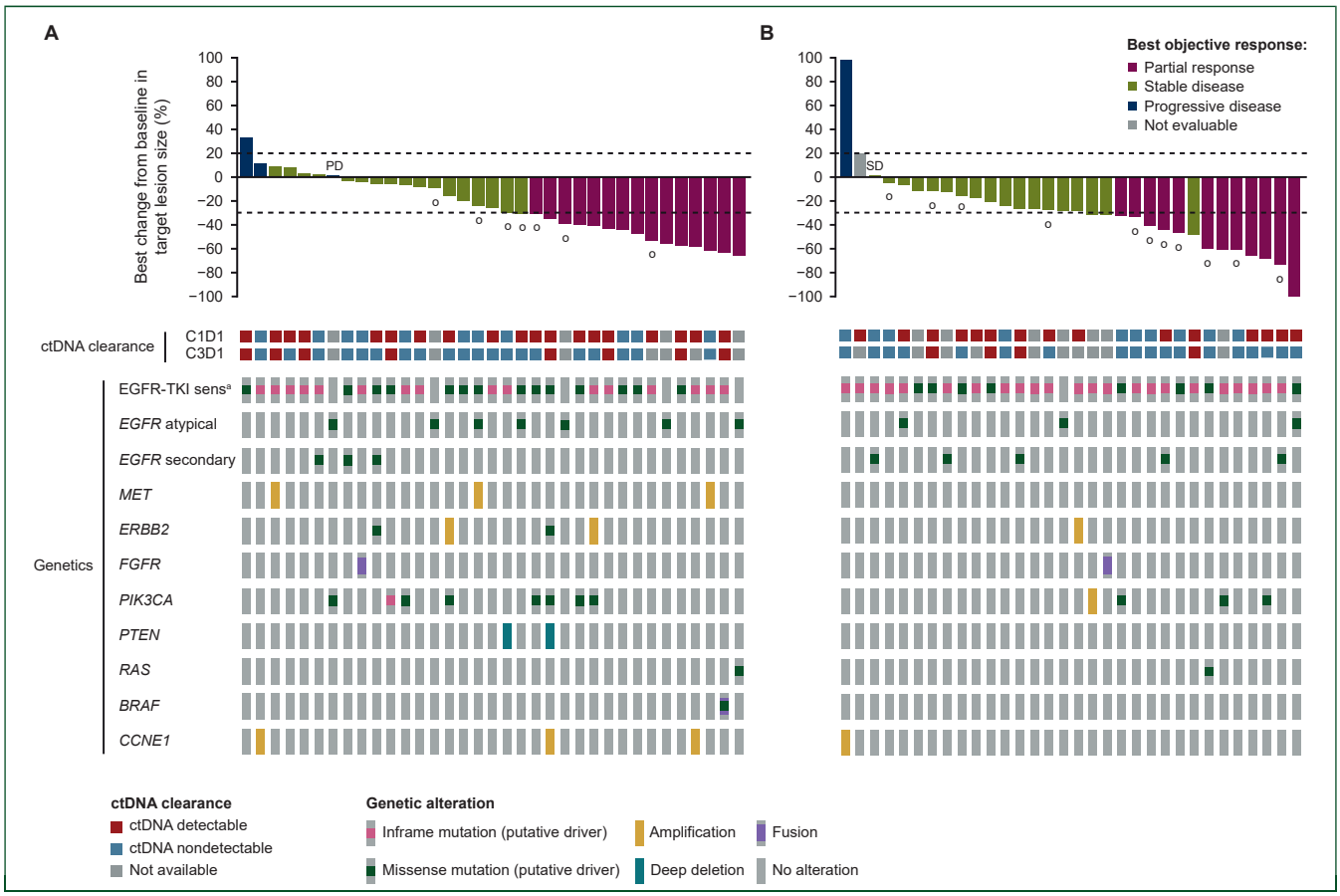


Figure 1. Best percentage change in target lesion size and molecular alterations. Shown are waterfall plots of the best percentage change in target lesion size and best objective response (top panel) and the molecular alterations identified for each patient based on next-generation sequencing analysis of a baseline (after progression on osimertinib) tissue biopsy (bottom panel), for osimertinib plus Dato-DXd 4 mg/kg (A) and osimertinib plus Dato-DXd 6 mg/kg (B). ctDNA clearance was defined as detected baseline plasma EGFR-TKI sensitizing mutations (Ex19del/L858R; detected by droplet digital polymerase chain reaction) that became nondetected at day 1 of cycle 3. 'o' indicates patients ongoing treatment at data cut-off. *BRAF* alteration includes *BRAF* fusions and/or V600E mutation. *EGFR* secondary mutation includes five patients with *EGFR* C797S mutation and three patients with *EGFR* L718V mutation. Four patients had multiple co-existing resistance mechanisms: one patient with *EGFR* secondary mutation and *ERBB2* mutation; two patients with *ERBB2* amplification and *PIK3CA* mutation; and one patient with *ERBB2* mutation, *PIK3CA* mutation, *PTEN* deletion, and *CCNE1* amplification

C, Cycle; ctDNA, circulating tumor DNA; D, Day; Dato-DXd, datopotamab deruxtecan; EGFR, epidermal growth factor receptor; PD, progressive disease; sens, sensitizing; SD, stable disease; TKI, tyrosine kinase inhibitor.

[a]For EGFR-TKI sensitizing mutations, all missense mutations are L858R and all inframe mutations are Ex19del.

AEs leading to osimertinib dose reduction occurred in 6 (17%) and 0 patients in the 4 and 6 mg/kg cohorts, respectively; AEs leading to Dato-DXd dose reduction occurred in 8 (23%) and 20 (59%) patients (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2026.02.014). The most common AEs leading to osimertinib dose reduction were paronychia and hyperamylasemia (6% each, in the 4 mg/kg cohort), while the most common AEs leading to Dato-DXd dose reduction were stomatitis [9% (4 mg/kg) and 24% (6 mg/kg)] and nausea [0% (4 mg/kg) and 9% (6 mg/kg)] (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2026.02.014). AEs leading to treatment discontinuation are shown in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2026.02.014.

AEs of special interest (AESI) with regards to Dato-DXd are shown in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2026.02.014. Stomatitis/oral mucositis occurred in 24 (69%) and 29 (85%) of patients in the 4 and 6 mg/kg cohorts, respectively, and ocular surface events occurred in 5 (14%) and 9 (26%) patients. ILD/pneumonitis (adjudicated) was reported in one (3%) patient (grade 4) in the 4 mg/kg cohort and five (15%) patients (one grade 1, two grade 2, two grade 3) in the 6 mg/kg cohort. Of these, 1/1 (100%) and 3/5 (60%) patients, respectively, were Asian.

Association between baseline molecular alterations and treatment response

All patients had *EGFR* mutations detected in a baseline (postprogression on first-line osimertinib) tissue biopsy (Figure 1). Among the overall cohort, tumor shrinkages were observed in all patients with a *RAS* mutation ($n = 2$), *BRAF* alteration (co-occurring *BRAF* V600E and *BRAF* BRWD1 fusion; $n = 1$), *ERBB2* amplification/mutation ($n = 5$), and multiple co-existing resistance mechanisms ($n = 4$). Tumor shrinkages were also observed in 2/3 (67%) patients with *MET* amplification, 6/8 (75%) patients with *EGFR*

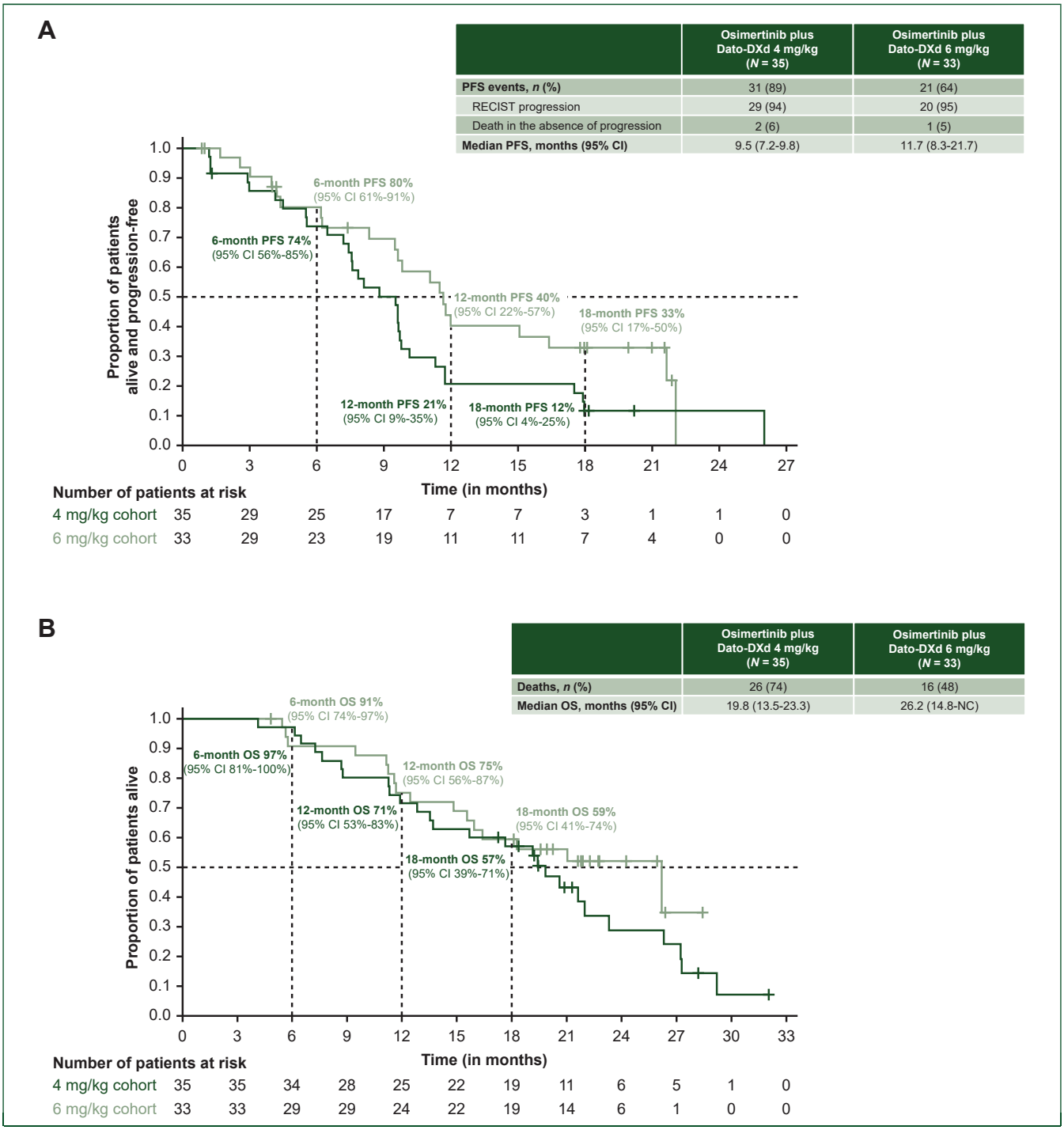


Figure 2. Progression-free survival and overall survival. Shown are Kaplan—Meier estimates of progression-free survival (A) and overall survival (B). + indicates a censored observation.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; NC, not calculable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

secondary mutations (5/8 C797S and 3/8 L718V), and 12/13 (92%) of patients with *PIK3CA*/*PTEN* alterations (Figure 1). Two of four (50%) patients with *CCNE1* amplification showed no tumor shrinkage, with a best response of PD (Figure 1). In both cohorts, the presence of resistance alterations did not affect clinical response (Supplementary Figure S8, available at https://doi.org/10.1016/j.annonc.2026.02.014).

Plasma ctDNA analysis

Fifty-six patients had valid plasma ddPCR results at baseline; of these, 33 (59%) had a detected baseline plasma *EGFR* mutation (Ex19del/L858R) (Figure 1). Of the 33 patients with baseline-detected plasma *EGFR* mutation, 29 also had a valid ddPCR result at cycle 3 day 1 and thus had available data for analysis of ctDNA clearance. ctDNA clearance was observed in 9/17 (53%) and 8/12 (67%)

Table 3. Treatment-emergent adverse events reported in ≥10% of patients

Preferred term, *n* (%)	Osimertinib plus Dato-DXd 4 mg/kg (*N* = 35)		Osimertinib plus Dato-DXd 6 mg/kg (*N* = 34)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	35 (100)	17 (49)	34 (100)	26 (76)
Stomatitis	23 (66)	5 (14)	26 (76)	4 (12)
Nausea	20 (57)	0	25 (74)	3 (9)
Alopecia	18 (51)	0	23 (68)	0
Constipation	16 (46)	0	14 (41)	0
Diarrhea	16 (46)	1 (3)	12 (35)	1 (3)
Cough	9 (26)	0	18 (53)	0
Decreased appetite	12 (34)	0	14 (41)	3 (9)
Vomiting	6 (17)	0	17 (50)	3 (9)
Fatigue	10 (29)	0	12 (35)	3 (9)
Paronychia	11 (31)	0	11 (32)	0
Asthenia	4 (11)	2 (6)	10 (29)	0
COVID-19	8 (23)	0	6 (18)	1 (3)
Oropharyngeal pain	5 (14)	0	8 (24)	0
Dyspnea	5 (14)	0	7 (21)	0
Pruritus	5 (14)	0	7 (21)	0
Amylase increased	4 (11)	2 (6)	7 (21)	3 (9)
Anemia	5 (14)	1 (3)	6 (18)	1 (3)
Pyrexia	5 (14)	0	6 (18)	0
Rash	3 (9)	0	8 (24)	0
Dry skin	4 (11)	0	6 (18)	0
Malaise	3 (9)	0	7 (21)	0
Rash maculopapular	4 (11)	1 (3)	6 (18)	0
Upper respiratory tract infection	6 (17)	0	4 (12)	0
Urinary tract infection	7 (20)	1 (3)	3 (9)	0
Weight decreased	5 (14)	0	5 (15)	1 (3)
Dyspepsia	6 (17)	0	3 (9)	0
Headache	3 (9)	0	6 (18)	0
Pneumonia	4 (11)	3 (9)	5 (15)	3 (9)
Arthralgia	5 (14)	0	3 (9)	1 (3)
Back pain	3 (9)	0	5 (15)	1 (3)
Dysgeusia	2 (6)	0	6 (18)	0
Gastroesophageal reflux disease	1 (3)	0	7 (21)	0
Infusion-related reaction	6 (17)	0	1 (3)	0
Nasopharyngitis	4 (11)	0	3 (9)	0
Dizziness	2 (6)	0	4 (12)	0
Insomnia	4 (11)	0	2 (6)	0
Edema peripheral	4 (11)	0	2 (6)	0
Pneumonitis	2 (6)	1 (3)	4 (12)	0
Skin fissures	2 (6)	0	4 (12)	0
Skin hyperpigmentation	2 (6)	0	4 (12)	0
Abdominal pain	1 (3)	0	4 (12)	0
Dermatitis acneiform	4 (11)	0	1 (3)	0
Dysphonia	4 (11)	0	1 (3)	0
Lacrimation increased	0	0	5 (15)	0

Patients with more than one event in the same preferred term were counted only once in that preferred term. Patients with events in more than one preferred term were counted once in each of those preferred terms. A TEAE was defined as an event with an onset date or worsening on or after the date of first dose of any study treatment and up to and including 35 days following the last dose of study treatment or the date of start of subsequent cancer therapy, whichever occurred first. TEAEs were graded using CTCAE version 5.0. MedDRA version 28.0.
CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

patients in the 4 and 6 mg/kg cohorts, respectively; of these, 3/9 (33%) and 5/8 (63%) patients had a best response of PR (Figure 1).

Acquired mechanisms of resistance

Fifteen patients had paired plasma samples (baseline and after PD on osimertinib plus Dato-DXd) with evaluable results from ctDNA NGS analysis (Supplementary Figure S9, available at https://doi.org/10.1016/j.annonc.2026.02.014). Overall, resistance alterations present at baseline in 4/15 (27%) patients were undetected at PD (patients #1—4; included *EGFR* secondary mutations, *MET* amplification, *ERBB2* mutation/amplification, and *PIK3CA* mutation). In addition, 3/15 (20%) patients had acquired resistance alterations at PD (patients #5—7; included *ERBB3* amplification, *MET* amplification, *PIK3CA* amplification, and *BRAF* mutation).

DISCUSSION

This module of the ORCHARD study evaluated the efficacy and safety/tolerability of osimertinib plus Dato-DXd in patients with *EGFR*-mutated, locally advanced/metastatic NSCLC whose disease had progressed on first-line osimertinib. In this final analysis of 69 patients, osimertinib plus Dato-DXd 6 mg/kg (*N* = 33) treatment led to a confirmed ORR of 36%, with 50% of responders maintaining a response for ≥12 months. A similar ORR was observed in the 4 mg/kg cohort, although DoR was shorter. The safety profile of the combination was consistent with the profiles of the individual drugs,[2,4,23-25] and no new safety signals were identified. These data confirm the results of the interim analysis,[26] and demonstrate the promising and durable efficacy of this combination in a population with limited treatment options and poor prognosis after progression on osimertinib. Based upon the ORR result applied to the decision framework and the observed PFS, DoR, and OS data, the efficacy results are supportive of further development of the osimertinib plus Dato-DXd combination.

Before the recent approvals of new treatment options,[15-17] following progression on first-line osimertinib, most patients traditionally received platinum-based chemotherapy,[27] despite the limited clinical benefit.[2,28] To overcome the unmet needs in this setting, which remain even with the new treatment options,[23,25,28] many different targeted treatments are under investigation, including those evaluated in other ORCHARD modules. However, many patients do not have known actionable resistance mutations at progression that can be matched to targeted therapies; these patients may benefit from treatments with alternative cytotoxic mechanisms. In this module of ORCHARD, osimertinib plus Dato-DXd 6 mg/kg led to a median PFS of 11.7 months (8.3-21.7 months) and a median OS of 26.2 months (14.8 months-NC); while not stable, median OS was at least the same or longer than in the 4 mg/kg cohort (19.8 months). In AURA3,[2,3] treatment with second-line platinum doublet chemotherapy in patients who progressed on a first- or second-generation EGFR-TKI achieved a median PFS of 4.4 months and median OS of 22.5 months. In the MARIPOSA-2 trial, the combination of

amivantamab plus chemotherapy achieved a median PFS of 6.3 months in patients with *EGFR*-mutated NSCLC with PD on or after osimertinib monotherapy.[28] In addition to being evaluated in combination with osimertinib, Dato-DXd was investigated as monotherapy for *EGFR*-mutated NSCLC in the phase III TROPION-Lung01 and phase II TROPION-Lung05 trials.[23,25] In a pooled analysis, Dato-DXd monotherapy led to a median PFS of 5.8 months and median OS of 15.6 months in the post-EGFR-TKI, post-platinum-based chemotherapy setting.[21] The results achieved in ORCHARD with continued osimertinib plus Dato-DXd are promising and suggest that continuing osimertinib beyond progression may provide clinical benefit, although further randomized studies are required to compare osimertinib plus Dato-DXd with standard-of-care treatment and demonstrate a clinically meaningful benefit in this setting. Evidence supporting continued osimertinib was recently provided by the COMPEL study, where patients with *EGFR*-mutated advanced NSCLC and PD on first-line osimertinib who received platinum-based chemotherapy were shown to benefit from continuing osimertinib beyond progression (in comparison with placebo).[29] Results from two ongoing phase III randomized trials, TROPION-Lung14 (NCT06350097)[30] and TROPION-Lung15 (NCT06417814),[31] will provide additional evidence on the role of osimertinib plus Dato-DXd in patients with *EGFR*-mutated advanced NSCLC in the treatment-naïve and post-osimertinib progression settings, respectively. TROPION-Lung15 will also enable direct comparison of the combination to platinum-based chemotherapy.

In ORCHARD there were fewer progression events in the 6 versus 4 mg/kg cohort, and there was also a separation of the PFS Kaplan—Meier curves at 6 months in favor of the 6 mg/kg cohort. Moreover, time to response was shorter in the 6 versus 4 mg/kg cohort, and treatment with Dato-DXd 6 mg/kg led to an encouraging DoR, with more patients continuing to respond past 12 and 18 months than in the 4 mg/kg cohort (despite the higher proportion of patients who subsequently required a Dato-DXd dose reduction, suggesting the importance of the higher initial dose). A lower proportion of patients with baseline CNS metastases and longer time to progression on first-line osimertinib in the 6 versus 4 mg/kg cohort may have influenced the efficacy results, but this is inconclusive based on the current analysis. Subgroup analyses suggest that PFS is not affected by time to progression on first-line osimertinib for this combination.

Dato-Dxd has previously demonstrated CNS efficacy as a single agent and the continuation of osimertinib after progression provides the opportunity for additional CNS activity.[32] Interpretation of CNS activity of the combination in this study is limited due to CNS imaging only being required at baseline, unless baseline CNS metastases were present or at the treating investigator's discretion. Additionally, study imaging stopped after any PD or cessation of study treatment if treated beyond PD, and CNS metastases were recorded as nontarget lesions only. Results from a limited *post hoc* analysis of patients with baseline CNS metastases from both dose cohorts are encouraging preliminary data supporting potential CNS activity of the combination, with most first progression events occurring outside the CNS, and encouraging overall PFS maintained among patients with baseline CNS metastases.

In ORCHARD, osimertinib plus Dato-DXd demonstrated efficacy across multiple genetic subgroups (based on molecular alterations identified at progression on first-line osimertinib monotherapy). Patients harboring single or multiple resistance mechanisms, including bypass tract alterations, had comparable extent of tumor shrinkage to those without confirmed resistance alterations. In contrast to TROPION-Lung01[23] and TROPION-Lung05,[25] analysis of molecular alterations was conducted after first-line osimertinib and before additional cytotoxic therapy, allowing a more accurate assessment of efficacy in genetic subpopulations based on potential mechanism of resistance to first-line therapy. Additionally, evaluation of changes in resistance patterns at PD suggests successful targeting of resistant tumor clones in a modest portion of patients. The presence of *EGFR* mutations across all samples supports the rationale for continuing osimertinib beyond progression. Under the continued selection pressure of osimertinib, a small subset of patients (3/15; 20%) had bypass tract alterations emerge after PD on osimertinib plus Dato-DXd, underscoring the importance of repeating molecular profiling at progression to inform subsequent treatment decisions.

The safety of the osimertinib plus Dato-DXd combination was consistent with the known profiles of the individual drugs. However, the 6 mg/kg dose was less well tolerated than the lower dose, with a higher proportion of patients with Dato-DXd dose reductions, Dato-DXd dose interruptions, and grade $\geq$3 AEs. Dato-DXd dose reduction occurred in 59% of patients in the 6 mg/kg cohort versus 23% at 4 mg/kg, most commonly due to stomatitis and nausea. There was also an increased frequency of AEs in the 6 mg/kg cohort, with notable differences in the frequency of stomatitis, nausea, alopecia, vomiting, cough, asthenia, rash, gastroesophageal reflux disease, ocular surface events (attributed to a greater number of patients with lacrimation increased at 6 mg/kg), and ILD/pneumonitis (adjudicated). Two-thirds (four out of six) of the overall ILD/pneumonitis (adjudicated) cases were observed in Asian patients despite this subgroup comprising only one-third of the overall population in this module. Low patient numbers precluded any formal analysis to determine whether race is a risk factor, though this is an area of interest for EGFR-TKIs and ILD.[33] To optimize the effectiveness of the 6 mg/kg Dato-DXd dose with the greater frequency and severity of AEs, use of prophylaxis and close management of AEs related to Dato-DXd is crucial, particularly in relation to gastrointestinal toxicity, ILD/pneumonitis, and stomatitis. Prophylaxis guidance used in this study is detailed in the Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2026.02.014. Despite a large proportion of patients with Dato-DXd dose reduction in the 6 mg/kg cohort, most remained on Dato-DXd at the 4 mg/kg dose through the rest of the study. The suggestion of

more favorable efficacy at the 6 mg/kg dose, despite more frequent dose reduction, points to the potential importance of optimizing the dose intensity of Dato-DXd at the initiation of treatment.

The results of this study should be interpreted in the context of the following limitations. Firstly, the lack of a comparator prevents direct comparison with standard-of-care treatment or Dato-DXd monotherapy. Secondly, analyses are based on small sample sizes, with some imbalances in baseline characteristics, as mentioned previously, and so the data should be interpreted with caution. Additionally, the CNS exploratory analysis is further limited by nontarget lesion designation, lack of serial imaging in patients without baseline CNS tumors, and absence of further imaging after progression.

In conclusion, osimertinib plus Dato-DXd demonstrated encouraging clinical benefit (particularly in the 6 mg/kg cohort) in patients who had progressed after first-line osimertinib, supporting the rationale for continuing osimertinib beyond progression and combining it with a cytotoxic, biomarker-agnostic treatment. AEs among patients in the 6 mg/kg cohort were of higher frequency and severity but could be managed with careful monitoring and dose reduction to allow continuation of treatment. Considering the overall benefit—risk profile, 6 mg/kg is suggested as the preferred Dato-DXd starting dose for combining with osimertinib 80 mg. This combination may provide an alternative treatment option after progression for patients with *EGFR*-mutated advanced NSCLC regardless of the mechanism of resistance. Osimertinib plus Dato-DXd 6 mg/kg will be assessed further in the TROPION-Lung14 and TROPION-Lung15 studies.[30,31]

ACKNOWLEDGMENTS

The authors thank all the patients and their families, as well as the staff and investigators at all study sites. The authors also thank Jan Cosaert, formerly of AstraZeneca, for his contributions to the study. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Alice Carruthers, PhD, of Ashfield MedComms, an Inizio company, and funded by AstraZeneca in accordance with Good Publications Practice guidelines (in the http://www.ismpp.org/gpp-2022).

FUNDING

This study (ClinicalTrials.gov identifier NCT03944772) was funded by AstraZeneca. The study was designed by the sponsor in collaboration with the coordinating investigator, Helena A. Yu, and steering committee. Data were collected by the investigators and analyzed and interpreted jointly with the sponsor. All authors were involved in manuscript development, with medical writing support funded by the sponsor.

DISCLOSURE

JWR: advisory roles with Amgen, ArriVent, AstraZeneca, Bristol Myers Squibb (BMS), Catalyst, GSK, Janssen, Merck, Merus NV, Nuvalent, Oncohost, Pfizer, Regeneron, Roche/Genentech, and Sanofi; consulting fees from Daiichi Sankyo; and grants/funds from ArriVent, AstraZeneca/MedImmune, Avistone, Boehringer Ingelheim, IO Biotech, Merck, Novartis, Nuvalent, Pfizer, Prelude Therapeutics, Revolution Medicines, and Summit Therapeutics. HAY: honoraria from AstraZeneca, Blueprint Medicines, C4 Therapeutics, Daiichi Sankyo, and Janssen, and grants/funds from AstraZeneca, Cullinan, Daiichi Sankyo, Eli Lilly, Novartis, and Pfizer. XL: advisory board or committee participation with AbbVie, Abion, ArriVent, AstraZeneca, Bayer, BlossomHill Therapeutics, Blueprint Medicines, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, EMD Serono (Merck KGaA), Hengrui Therapeutics, Janssen, Novartis, Regeneron, Sensei Biotherapeutics, Spectrum Pharmaceutics, SystImmune, Taiho, and Teligene, and grants/funds from ArriVent, Boehringer Ingelheim, Dizal, Eli Lilly, EMD Serono, Janssen, Regeneron, Takeda, Teligene, and ThermoFisher. AJdeL: advisory board or committee participation with AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Merck & Co (MSD), Pfizer, and Roche, and grants/funds from AstraZeneca, BMS, Boehringer Ingelheim, and MSD. BCC: employment with Yonsei University Health System, stocks/shares with BridgeBio Therapeutics, Cyrus Therapeutics, Gencurix Inc, Interpark Bio Convergence Corp., J INTS BIO, Kanaph Therapeutic Inc., and TheraCanVac Inc.; advisory roles with BridgeBio Therapeutics, Cyrus Therapeutics, Guardant Health, J INTS BIO, Kanaph Therapeutic Inc., and Therapex Co., Ltd.; board of directors for J INTS BIO, consulting fees from Amgen, AnHeart Therapeutics, ArriVent, AstraZeneca, BeiGene, BMS, Boehringer Ingelheim, CJ, Cyrus Therapeutics, Daiichi Sankyo, Eli Lilly, Gilead, GSK, Harpoon Therapeutics, Janssen, Merck Sharpe & Dohme (MSD), Novartis, Ono, Pfizer, Regeneron, Roche, Sanofi, Seagen, Takeda, and Yuhan; grants/funds from AstraZeneca, Champions Oncology, CJ Bioscience, Cyrus, Dong-A ST, GI Innovation, ImmuneOncia, J INTS BIO, Janssen, MSD, Therapex, Vertical Bio AG, and Yuhan; royalties from Champions Oncology, Crown Bioscience, Imagen, and PearlRiver Bio GmbH; founder of DAAN Biotherapeutics; and invited speaker for American Society of Clinical Oncology (ASCO), AstraZeneca, European Society for Medical Oncology (ESMO), Guardant, International Association for the Study of Lung Cancer (IASLC), Korean Cancer Association, Korean Cancer Study Group, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, MSD, Novartis, Pfizer, Roche, The Chinese Thoracic Oncology Society, and Zailab. ZP: honoraria from AstraZeneca, Blueprint Medicines, Boehringer Ingelheim, Eli Lilly, and Janssen; consulting fees from AbbVie, AstraZeneca, Bayer, Black Diamond Therapeutics, BlossomHill Therapeutics, Blueprint Medicines, Boehringer Ingelheim, C4 Therapeutics, Cullinan, Daiichi Sankyo, Eli Lilly, Genentech, Genmab, Gilead, Janssen, Merck, Natera, Revolution Medicines, Sanofi/Genzyme, Summit Therapeutics, Taiho, Takeda, and Tubulis; grants/funds from AbbVie, AstraZeneca, BlossomHill Therapeutics, Blueprint Medicines, Cullinan, Daiichi Sankyo, Janssen, Novartis, Nuvalent,

Spectrum, SystImmune, Takeda, and Tesaro/GSK, and travel support from AstraZeneca and Janssen. LELH: research funding (all to institution) from Amgen (under negotiation), AstraZeneca, Boehringer Ingelheim, Gilead, Genentech, Merck, Novartis, Pfizer, Roche, Summit Therapeutics (under negotiation), and Takeda; speaker educational/webinars with AstraZeneca, Bayer, Eli Lilly, GSK, high5oncology, Janssen, MSD, Pfizer, Sanofi, and Takeda (to institution), and Benecke, Medimix, Medtalks, and VJOncology (to self); advisory board participation (all to institution) with AbbVie, Amgen, Anhearth, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, Gilead, GSK, Janssen, Eli Lilly, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Summit Therapeutics, and Takeda; member of guideline committees with the Dutch guidelines on NSCLC, brain metastases, and leptomeningeal metastases (payment to self), ESMO guidelines on metastatic NSCLC, and non-metastatic NSCLC and SCLC (nonfinancial); other (nonfinancial) includes former secretary and current chair Dutch Association of Physicians for Pulmonary Diseases and Tuberculosis (NVALT) studies foundation, subchair European Organisation for Research and Treatment of Cancer (EORTC) metastatic NSCLC systemic therapy, and vice-chair scientific committee Dutch Thoracic Group; and local principal investigator of clinical trials (all to institution) with AbbVie (also steering committee), Amgen, AstraZeneca, Blueprint, Boehringer Ingelheim, BMS, Daiichi Sankyo, Gilead, GlaxoSmithKline, MSD, Mirati, Novartis, Pfizer, Roche, and Takeda. AM: honoraria from AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Pierre Fabre, Pfizer, Roche, and Takeda. LB: speaker fee or advisory board honoraria from AstraZeneca, BMS, Janssen, MSD, Novartis, Pfizer, Roche, and Takeda; committee participation with AstraZeneca; and institutional research funding from AstraZeneca. OTB: institutional fees/grants/funds from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, MSD, Novartis, Pfizer, Roche, Sanofi, and Takeda. TOH: advisory board participation with AstraZeneca, Sanofi, and Immedica; honoraria from AstraZeneca, Johnson & Johnson, MSD, Pfizer, and Takeda; and research funding from AstraZeneca and Roche. YJK: research funding for their institution from Amgen, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Bridge Biotherapeutics, BMS, Daiichi Sankyo, Eli Lilly, GSK, Janssen, MSD, Pfizer, Roche, Taiho, Voronoi, and Yuhan. KAM: consultancy/advisory role with Amgen, AstraZeneca, BMS, Eli Lilly, Merus, Regeneron, Revolution Medicines, and research funding (to institution) with BMS and Mirati. YS: honoraria from AstraZeneca, BMS, Chugai, Kyowa Kirin, Ono, and Taiho, and grants/funds from Chugai. JWG: advisory board or committee participation with AbbVie, AstraZeneca, BMS, Genentech, Jazz, Eli Lilly, Pfizer, and Summit Therapeutics; consulting fees from AbbVie, AstraZeneca, BMS, Genentech, Jazz, Eli Lilly, Pfizer, and Summit Therapeutics; and grants/funds from AbbVie, Advaxis, AstraZeneca/MedImmune, BMS, Corvus Pharmaceuticals, Genentech/Roche, Eli Lilly, Lyell, Pfizer, and Spectrum Pharmaceuticals. HA: employment and stocks/shares with AstraZeneca. PES: consulting fees from AstraZeneca. PGF: employment and stocks/shares with AstraZeneca. KHT: employment and stocks/shares with AstraZeneca. JML: employment and stocks/shares with AstraZeneca. SBG: research funding from Adela, AstraZeneca, Boehringer Ingelheim, and Mirati, and consulting/advisory board member for AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, Johnson & Johnson, Merck, Regeneron, Summit Therapeutics, Synthekine, and Tubulis.

DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecaclinicaltrials.com/our-transparency-commitments. Anonymized datasets may be available on request. Requests for access to data may be submitted at https://search.vivli.org/. The request will undergo an internal review process, and if approved, data will be prepared and shared with specified accessors named on the request form for 12 months via Vivli Secure Research Environment.

REFERENCES

1. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*. 2014;4(9):1046-1061.
2. Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum—pemetrexed in EGFR T790M—positive lung cancer. *N Engl J Med*. 2017;376(7):629-640.
3. Papadimitrakopoulou VA, Mok TS, Han JY, et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. *Ann Oncol*. 2020;31(11):1536-1544.
4. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non—small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125.
5. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50.
6. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected *EGFR*-mutated non—small-cell lung cancer. *N Engl J Med*. 2020;383(18):1711-1723.
7. Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected *EGFR*-mutated NSCLC. *N Engl J Med*. 2023;389(2):137-147.
8. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol*. 2018;36(33):3290-3297.
9. Wu YL, Ahn MJ, Garassino MC, et al. CNS efficacy of osimertinib in patients with T790M-positive advanced non—small-cell lung cancer: data from a randomized phase III trial (AURA3). *J Clin Oncol*. 2018;36(26):2702-2709.
10. Ahn MJ, Chiu CH, Cheng Y, et al. Osimertinib for patients with leptomeningeal metastases associated with EGFR T790M-positive advanced NSCLC: the AURA leptomeningeal metastases analysis. *J Thorac Oncol*. 2020;15(4):637-648.
11. Yang JCH, Kim SW, Kim DW, et al. Osimertinib in patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer and leptomeningeal metastases: the BLOOM study. *J Clin Oncol*. 2020;38(6):538-547.
12. Reuss JE, Kuruvilla S, Ismaila N, et al. Therapy for stage IV non-small cell lung cancer with driver alterations: ASCO living guideline, version 2025.1. *J Clin Oncol*. 2025;43(4):e31-e44.

13. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121(9):725-737.
14. Hendriks LEL, Cortiula F, Martins-Branco D, Mariamidze E, Popat S, Reck M, ESMO Guidelines Committee. Updated treatment recommendations for systemic treatment: from the ESMO oncogene-addicted metastatic NSCLC living guideline. *Ann Oncol*. 2025;36(10):1227-1231.
15. U.S. Food & Drug Administration. FDA grants accelerated approval to datopotamab deruxtecan-dlnk for EGFR-mutated non-small cell lung cancer. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-datopotamab-deruxtecan-dlnk-egfr-mutated-non-small-cell-lung-cancer. Accessed July 16, 2025.
16. U.S. Food & Drug Administration. FDA approves amivantamab-vmjw with carboplatin and pemetrexed for non-small cell lung cancer with EGFR exon 19 deletions or L858R mutations. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-amivantamab-vmjw-carboplatin-and-pemetrexed-non-small-cell-lung-cancer-egfr-exon-19. Accessed July 16, 2025.
17. European Medicines Agency. Rybrevant 350 mg concentrate for solution for infusion. Summary of product characteristics. Available at https://www.ema.europa.eu/en/documents/product-information/rybrevant-epar-product-information_en.pdf. Accessed July 16, 2025.
18. Chmielecki J, Gray JE, Cheng Y, et al. Candidate mechanisms of acquired resistance to first-line osimertinib in EGFR-mutated advanced non-small cell lung cancer. *Nat Commun*. 2023;14(1):1070.
19. Chmielecki J, Gray JE, Cheng Y, et al. Author Correction: Candidate mechanisms of acquired resistance to first-line osimertinib in EGFR-mutated advanced non-small cell lung cancer. *Nat Commun*. 2023;14:3179.
20. Okajima D, Yasuda S, Maejima T, et al. Datopotamab deruxtecan, a novel TROP2-directed antibody-drug conjugate, demonstrates potent antitumor activity by efficient drug delivery to tumor cells. *Mol Cancer Ther*. 2021;20(12):2329-2340.
21. Ahn MJ, Lisberg A, Goto Y, et al. A pooled analysis of datopotamab deruxtecan in patients with *EGFR*-mutated NSCLC. *J Thorac Oncol*. 2025;20(11):1669-1682.
22. Yu HA, Goldberg SB, Le X, et al. Biomarker-directed phase II platform study in patients with EGFR sensitizing mutation-positive advanced/metastatic non-small cell lung cancer whose disease has progressed on first-line osimertinib therapy (ORCHARD). *Clin Lung Cancer*. 2021;22(6):601-606.
23. Ahn MJ, Tanaka K, Paz-Ares L, et al. Datopotamab deruxtecan versus docetaxel for previously treated advanced or metastatic non-small cell lung cancer: the randomized, open-label phase III TROPION-Lung01 study. *J Clin Oncol*. 2025;43(3):260-272.
24. Planchard D, Janne PA, Cheng Y, et al. Osimertinib with or without chemotherapy in *EGFR*-mutated advanced NSCLC. *N Engl J Med*. 2023;389(21):1935-1948.
25. Sands J, Ahn MJ, Lisberg A, et al. Datopotamab deruxtecan in advanced or metastatic non-small cell lung cancer with actionable genomic alterations: results from the phase II TROPION-Lung05 study. *J Clin Oncol*. 2025;43(10):1254-1265.
26. Le X, Hendriks L, Morabito A, et al. 1O: Osimertinib (osi) + datopotamab deruxtecan (Dato-DXd) in patients (pts) with EGFR-mutated (EGFRm) advanced NSCLC (aNSCLC) whose disease progressed on first-line (1L) osi: ORCHARD. *J Thorac Oncol*. 2025;20(3):S2-S4.
27. Robinson ND, Canavan ME, Zhan PL, et al. Treatment patterns and clinical outcomes in patients with EGFR-mutated non-small-cell lung cancer after progression on osimertinib. *Clin Lung Cancer*. 2025;26(1):9-17.e13.
28. Passaro A, Wang J, Wang Y, et al. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. *Ann Oncol*. 2024;35(1):77-90.
29. Peled N, Tufman A, Sequist LV, et al. COMPEL: osimertinib plus platinum-based chemotherapy in patients with EGFR-mutated advanced NSCLC and progression on first-line osimertinib. *ESMO Open*. 2025;10(10):105807.
30. Clinicaltrials.gov. Phase III, open-label study of first-line osimertinib with or without datopotamab deruxtecan for EGFRm locally advanced or metastatic non-small cell lung cancer (TROPION-Lung14). NCT06350097. Available at https://clinicaltrials.gov/study/NCT06350097. Accessed July 1, 2025.
31. Clinicaltrials.gov. A study to investigate the efficacy and safety of Dato-DXd with or without osimertinib compared with platinum based doublet chemotherapy in participants with EGFR-mutated locally advanced or metastatic non-small cell lung cancer (TROPION-Lung15). NCT06417814. Available at https://clinicaltrials.gov/study/NCT06417814. Accessed July 1, 2025.
32. Pons-Tostivint E, Okamoto I, Ahn MJ, et al. OA10.01 Intracranial efficacy of datopotamab deruxtecan (Dato-DXd) in patients with advanced/metastatic NSCLC in TROPION-Lung01. *J Thorac Oncol*. 2025;20(10):S30-S31.
33. Saito S, Lasky JA, Hagiwara K, Kondoh Y. Ethnic differences in idiopathic pulmonary fibrosis: the Japanese perspective. *Respir Investig*. 2018;56(5):375-383.