THERAPEUTIC ADVANCES in
Medical Oncology

Study Protocol

TROPION-Lung15: a randomized phase III study of osimertinib combined with datopotamab deruxtecan (Dato-DXd) or Dato-DXd alone versus platinum-doublet chemotherapy in patients with *EGFR*-mutated advanced non-small cell lung cancer and whose disease has progressed on prior osimertinib

Ther Adv Med Oncol

2025, Vol. 17: 1–12

DOI: 10.1177/17588359251385410

Daniel Shao-Weng Tan, Ernest Nadal, Parneet Cheema, Yi-Long Wu, Myung-Ju Ahn, Junko Tanizaki, Ellie Grainger, Emily Nizialek, Alessandra Forcina, Toon van der Gronde and Helena A. Yu

Correspondence to:
Helena A. Yu
Department of Medicine (Medical Oncology), Memorial Sloan-Kettering Cancer Center, 530 East 74th Street, New York, NY 10021, USA
YuH@mskcc.org

Daniel Shao-Weng Tan
Medical Oncology Department, National Cancer Centre Singapore, Singapore

Ernest Nadal
Medical Oncology Department, Catalan Institute of Oncology, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

Parneet Cheema
Medical Oncology Department, William Osler Health Sciences, Brampton, ON, Canada

Yi-Long Wu
Guangdong Provincial People's Hospital, Lung Cancer Institute, Guangzhou, Guangdong Province, China

Myung-Ju Ahn
Hematology–Oncology Department, Samsung Medical Center, Seoul, Republic of South Korea

Junko Tanizaki
Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan

Ellie Grainger
Biostatistics, AstraZeneca, Cambridge, UK

Emily Nizialek
Oncology R&D, AstraZeneca, Gaithersburg, MD, USA

Abstract

Background: Osimertinib is the preferred treatment for patients with *EGFR*-mutated advanced non-small cell lung cancer (NSCLC) in several settings; however, disease progression is common, and treatment options after progression are limited. Datopotamab deruxtecan (Dato-DXd), an antibody-drug conjugate comprising a humanized anti-trophoblast cell-surface antigen 2 (TROP 2) monoclonal antibody conjugated to a potent topoisomerase I inhibitor via a plasma-stable linker, has demonstrated efficacy in advanced NSCLC, including previously treated *EGFR*-mutated advanced NSCLC. Combining osimertinib and Dato-DXd may overcome heterogeneous osimertinib resistance mechanisms and limit tumor progression.

Objectives: TROPION-Lung15 is an ongoing, phase III, open-label, sponsor-blind, multicenter, randomized trial evaluating Dato-DXd ± osimertinib versus chemotherapy in patients with *EGFR*-mutated advanced NSCLC and disease progression on prior osimertinib.

Methods and design: Approximately 630 patients with histologically/cytologically confirmed non-squamous NSCLC, documented epidermal growth factor receptor tyrosine kinase inhibitor-sensitive mutations, and radiologic progression on prior osimertinib monotherapy will be enrolled. Patients will be randomized 1:1:1 to Dato-DXd (6 mg/kg intravenously every 3 weeks), osimertinib (80 mg orally once daily) plus Dato-DXd, or platinum-doublet chemotherapy, stratified by the history/presence of brain metastases (yes vs no), prior osimertinib therapy (adjuvant vs post-chemoradiotherapy/first-line vs second-line), and race. Treatment will continue until radiological progression (per Response Evaluation Criteria in Solid Tumors version 1.1), unacceptable toxicity, or another discontinuation criterion is met. The dual primary endpoints are progression-free survival (PFS) by blinded independent central review (BICR) for osimertinib + Dato-DXd and PFS by BICR for Dato-DXd alone versus chemotherapy. Secondary endpoints include overall survival, central nervous system PFS by BICR, and safety/tolerability.

Ethics: The study is approved by independent ethics committees/institutional review boards at each center. Patients will provide written informed consent.

Discussion: TROPION-Lung15 will assess Dato-DXd ± osimertinib in patients with *EGFR*-mutated advanced NSCLC and disease progression on prior osimertinib. Data from this study could lead to a new treatment option in this setting.

Trial registration: ClinicalTrials.gov identifier: NCT06417814 (date of registration: May 13, 2024).

Alessandra Forcina
Oncology R&D, AstraZeneca, Cambridge, UK

Toon van der Gronde
Oncology R&D, AstraZeneca, New York, NY, USA

Clinical Science, Daiichi Sankyo, Amsterdam, The Netherlands

Plain language summary

TROPION-Lung15: a clinical study comparing osimertinib in combination with datopotamab deruxtecan (Dato-DXd) or Dato-DXd alone versus standard chemotherapy in patients with non-small cell lung cancer (NSCLC) and mutations in the epidermal growth factor receptor *(EGFR)* gene whose disease has progressed after previous osimertinib therapy

Osimertinib is an anticancer drug that blocks the activity of a protein called EGFR on cancer cells and prevents their growth. It is the recommended first treatment for people with *EGFR*-mutated advanced NSCLC, *EGFR*-mutated NSCLC where the cancer has been removed by surgery, and *EGFR*-mutated NSCLC that cannot be removed by surgery and whose disease has not got worse during or after chemoradiotherapy (chemotherapy and radiotherapy). Unfortunately, osimertinib eventually stops working in many people and the cancer returns or starts growing again. Studies are therefore looking for new treatment combinations that might overcome resistance to osimertinib. Datopotamab deruxtecan (Dato-DXd) is an antibody–drug conjugate consisting of an antibody (datopotamab) and an anticancer drug (DXd), joined via a stable, cleavable linker. Dato-DXd has shown promising antitumor efficacy in previous studies in patients with previously-treated advanced/metastatic NSCLC, and in combination with osimertinib in patients with *EGFR*-mutated NSCLC whose disease had gotten worse on initial osimertinib treatment. The TROPION-Lung15 study will compare Dato-DXd with and without osimertinib versus standard chemotherapy in patients with *EGFR*-mutated advanced NSCLC whose disease has progressed after previously taking osimertinib. Eligible patients will be randomly assigned to receive osimertinib plus Dato-DXd, Dato-DXd alone, or chemotherapy. Patients will receive treatment until their disease gets worse, side effects become unacceptable, or they choose to leave the study. The main aim of the study is to see how long patients in the two Dato-DXd treatment groups live without their cancer growing or spreading (progression-free survival) compared with patients receiving chemotherapy. About 630 patients with *EGFR*-mutated advanced NSCLC whose cancer has progressed after previously taking osimertinib are expected to take part. The study is expected to end in 2027, with the first results available in 2026.

Keywords: antibody–drug conjugate, datopotamab deruxtecan, epidermal growth factor receptor, non-small cell lung cancer, osimertinib, trophoblast cell-surface antigen 2

Received: 9 July 2025; revised manuscript accepted: 16 September 2025.

Introduction

Osimertinib is a third-generation, irreversible, central nervous system (CNS)-active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI).[1–11] Osimertinib is recommended in several settings for the treatment of *EGFR*-mutated non-small cell lung cancer (NSCLC).[12–17] First-line osimertinib monotherapy for *EGFR*-mutated advanced NSCLC is recommended after demonstrating significant improvements in both progression-free survival (PFS) and overall survival (OS) compared with first-generation EGFR-TKIs (gefitinib or erlotinib) in patients with previously untreated locally advanced or metastatic NSCLC whose tumors had *EGFR* exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations in the randomized, phase III FLAURA study.[4,6] The addition of chemotherapy to first-line osimertinib treatment in the same setting has since been approved on the basis of results from the phase III FLAURA2 study, which showed superior PFS compared with osimertinib monotherapy.[8] Osimertinib is also recommended as adjuvant treatment for resected stage IB–IIIA *EGFR*-mutated NSCLC after demonstrating significantly longer disease-free

survival (DFS) and OS compared with placebo in the phase III ADAURA study,[7,9,18] and for patients with unresectable *EGFR*-mutated stage III NSCLC without progression during or after chemoradiotherapy, based on significantly prolonged PFS compared with placebo in the phase III LAURA study.[11] Finally, osimertinib demonstrated clinical benefit in patients with *EGFR* T790M-mutation positive locally advanced or metastatic NSCLC, who had progressed on prior systemic therapy including an EGFR-TKI, compared with platinum-based chemotherapy, in the phase III AURA study.[2] Notably, osimertinib has demonstrated marked efficacy in patients with CNS metastases, a common occurrence in *EGFR*-mutated NSCLC and a clinical priority, across these indications.[3,5,7,10,11] In addition, the safety profile reported for osimertinib monotherapy was manageable across studies, with the most commonly reported adverse events (AEs) being grade 1 or 2 rash/acne, diarrhea, dry skin, and paronychia; the incidence of interstitial lung disease (ILD) was $\leqslant$4%.[2,4,7]

Unfortunately, disease progression on osimertinib monotherapy is common, can be due to multiple different mechanisms, and the mechanism of resistance is unknown in up to 50% of cases.[19] In addition, although repeat biopsy following progression is recommended to guide subsequent therapies,[20] failure rates range from 5% to 30%.[21,22] The *EGFR*- and *MET*-directed antibody, amivantamab, in combination with chemotherapy, was recently approved for patients with *EGFR*-mutated advanced NSCLC with disease progression on or after osimertinib monotherapy, based on results of the MARIPOSA-2 study.[23] Median PFS was 6.3 months (95% confidence interval (CI) 5.6−8.4) with amivantamab plus chemotherapy compared with 4.2 months (95% CI 4.0−4.4) with chemotherapy alone (hazard ratio (HR) 0.48, 95% CI 0.36−0.64).[23] Amivantamab plus chemotherapy demonstrated a manageable safety profile, however, an elevated risk of AEs of grade $\geqslant$3 was reported compared with chemotherapy alone (72% vs 48%), which was mainly driven by hematologic toxicity.[23] It is thought that combining osimertinib with therapies with broad antitumor activity, such as an antibody–drug conjugate (ADC), following disease progression on osimertinib monotherapy, may have the potential to overcome osimertinib resistance and provide a non-biomarker directed approach to treatment, while minimizing toxicity associated with chemotherapy, maintaining the suppression of *EGFR*-mutant clones and preventing the occurrence or progression of CNS metastases.

Datopotamab deruxtecan (Dato-DXd) is an ADC comprising a humanized anti-trophoblast cell-surface antigen 2 (TROP2) monoclonal antibody (datopotamab) conjugated to a potent, cytotoxic topoisomerase I inhibitor via a tetrapeptide-based, plasma-stable, tumor-selective cleavable linker.[24] The efficacy and tolerability of Dato-DXd monotherapy have been demonstrated in several studies in NSCLC, including in patients with previously treated *EGFR*-mutated advanced NSCLC.[25] In the phase III TROPION-Lung01 trial, Dato-DXd significantly improved PFS versus docetaxel in patients with pretreated advanced/metastatic NSCLC, which was driven by patients with non-squamous histology.[26] Among the subgroup of patients with non-squamous NSCLC and actionable genomic alterations (including *EGFR* mutations), median PFS was 5.7 months (95% CI 4.2−8.2) with Dato-DXd versus 2.6 months (95% CI 1.4−3.7) with docetaxel (HR 0.35, 95% CI 0.21−0.60). A numerical improvement in OS was also observed in patients with non-squamous histology, although there was no statistically significant difference. Furthermore, in the phase II TROPION-Lung05 trial of Dato-DXd in patients with advanced/metastatic NSCLC with actionable genomic alterations progressing on or after targeted therapy and platinum-based chemotherapy, the confirmed objective response rate (ORR) in patients with *EGFR*-mutated tumors was 43.6% (95% CI 32.4−55.3), median PFS was 5.8 months (95% CI 5.4−8.3), and median OS was 18.3 months (95% CI 12.4−not evaluable).[27] Lastly, in a pooled analysis of patients with *EGFR*-mutated NSCLC from TROPION-Lung05 and TROPION-Lung01, the confirmed ORR by blinded independent central review (BICR) was 43%, median duration of response (DoR) was 7.0 months, and disease control rate was 86%.[28] The most common treatment-related AEs reported for Dato-DXd monotherapy are nausea, stomatitis, and alopecia, which were mostly low grade; the incidence of adjudicated drug-related ILD in these studies was 3.6%–8.8% and most cases were low grade.[26–28]

Preclinical evidence from animal models of *EGFR*-mutant NSCLC suggests that osimertinib treatment upregulates TROP2 expression, and that combination treatment with osimertinib and Dato-DXd shows enhanced efficacy compared with either drug alone, including in

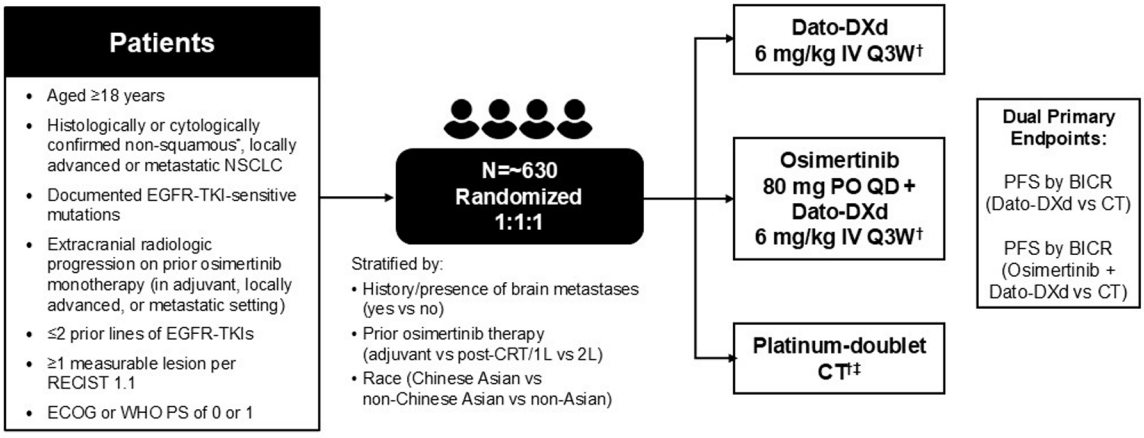

Figure 1. TROPION-Lung15 study design.
*NSCLC of mixed histology is allowed, as long as it is not predominantly squamous histology.
†Treatment will continue until RECIST 1.1-defined radiologic progression by investigator, unacceptable toxicity, or another discontinuation criterion is met. Following discontinuation of study treatment, participants will be followed for PFS2 and OS.
‡Platinum-doublet CT comprises pemetrexed 500 mg/m^2 plus carboplatin AUC5 or cisplatin 75 mg/m^2 IV Q3W × 4 cycles, followed by pemetrexed 500 mg/m^2 IV Q3W as maintenance.
1L, first-line; 2L, second-line; AUC, area under the curve; BICR, blinded independent central review; CRT, chemoradiotherapy; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PFS2, second PFS; PO, by mouth; Q3W, every 3 weeks; QD, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.

osimertinib-resistant models.[29] Notably, in the phase II ORCHARD study, the combination of osimertinib plus Dato-DXd demonstrated promising efficacy (at a median follow-up of 13.8 months, median PFS was 11.7 months (95% CI 8.3−not calculable); ORR was 36%) with no new safety signals, in patients with *EGFR*-mutated NSCLC whose disease had progressed after first-line osimertinib.[30] When used in combination with osimertinib, the safety profile of Dato-DXd was consistent with that of monotherapy, and no new safety findings were reported.[30]

Here, we describe the design of TROPION-Lung15, which aims to evaluate the efficacy and safety of osimertinib plus Dato-DXd or Dato-DXd monotherapy compared with platinum-based chemotherapy in patients with *EGFR*-mutated advanced NSCLC whose disease has progressed on prior osimertinib treatment.

Methods

Study design

TROPION-Lung15 (NCT06417814) is a global, phase III, open-label, sponsor-blind, three-arm, multicenter, randomized trial evaluating the efficacy and safety of Dato-DXd ± osimertinib compared with platinum-based doublet chemotherapy (carboplatin or cisplatin plus pemetrexed) in patients with *EGFR*-mutated advanced NSCLC and disease progression on prior osimertinib monotherapy (Figure 1). Patients will be enrolled from approximately 280 sites in 26 countries across the Americas, Europe, Middle East, and Asia-Pacific regions and will be randomized 1:1:1 to receive osimertinib (80 mg orally once daily) plus Dato-DXd (6 mg/kg intravenously (IV) every 3 weeks (Q3W)), Dato-DXd (6 mg/kg IV Q3W), or platinum-doublet chemotherapy (carboplatin area under the curve 5 or cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 IV Q3W for four cycles, followed by pemetrexed 500 mg/m^2 IV Q3W as maintenance). Randomization will be stratified based on history or presence of brain metastases (yes vs no), setting of prior osimertinib therapy (adjuvant vs post-chemoradiotherapy or first-line vs second-line), and race (Chinese Asian vs non-Chinese Asian vs non-Asian race). Dose modifications of study medications are permitted to manage treatment-related toxicities. Treatment will continue until radiologic progression by investigator assessment per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), unacceptable toxicity, or another discontinuation criterion is met. However, if during the intervention period, the investigator judges that patients are continuing to show clinical benefit, they may be able to continue

Table 1. TROPION-Lung15: Key inclusion criteria.

Inclusion criteria
• Age ⩾18 years at time of signing the informed consent form
• Histologically or cytologically confirmed, non-squamous NSCLC
• ⩾1 documented EGFR-TKI-sensitive mutation (e.g., Ex19del, L858R, G719X, S768I, or L861Q), either alone or in combination with other *EGFR* mutations, which may include T790M
• Extracranial radiological progression on prior osimertinib monotherapy as most recent line of treatment in the adjuvant, post-chemoradiotherapy, locally advanced (stage IIIB/IIIC not amenable to curative therapy) or metastatic (stage IVA/IVB) disease settings, per the IASLC Cancer Staging Manual in Thoracic Oncology version 9
• Patients with locally advanced or metastatic disease who were treated with a first- or second-generation EGFR-TKI in the first-line setting followed by progression on osimertinib in the second-line setting are eligible
• ⩽2 prior lines of EGFR-TKIs in the advanced or metastatic setting
• No more than 28 days off osimertinib prior to randomization
• ECOG/WHO PS of 0 or 1
• ⩾1 measurable lesion per RECIST 1.1, not previously irradiated
• Life expectancy >12 weeks at screening
• Tumor biopsy or archival tissue for retrospective evaluation of exploratory biomarkers
• Adequate bone marrow reserve and organ function within 7 days before randomization

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; IASLC, International Association for the Study of Lung Cancer; NSCLC, non-small cell lung cancer; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor; WHO PS, World Health Organization performance status.

to receive the same treatment beyond RECIST 1.1-defined disease progression.

The trial is being conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization Good Clinical Practice Guidelines, and all applicable legal and regulatory requirements. Written, informed consent will be provided by all patients, and the study protocol will be approved by the independent ethics committees or institutional review boards at each site. The reporting of this study conforms to the SPIRIT 2025 statement[31] (Supplemental Table 1).

Eligibility criteria

Key inclusion and exclusion criteria are presented in Tables 1 and 2, respectively. Briefly, patients (aged ⩾18 years old) with histologically or cytologically confirmed non-squamous, locally advanced, or metastatic NSCLC, documented EGFR-TKI-sensitive mutations (at least one Ex19del, L858R, G719X, S768I, or L861Q mutation, alone or in combination with other *EGFR* mutations, which may include T790M), extracranial radiologic progression on prior osimertinib monotherapy (in the adjuvant, locally advanced, or metastatic setting), ⩽2 prior lines of EGFR-TKIs in the advanced or metastatic setting, ⩾1 measurable lesion per RECIST 1.1, and an Eastern Cooperative Oncology Group (ECOG) or World Health Organization performance status (WHO PS) score of 0 or 1 will be enrolled. Prior treatment with a third-generation EGFR-TKI other than osimertinib is not allowed, nor is receipt of any other anticancer therapy in the palliative setting or platinum-based chemotherapy or immunotherapy in the curative setting within 12 months prior to randomization. Patients with stable spinal cord compression and/or brain metastases after completion of local therapy and stable neurological status for ⩾2 weeks after completion of local therapy (confirmed by brain magnetic resonance imaging (MRI)) can be enrolled. However, patients with unstable spinal cord compression and/or brain metastases are ineligible. A baseline tumor biopsy for retrospective evaluation of exploratory biomarkers is highly recommended; archival tissue should be provided if a tumor biopsy is not available.

Endpoints

Endpoints for the study are presented in Table 3. Unless otherwise specified, these endpoints relate to the comparisons of Dato-DXd ± osimertinib versus chemotherapy. The dual primary endpoints are PFS by BICR for Dato-DXd monotherapy versus chemotherapy, and PFS by BICR for osimertinib plus Dato-DXd versus

Table 2. TROPION-Lung15: Key exclusion criteria.

Exclusion criteria
• History of another primary malignancy except for malignancy treated with curative intent with no known active disease within 2 years before the first dose of study medication, and of low potential risk for recurrence • Persistent toxicities caused by previous anticancer therapy (excluding alopecia) not yet improved to grade ⩽1 or baseline • Unstable spinal cord compression and/or brain metastases; patients with stable spinal cord compression and/or brain metastases after completion of local therapy and stable neurological status for at least 2 weeks after completion of the local therapy (confirmed by brain MRI) can be enrolled • Significant third-space fluid retention (e.g., ascites or pleural effusion) not amenable for required repeated drainage • Clinically significant corneal disease • Any evidence of severe or uncontrolled systemic diseases, including, but not limited to active bleeding diseases, active infection, active ILD/pneumonitis, or cardiac disease • Active or uncontrolled HBV/HCV infection, uncontrolled HIV, uncontrolled infection requiring intravenous antimicrobials, suspected infection, an inability to rule out infection, or active tuberculosis • History of ILD/pneumonitis, including radiation pneumonitis requiring steroids or drug-induced ILD, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging • Severe pulmonary function compromise resulting from intercurrent pulmonary illnesses • Prior treatment with a third-generation EGFR-TKI other than osimertinib • Any other anticancer therapy in the palliative (first- or second-line) setting • Platinum-based chemotherapy in the non-metastatic setting within 12 months prior to randomization

EGFR, epidermal growth factor receptor; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ILD, interstitial lung disease; MRI, magnetic resonance imaging; TKI, tyrosine kinase inhibitor.

chemotherapy. PFS is defined as the time from randomization to disease progression per RECIST 1.1 (assessed by BICR) or death due to any cause, regardless of whether the participant withdraws from study therapy, receives other anticancer therapy, or clinically progresses.

Key secondary endpoints are OS, defined as the time from randomization until the date of death due to any cause, and CNS PFS per modified RECIST 1.1, defined as the time from randomization to BICR-confirmed progression in the CNS or death due to any cause, regardless of whether the participant withdraws from study therapy, receives other anticancer therapy, or clinically progresses prior to BICR-confirmed CNS modified RECIST 1.1 progression. Other secondary endpoints include: ORR and DoR per RECIST 1.1 by BICR; second PFS (PFS2), defined as the time from randomization to the earliest of a progression event (following initial investigator-assessed progression) after first subsequent therapy, or death; CNS ORR and CNS DoR per modified CNS RECIST 1.1; and patient-reported outcomes (time to deterioration in lung cancer symptoms, physical functioning, and global health status/quality of life (GHS/QoL)). The pharmacokinetics and immunogenicity of Dato-DXd ± osimertinib will also be investigated. Safety and tolerability parameters include AEs graded by Common Terminology Criteria for Adverse Events version 5.0, laboratory parameters, vital signs, physical examination, weight, left ventricular ejection fraction, electrocardiogram parameters, ECOG or WHO PS, and ophthalmologic assessments.

PFS, OS, CNS PFS, ORR, and DoR will also be evaluated for the secondary comparison of osimertinib plus Dato-DXd versus Dato-DXd.

Study procedures and assessments

After providing informed consent, patients will enter screening, with randomization scheduled to occur within 28 days. Following randomization, tumor assessments per RECIST 1.1 will be undertaken every 6 weeks up to Week 48 and every 12 weeks thereafter until radiologic progression by investigator assessment using computed tomography (CT; preferred) or MRI scans. In the event of radiologic progression, a confirmatory scan will be taken. All patients will also undergo brain MRI (preferred) or brain CT with contrast every 12 weeks and at the time of radiologic progression for evaluation of CNS PFS, CNS ORR, and CNS DoR per modified RECIST 1.1.

Table 3. TROPION-Lung15 endpoints.

Endpoint	Dato-DXd vs chemotherapy	Dato-DXd + osimertinib vs chemotherapy	Dato-DXd + osimertinib vs Dato-DXd
Dual primary endpoints*	PFS per RECIST 1.1 by BICR		–
Key secondary endpoints	OS		–
	CNS PFS per modified RECIST 1.1 by BICR		
Secondary efficacy endpoints	ORR and DoR per RECIST 1.1 by BICR		
	PFS2		
	CNS ORR and CNS DoR per modified CNS RECIST 1.1		
	Patient-reported outcomes • TTD in pulmonary symptoms (dyspnea, cough, and chest pain) and overall lung cancer symptoms, as measured by the NSCLC-SAQ • TTD in physical functioning, as measured by the PROMIS Physical Function short form 8c • TTD in GHS/QoL, as measured by the GHS/QoL scale from the EORTC IL172		PFS per RECIST 1.1 by BICR OS CNS PFS per modified RECIST 1.1 ORR and DoR per RECIST 1.1 by BICR
	Pharmacokinetics of Dato-DXd		
	Immunogenicity of Dato-DXd		
Safety endpoints	AEs graded by CTCAE version 5.0		–
Exploratory endpoints	TFST		–
	TSST		

PFS is defined as the time from randomization to BICR-assessed progression per RECIST 1.1 or death due to any cause, regardless of whether the participant withdraws from study therapy, receives other anticancer therapy, or clinical progresses. OS is defined as the time from randomization until the date of death due to any cause. CNS PFS is defined as the time from randomization to BICR-confirmed progression in the CNS or death due to any cause, regardless of whether the participant withdraws from study therapy, receives other anticancer therapy, or clinically progresses prior to BICR-confirmed CNS modified RECIST 1.1 progression. ORR is defined as the proportion of patients with a confirmed CR or PR, as determined by BICR per RECIST 1.1. DoR is defined as the time from the date of first documented response until the date of documented progression per RECIST 1.1, as assessed by BICR or death due to any cause. PFS2 is defined as the time from randomization to the earliest of a progression event (following initial investigator-assessed progression) after first subsequent therapy or death. TTD is defined as the time from randomization until the date of deterioration, where deterioration is defined as change from baseline that reaches a meaningful change threshold. TFST is defined as the time from randomization until the start date of the first subsequent anticancer therapy after discontinuation of randomized treatment, or death due to any cause. TSST is defined as the time from randomization until the start date of the second subsequent anticancer therapy after discontinuation of randomized treatment and or death due to any cause. DCR at 24 weeks is defined as the percentage of participants with a confirmed CR or PR, or SD per RECIST 1.1 as assessed by BICR, and derived from raw tumor data for at least 23 weeks after randomization.
*Dual primary endpoints refer to PFS by BICR for Dato-DXd monotherapy versus chemotherapy and PFS by BICR for osimertinib plus Dato-DXd versus chemotherapy.
AE, adverse event; BICR, blinded independent central review; CNS, central nervous system; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; EORTC, European Organization for Research and Treatment of Cancer; GHS, Global Health Status; IL, item library; NSCLC-SAQ, Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; PR, partial response; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy; TTD, time to deterioration.

Patients will be followed up for PFS2 until second progression on subsequent treatment, death, withdrawal of consent, or the end of the study. OS evaluations will be conducted every 12 weeks following objective disease progression or treatment discontinuation until death, withdrawal of consent, or the end of the study.

AEs will be recorded from screening until the end of the safety follow-up period following

discontinuation of all study interventions, except for ILD/pneumonitis or any serious AEs, which will be recorded beyond the safety follow-up period, regardless of severity. Pulmonary function tests and high-resolution chest CT should be undertaken if ILD or pneumonitis is suspected, and an independent ILD Adjudication Committee will review all cases of potential ILD/pneumonitis. For AEs of special interest, there are specific risk mitigation strategies including appropriate prophylaxis, management guidelines, and a remote patient monitoring tool to enable early identification and management of stomatitis and pulmonary symptoms. PS, laboratory parameters, weight, physical examination, pulse oximetry, and vital signs will be assessed at the start of each cycle prior to the infusion of study intervention, and at the end-of-treatment visit (scheduled to take place within 35 days of discontinuation of all study interventions). Ophthalmologic evaluations will be conducted at screening, as clinically indicated, and at the end of treatment. Changes in patient-reported lung cancer symptoms, physical functioning, and GHS/QoL will be measured using the NSCLC Symptom Assessment Questionnaire, Patient-Reported Outcomes Measurement Information System Physical Function short form 8c, and European Organization for Research and Treatment of Cancer IL172 questionnaires, respectively.

A daily oral care plan for prophylaxis of stomatitis will be provided to all patients; a steroid-containing mouthwash (dexamethasone, or an alternative per local guidelines) is recommended for patients randomized to Dato-DXd monotherapy or osimertinib plus Dato-DXd, and prophylactic cryotherapy (e.g., ice chips or ice water held in the mouth) should be considered during Dato-DXd infusion.

Statistical methods

All efficacy analyses will be performed on the full analysis set, defined as all patients randomized to study intervention. The safety analysis set will comprise all patients who received any randomized treatment, regardless of group assignment. Approximately 630 patients (210 per arm) will be randomized to study treatment.

The study is powered to demonstrate the superiority of Dato-DXd ± osimertinib versus chemotherapy in terms of PFS per RECIST 1.1 by BICR in the full analysis set. To preserve the overall type 1 error (familywise error rate) a multiple testing procedure will be implemented for the primary and key secondary endpoints.

Time-to-event comparisons between treatment arms will be carried out using a stratified log-rank test adjusting for the stratification factors. A stratified Cox proportional hazards model will be used to estimate HRs and associated CIs, and Kaplan–Meier plots will be presented by treatment arm. Safety and other data will be presented using descriptive statistics.

Discussion

Osimertinib monotherapy remains a standard of care for patients with *EGFR*-mutated NSCLC, including those with advanced disease[12–17]; however, disease progression often occurs,[19] and new interventions are required to improve patient outcomes. Dato-DXd has demonstrated efficacy in patients with previously-treated advanced NSCLC.[26–28,32,33] Preclinical evidence has suggested that combination treatment with osimertinib and Dato-DXd shows enhanced efficacy compared with osimertinib alone, including in osimertinib-resistant models,[29] and combination treatment with osimertinib plus Dato-DXd demonstrated promising efficacy in patients with *EGFR*-mutated NSCLC who had progressed on prior first-line osimertinib therapy in the phase II ORCHARD study.[30] Therefore, there is a rationale for phase III trials combining osimertinib with Dato-DXd to overcome resistance following disease progression on osimertinib monotherapy. As described, TROPION-Lung15 is a phase III trial assessing the efficacy and safety of adding Dato-DXd to osimertinib or Dato-DXd alone versus platinum-doublet chemotherapy in patients with *EGFR*-mutated advanced NSCLC and disease progression on prior osimertinib. TROPION-Lung15 aims to build on data from studies of Dato-DXd monotherapy in previously-treated advanced NSCLC (TROPION-Lung01 and TROPION-Lung05), which included patients with tumors harboring *EGFR* mutations.[26,27] It also complements the ongoing, phase III, randomized, open-label TROPION-Lung14 study (NCT06350097), which is comparing osimertinib plus Dato-DXd with osimertinib alone as first-line therapy for patients with *EGFR*-mutated (Ex19del and/or L858R) locally advanced or metastatic NSCLC. Results from TROPION-Lung15 will contribute to the

evolving treatment landscape for *EGFR*-mutated NSCLC and the search for novel therapeutic strategies to improve prognoses for patients whose disease progresses on osimertinib monotherapy.[34] Enrollment is ongoing; this study is expected to end in 2027, with the first results available in 2026.

Declarations

Ethics approval and consent to participate

This study is being performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization Good Clinical Practice Guidelines, and applicable laws and regulations. The study protocol will be approved by independent ethics committees or institutional review boards at each study site. All participants will provide written informed consent before any study-specific procedures are undertaken.

Consent for publication

Not applicable; no data from individual participants are included in this article.

Author contributions

Daniel Shao-Weng Tan: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Ernest Nadal: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Parneet Cheema: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Yi-Long Wu: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Myung-Ju Ahn: Conceptualization; Data curation; Investigation; Project administration; Resources; Supervision; Writing – review & editing.

Junko Tanizaki: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Ellie Grainger: Data curation; Methodology; Supervision; Visualization; Writing – review & editing.

Emily Nizialek: Conceptualization; Data curation; Methodology; Project administration; Supervision; Visualization; Writing – review & editing.

Alessandra Forcina: Conceptualization; Data curation; Methodology; Project administration; Supervision; Visualization; Writing – review & editing.

Toon van der Gronde: Conceptualization; Data curation; Methodology; Project administration; Supervision; Visualization; Writing – review & editing.

Helena A. Yu: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Acknowledgements

Medical writing support for the development and submission of this manuscript, under the direction of the authors, was provided by Ella Spencer, MSci, of Ashfield MedComms (London, UK), an Inizio company, in accordance with Good Publications Practice (GPP) guidelines (https://www.ismpp.org/gpp-2022), and was funded by AstraZeneca.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: TROPION-Lung15 study (NCT06417814; https://clinicaltrials.gov/study/NCT06417814, date of registration May 13, 2024) is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialization collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd).

Competing interests

DS-WT has received honoraria (institution) from Novartis, Pfizer, Roche, and Takeda; has acted as a consultant or advisor (institution) for Amgen, AstraZeneca, Bayer, DKSH, Genmab, Merck, Pfizer, Roche, and Zymeworks; has received research funding (institution) from ACM Biolabs, AstraZeneca, GlaxoSmithKline, Novartis, and Pfizer; and has received travel, accommodations, and/or expenses from Boehringer Ingelheim, Pfizer, and Roche. Er.N. has acted as a consultant

or advisor for Amgen, Apollomics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Genmab, Janssen, Lilly, Merck Serono, Merck Sharp & Dohme, Pfizer, Pierre Fabre, Qiagen, Roche, Sanofi, and Takeda; has received research funding (institution) from Bristol Myers Squibb, Merck Serono, Pfizer, and Roche; and has received travel, accommodations, and/or expenses from Bristol Myers Squibb, Lilly, Merck Sharp & Dohme, Pfizer, and Roche. P.C. has received honoraria from AstraZeneca, GlaxoSmithKline, Roche, Merck, Novartis, Pfizer, and Takeda; and has acted as a consultant or advisor for Amgen, AstraZeneca, Bristol Myers Squibb, EMD Serono, Genomic Health, GlaxoSmithKline, Roche, Merck, Novartis, Pfizer, and Takeda. Y-LW has received honoraria from AstraZeneca, BeiGene Beijing, Boehringer Ingelheim, Bristol Myers Squibb, Hengrui Pharmaceutical, Merck Sharp & Dohme, Pfizer, and Roche; has acted as a consultant or advisor for AstraZeneca, Boehringer Ingelheim, Roche, and Takeda; and has received research funding (institution) from Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, and Roche. M.-J.A. has received honoraria from Amgen, AstraZeneca, Daiichi Sankyo, Lilly, Merck Serono, Merck Sharp & Dohme, Takeda, and Yuhan; has acted as a consultant or advisor for Alpha Pharmaceuticals, Amgen, Arcus Ventures, AstraZeneca, Daiichi Sankyo, Lilly, Merck Serono, Merck Sharp & Dohme, Pfizer, Takeda, and Yuhan; and has received research funding from Yuhan. J.T. has received honoraria from AstraZeneca, AbbVie, Boehringer Ingelheim Japan, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan, Janssen, Merck Sharp & Dohme, Nihon Medi-Physics, Nippon Kayaku, Ono Pharmaceutical, Pfizer Japan, Taiho Pharmaceutical, and Takeda. E.G. is an employee of AstraZeneca and owner of AstraZeneca stocks. Em.N. is an employee of AstraZeneca. A.F. is an employee of AstraZeneca. T.v.d.G. was previously an employee of AstraZeneca and is a current employee of Daiichi Sankyo, and owner of AstraZeneca stocks and Daiichi Sankyo stocks. H.A.Y. has acted as a consultant or advisor for AbbVie, AstraZeneca, Black Diamond Therapeutics, Blueprint Medicines, C4 Therapeutics, Cullinan Oncology, Daiichi Sankyo, Janssen, Novocure, and Taiho Oncology; has received research funding (institution) from Astellas Pharma, AstraZeneca, Black Diamond Therapeutics, Blueprint Medicines, Cullinan Oncology, Daiichi Sankyo, Erasca, Janssen, Lilly, Novartis, Pfizer, and Systimmune; and reports other relationships with Astellas Pharma.

Availability of data and materials

This is a clinical trial protocol manuscript, and no data are being reported. On completion of the trial, data will be available in accordance with AstraZeneca's data sharing policy described at https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/

ORCID iD

Helena A. Yu https://orcid.org/0000-0002-0377-9510

Supplemental material

Supplemental material for this article is available online.

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: 1046–1061.
2. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 2017; 376: 629–640.
3. 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: 3290–3297.
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: 113–125.
5. 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: 2702–2709.
6. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med* 2020; 382: 41–50.

7. Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 2020; 383: 1711–1723.
8. Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC. *N Engl J Med* 2023; 389: 1935–1948.
9. Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med* 2023; 389: 137–147.
10. Jänne PA, Planchard D, Kobayashi K, et al. CNS efficacy of osimertinib with or without chemotherapy in epidermal growth factor receptor-mutated advanced non-small-cell lung cancer. *J Clin Oncol* 2024; 42: 808–820.
11. Lu S, Kato T, Dong X, et al. Osimertinib after chemoradiotherapy in stage III EGFR-mutated NSCLC. *N Engl J Med* 2024; 391: 585–597.
12. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; 34: 358–376.
13. Hendriks L, Cortiula F, Mariaidze E, et al. ESMO oncogene-addicted metastatic non-small-cell lung cancer living guideline, v1.2 (Original publication: Clinical Practice Guideline citation. *Ann Oncol* 2023; 34(4): 339–333), https://www.esmo.org/living-guidelines/esmo-oncogene-addicted-non-small-cell-lung-cancer-living-guideline (2025, accessed August 29, 2025).
14. Owen DH, Ismaila N, Ahluwalia A, et al. Therapy for stage IV non-small cell lung cancer with driver alterations: ASCO Living Guideline, Version 2024.3. *J Clin Oncol* 2025; 42: e44–e59.
15. Remon J, Soria JC and Peters S; ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. *Ann Oncol* 2021; 32: 1637–1642.
16. Pisters K, Kris MG, Gaspar LE, et al. Adjuvant systemic therapy and adjuvant radiation therapy for stage I–IIIA completely resected non-small-cell lung cancer: ASCO Guideline rapid recommendation update. *J Clin Oncol* 2022; 40: 1127–1129.
17. Daly ME, Singh N and Ismaila N. Management of stage III non-small cell lung cancer: ASCO guideline rapid recommendation update. *J Clin Oncol* 2024; 42: 3058–3060.
18. Herbst RS, Wu YL, John T, et al. Adjuvant osimertinib for resected EGFR-mutated stage IB–IIIA non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. *J Clin Oncol* 2023; 41: 1830–1840.
19. Gomatou G, Syrigos N and Kotteas E. Osimertinib resistance: molecular mechanisms and emerging treatment options. *Cancers* 2023; 15: 841.
20. Passaro A, Leighl N, Blackhall F, et al. ESMO expert consensus statements on the management of EGFR mutant non-small-cell lung cancer. *Ann Oncol* 2022; 33: 466–487.
21. Oh DK, Ji WJ, Kim WS, et al. Efficacy, safety, and resistance profile of osimertinib in T790M mutation-positive non-small cell lung cancer in real-world practice. *PLoS One* 2019; 14: e0210225.
22. Nosaki K, Satouchi M, Kurata T, et al. Re-biopsy status among non-small cell lung cancer patients in Japan: a retrospective study. *Lung Cancer* 2016; 101: 1–8.
23. 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: 77–90.
24. 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: 2329–2340.
25. Su PL, Furuya N, Asrar A, et al. Recent advances in therapeutic strategies for non-small cell lung cancer. *J Hematol Oncol* 2025; 18: 35.
26. 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* 2024; 43: 260–272.
27. 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: 1254–1265.
28. Ahn MJ, Lisberg A, Goto Y, et al. A pooled analysis of datopotamab deruxtecan in patients with EGFR-mutated NSCLC. *J Thorac Oncol*. Epub ahead of print June 2025, DOI: 10.1016/j.jtho.2025.06.002.
29. Martin M, Koers A, Calero F, et al. *Osimertinib treatment drives expression of TROP2, and combination treatment with datopotamab deruxtecan*

(Dato-DXd), a TROP2-directed antibody-drug conjugate, enhances its efficacy in PDX models of EGFR mutant non small-cell lung cancer. Poster LBA458 presented at the American Association for Cancer Research (AACR) Annual Meeting, 25–30 April 2025, Chicago, IL, USA.

30. Le X, Hendriks L, Morabito A, et al. *Osimertinib + datopotamab deruxtecan in patients with EGFR-mutated advanced NSCLC whose disease progressed on first-line osimertinib: ORCHARD. Oral presentation 10 at the European Lung Cancer Congress (ELCC)*, 26–29 March 2025, Paris, France.
31. Chan A-W, Boutron I, Hopewell S, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. *BMJ* 2025; 389: e081477.
32. Shimizu T, Sands J, Yoh K, et al. First-in-human, phase I dose-escalation and dose-expansion study of trophoblast cell-surface antigen 2-directed antibody-drug conjugate datopotamab deruxtecan in non-small-cell lung cancer: TROPION-PanTumor01. *J Clin Oncol* 2023; 41: 4678–4687.
33. Garon E, Johnson M, Lisberg A, et al. TROPION-PanTumor01: updated results from the NSCLC cohort of the phase 1 study of datopotamab deruxtecan in solid tumors. *J Thorac Oncol* 2021; 16: S892–S893.
34. Araki T, Kanda S, Horinouchi H, et al. Current treatment strategies for EGFR-mutated non-small cell lung cancer: from first line to beyond osimertinib resistance. *Jpn J Clin Oncol* 2023; 53: 547–561.