THERAPEUTIC ADVANCES in
Medical Oncology

Study Protocol

TROPION-Lung14 study protocol: a phase III study of osimertinib in combination with datopotamab deruxtecan versus osimertinib alone as first-line treatment for patients with *EGFR*-mutated locally advanced or metastatic non-small cell lung cancer

Ther Adv Med Oncol

2026, Vol. 18: 1–10

DOI: 10.1177/17588359261430561

Shun Lu, Mariano Provencio Pulla, Eldsamira Mascarenhas, Junko Tanizaki, Hye Ryun Kim, Yinglei Liu, Shengmei Feng, Biao Zhang, Laurence Toms, James Chih-Hsin Yang and Sarah B. Goldberg

Correspondence to:
Shun Lu
Medical Oncology Department, Shanghai Chest Hospital, Shanghai 200030, China
shunlu@sjtu.edu.cn

Mariano Provencio Pulla
Department of Medical Oncology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

Eldsamira Mascarenhas
Clinical Oncology, Hospital Sao Rafael, Salvador, Brazil

Instituto D'Or de Pesquisa e Ensino (IDOR), Salvador, Brazil

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

Hye Ryun Kim
Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Yinglei Liu
Shengmei Feng
Biao Zhang
AstraZeneca, R&D, Shanghai, China

Laurence Toms
AstraZeneca, R&D, Cambridge, UK

James Chih-Hsin Yang
Medical Oncology Department, National Taiwan University Hospital, Taipei City, Taiwan

Sarah B. Goldberg
Yale School of Medicine, New Haven, CT, USA

Abstract

Background: Osimertinib is a first-line (1L) treatment option for patients with locally advanced/metastatic epidermal growth factor receptor (*EGFR*)-mutated non-small-cell lung cancer (NSCLC). Resistance to 1L osimertinib often develops and treatment options after disease progression are limited. The clinical benefit of 1L osimertinib in combination with agents which have broad antitumor activity has been demonstrated in phase III trials. Datopotamab deruxtecan (Dato-DXd), an antibody–drug conjugate composed of a humanized anti-trophoblast cell-surface antigen 2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor, has demonstrated efficacy as monotherapy and in combination with osimertinib in NSCLC, including patients with *EGFR*-mutated advanced NSCLC.

Objectives: TROPION-Lung14 (NCT06350097), an ongoing phase III, open-label, sponsor-blind, multicenter, randomized study, is evaluating the efficacy and safety of osimertinib + Dato-DXd, versus osimertinib, as 1L therapy in patients with *EGFR*-mutated LA/M NSCLC.

Methods and design: The study is enrolling adults with histologically/cytologically confirmed stage IIIB/IIIC or intravenously (IV) non-squamous, *EGFR*-mutated (exon 19 deletion (Ex19del) or L858R) NSCLC, and no prior EGFR-TKI or other systemic therapy for stage IIIB/IIIC or IV disease. Prior to the randomized study period, ~20 patients will receive osimertinib + Dato-DXd in a safety run-in. Following safety run-in, ~562 patients will be randomized 1:1 to osimertinib (80 mg orally once daily (PO QD)) + Dato-DXd (6 mg/kg IV every 3 weeks) or osimertinib (80 mg PO QD). Patients will be stratified by *EGFR* mutation type (Ex19del vs L858R), World Health Organization performance status (0 vs 1), and central nervous system metastasis (yes vs no). Treatment will continue until Resist Evaluation Criteria in Solid Tumors version 1.1-defined progression or unacceptable toxicity. The primary endpoint is progression-free survival by blinded independent central review. Overall survival is a key secondary endpoint.

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

Discussion: TROPION-Lung14 will assess 1L osimertinib + Dato-DXd versus osimertinib alone in patients with *EGFR*-mutated LA/M NSCLC, potentially providing a new treatment option.

Trial registration: ClinicalTrials.gov identifier: NCT06350097 (Registration Date: April 5, 2024).

Plain language summary

TROPION-Lung14: a clinical study comparing osimertinib in combination with datopotamab deruxtecan or osimertinib alone as the first line of treatment for patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with a mutation in the epidermal growth factor receptor (*EGFR*) gene

Epidermal growth factor receptor (*EGFR*) is a protein that controls cell growth and division. In some cancer cells the gene is mutated and allows cells to grow uncontrollably. Osimertinib is a medicine that blocks the activity of mutated *EGFR* on cancer cells, stopping their growth and is an option for treatment for people with *EGFR*-mutated NSCLC in various clinical situations. Most patients develop resistance to osimertinib and treatment options after the cancer gets worse are limited. Researchers are looking to see if osimertinib would be more effective when it is combined with other medicines. Datopotamab deruxtecan (Dato-DXd) is an antibody–drug conjugate that consists of an antibody (datopotamab) and an anticancer drug (DXd), joined via a plasma-stable cleavable linker. Dato-DXd has shown promising antitumor efficacy in previous studies in people with advanced or metastatic NSCLC. This study, called TROPION-Lung14, is designed to compare the combination of osimertinib and Dato-DXd with osimertinib alone as a first treatment for people with *EGFR*-mutated advanced NSCLC. Eligible patients will be randomly assigned to receive either osimertinib plus Dato-DXd or osimertinib alone. Patients will continue to receive treatment until their disease progresses, side effects become unacceptable, or they choose to leave the study. The main objective of the study is to see how long patients remain alive without their cancer growing or spreading (known as progression-free survival). The first results are expected to be available in early 2028, with the study expected to end in mid-2032.

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

Received: 21 November 2025; revised manuscript accepted: 17 February 2026.

Introduction

Osimertinib is a third-generation, irreversible, central nervous system (CNS)-active, epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI).[1–5] Osimertinib is an option for first-line (1L) treatment for *EGFR*-mutated advanced non-small-cell lung cancer (NSCLC) as monotherapy or in combination with platinum-based chemotherapy, based on the phase III, randomized FLAURA and FLAURA2 trials[2,6,7]; and in patients with early-stage, unresectable stage III, and locally advanced or metastatic *EGFR*-mutated NSCLC.[1,3,8,9]

The 1L approval for osimertinib was based on the FLAURA study, a double-blind, phase III trial, which compared osimertinib versus standard of care (SoC; gefitinib or erlotinib) in patients with previously untreated *EGFR*-mutated NSCLC (exon 19 deletion (Ex19del) or L858R).[2] Median progression-free survival (PFS) and overall survival (OS) were significantly longer with osimertinib versus SoC.[4] Safety was manageable with the most commonly reported adverse events (AEs) for osimertinib being rash or acne (58%), diarrhea (58%), and dry skin (36%).[2] Despite the clinical benefit seen with osimertinib, disease progression is common and due to multiple different resistance mechanisms.[10,11] One potential strategy to extend the efficacy of osimertinib and delay the onset of resistance is the use of a combination regimen with treatment(s) with broad antitumor

activity. Data from the 1L phase III FLAURA2 trial demonstrated the feasibility of this approach with a statistically significant improvement in PFS and OS with osimertinib plus platinum-pemetrexed doublet chemotherapy versus osimertinib alone in patients with *EGFR*-mutated advanced NSCLC.[6,12]

Datopotamab deruxtecan (Dato-DXd) is an antibody–drug conjugate (ADC) comprising a humanized anti-trophoblast cell-surface antigen 2 (TROP 2) monoclonal antibody (Dato-DXd) conjugated to a potent, cytotoxic topoisomerase I (Topo-I) inhibitor via a plasma-stable, tetrapeptide-based, tumor-selective cleavable linker.[13] 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. A numerical improvement in OS was also observed in patients with non-squamous histology, although there was no statistically significant difference.[14] In the TROPION-Lung05 and TROPION-PanTumor01 studies, Dato-DXd demonstrated activity in patients with actionable genomic alterations, including *EGFR*.[15,16] A pooled analysis of patients with *EGFR*-mutated NSCLC from TROPION-Lung01 and TROPION-Lung05 trials also demonstrated a confirmed objective response rate (ORR) for Dato-DXd by blinded independent central review (BICR) of 43%.[17] Based on data from the TROPION-Lung05 trial and supported by data from TROPION-Lung01, Dato-DXd was recently approved for the treatment of patients with locally advanced or metastatic *EGFR*-mutated NSCLC who have received prior *EGFR*-directed therapy and platinum-based chemotherapy.[18] Dato-DXd is also approved for the treatment of patients with unresectable or metastatic hormone receptor-positive, human EGFR 2-negative breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease, based on data from the phase III TROPION-Breast01 study.[18]

Preclinical evidence has shown that osimertinib given in combination with Dato-DXd has enhanced efficacy compared with each agent given as monotherapy; osimertinib treatment was also shown to upregulate TROP2 expression both at the mRNA and protein level.[19] Furthermore, results from the phase II ORCHARD study demonstrated promising efficacy for osimertinib plus Dato-DXd in patients with *EGFR*-mutated advanced or metastatic NSCLC who had progressed on 1L osimertinib. For those receiving osimertinib (80 mg) with Dato-DXd (6 mg/kg) median PFS (95% confidence interval (CI)) was 11.7 (8.3–not calculable) months and ORR (80% CI) was 36 (25%–49)%.[20] As monotherapy, Dato-DXd has demonstrated a manageable safety profile with the most common treatment-related AEs being nausea, stomatitis, and alopecia.[14–16] In combination studies, the safety profile of Dato-DXd was consistent with that reported for monotherapy and no new safety findings were observed.[20–22] Nevertheless, as the TROPION-Lung14 study will assess the combination of osimertinib and Dato-DXd as 1L therapy, and as there is a potential for overlapping toxicity between osimertinib and Dato-DXd, a safety run-in period is being included in the study. The safety and tolerability data from this limited number of patients during the run-in period will be reviewed by a Safety Review committee who will recommend whether the data support the initiation of the randomized period of the study. Furthermore, combined toxicity management guidelines have been developed for osimertinib and Dato-DXd, with interstitial lung disease (ILD)/pneumonitis identified as one of the overlapping toxicities for this combination; these guidelines will be regularly reviewed throughout the course of the study.

Here we describe the design of TROPION-Lung14, which is assessing the efficacy and safety of osimertinib in combination with Dato-DXd versus osimertinib alone in patients with previously untreated and unresectable *EGFR*-mutated NSCLC.

Methods

Study design

TROPION-Lung14 (NCT06350097) is an ongoing, phase III, two-arm, parallel, randomized multicenter study (Figure 1) investigating the efficacy and safety of osimertinib in combination with Dato-DXd compared with osimertinib alone in patients with locally advanced or metastatic *EGFR*-mutated NSCLC, who have not received any prior anticancer therapy for advanced disease. Patients will be enrolled from approximately 170 sites in 18 countries across the Americas, Europe, Middle East, and Asia-Pacific regions. Prior to randomization, a single-arm safety run-in

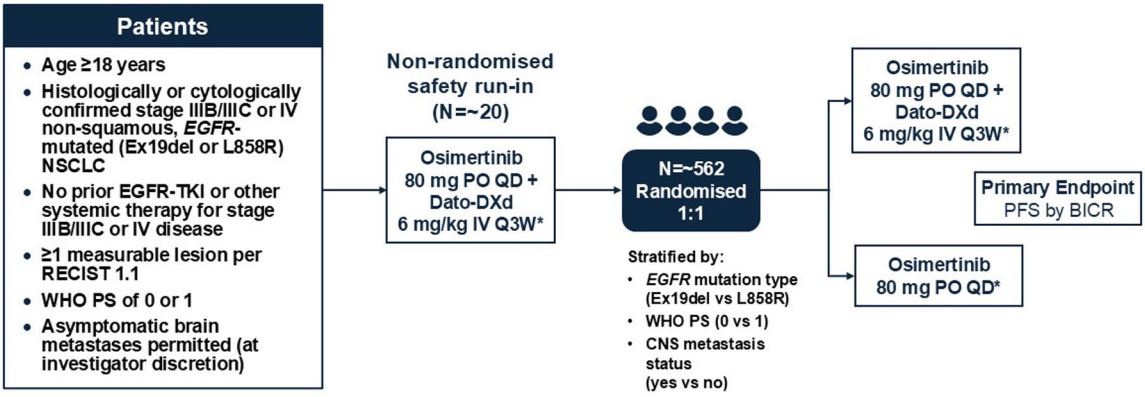

Figure 1. TROPION-Lung14 study design. Treatment will continue until RECIST v1.1-defined progression by investigator, unacceptable toxicity, or another discontinuation criterion is met. Following discontinuation, the choice of subsequent therapy will be at the discretion of the investigator. Patients will be followed for second progression on a subsequent treatment, defined according to local practice, and for OS.
BICR, blinded independent central review; CNS, central nervous system; Dato-DXd, datopotamab deruxtecan; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PO, orally; QD, once daily; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor; WHO PS, World Health Organization performance status.

period will evaluate safety and tolerability of osimertinib (80 mg orally once daily (QD)) in combination with Dato-DXd (6 mg/kg intravenously (IV) every 3 weeks (Q3W)) in approximately 20 patients. During the safety run-in period, safety and tolerability data will be reviewed by a Safety Review Committee (SRC), which will convene when safety data are available from at least 16 patients who have either received ⩾3 cycles of study treatment (osimertinib or Dato-DXd) or who have discontinued study treatment (either osimertinib or Dato-DXd) due to unacceptable toxicity. Following completion of their review, the SRC will make a recommendation based on the safety data and the trial will continue with the randomized study period. Patients included in the safety run-in period will not be eligible for inclusion in the randomized study period but may continue their allocated treatment, according to the study protocol.

In the randomized study, approximately 562 patients will be enrolled and randomized 1:1 to either osimertinib (80 mg orally QD) in combination with Dato-DXd (6 mg/kg IV Q3W) or osimertinib (80 mg orally QD) monotherapy. Recruitment of patients from Asian populations is expected to be approximately 70% of the total randomized patients. Randomization will be stratified by *EGFR* mutation type (Ex19del vs L858R), World Health Organization performance status (WHO PS) score (0 vs 1), and CNS metastasis status (Yes vs No). Treatment will continue until radiologic progression by Investigator assessment per Resist Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), unacceptable toxicity, or another discontinuation criterion is met. Dose modifications of study medications are permitted to manage treatment-related toxicities. Osimertinib monotherapy may continue for as long as a patient continues to derive clinical benefit after RECIST v1.1 progression, in the absence of any discontinuation criteria, and at the discretion of the study investigator.

The trial is being conducted in accordance with the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice Guidelines, and all applicable legal and regulatory requirements. Written, informed consent will be provided by 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 (Supplemental Table 1).[23]

Eligibility criteria

Key inclusion and exclusion criteria are presented in Tables 1 and 2, respectively. Eligible patients must be aged ⩾18 years (patients from Japan must be aged ⩾20 years), with histologically or cytologically confirmed non-squamous or mixed, locally advanced or metastatic NSCLC (based on the American Joint Committee on Cancer 8th Edition),[24] documented *EGFR*-TKI-sensitive

Table 1. TROPION-Lung14: key inclusion criteria.

Inclusion criteria
• Age ⩾18 years (⩾20 years in Japan) at the time of signing the informed consent form • Histologically or cytologically confirmed non-squamous NSCLC; mixed histology is also allowed • Locally advanced (stage IIIB/IIIC) or metastatic (stage IV) NSCLC or recurrent NSCLC (based on the American Joint Committee on Cancer 8th Edition) not amenable to curative surgery or definitive chemoradiation at the time of randomization • ⩾1 documented EGFR-TKI sensitive mutation (Ex19del or L858R), either alone or in combination with other *EGFR* mutations, which may include T790M • Have not received prior EGFR TKIs or other systemic therapy for locally advanced or metastatic NSCLC. Prior adjuvant and/or neo-adjuvant therapies (target therapy, chemotherapy, radiotherapy, immunotherapy, biologic therapy, investigational agents), or definitive radiation/chemoradiation with or without regimens including target therapy, biologic therapy, investigational agents, are permitted as long as treatment was completed at least 12 months prior to the development of recurrent disease • For patients enrolled in the randomization period, mandatory provision of an unstained, archival tumor tissue sample for central confirmation of the *EGFR* mutation status, and a baseline plasma sample for retrospective plasma *EGFR* testing • WHO PS of 0 or 1 • Life expectancy >12 weeks at screening • ⩾1 measurable lesion per RECIST v1.1 not previously irradiated • Adequate bone marrow reserve and organ function within 7 days before the first dose of study intervention

EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor; WHO PS, World Health Organization performance status.

Table 2. TROPION-Lung14: key exclusion criteria.

Exclusion criteria
• History of another primary malignancy except for malignancy treated with curative intent with no known active disease within 3 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 can be enrolled. Participants with asymptomatic untreated brain metastases are eligible for inclusion if, in the opinion of the investigator, immediate definitive treatment is not indicated • 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 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, active tuberculosis, or suspected ILD/pneumonitis that cannot be ruled out by imaging • History of ILD/pneumonitis, including drug-induced ILD or radiation pneumonitis requiring steroids, or current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging • Severe pulmonary function compromise resulting from intercurrent pulmonary illnesses • Resting ECG with clinically abnormal findings • Receipt of prior adjuvant and/or neo-adjuvant therapies within 12 months prior to the development of recurrent disease • Prior exposure to any agent including an ADC containing a chemotherapeutic agent targeting topoisomerase I, TROP2-targeted therapy • Previous treatment allocation (safety run-in period) or randomization (randomization period) in the present study

ADC, antibody–drug conjugate; ECG, electrocardiogram; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ILD, interstitial lung disease; TROP2, trophoblast cell surface antigen 2.

mutations (at least one Ex19del or L858R, either alone or in combination with other *EGFR* mutations, which may include T790M), ⩾1 measurable lesion per RECIST v1.1, WHO PS of 0 or 1, and not amenable for surgical resection or definitive chemoradiation. Prior treatment with an *EGFR*-TKI other than osimertinib is not allowed, nor is receipt of any other systemic therapy for advanced or metastatic NSCLC. Prior adjuvant and/or neo-adjuvant therapies are permitted if treatment was

Table 3. Primary and secondary endpoints.

Endpoints	Osimertinib + Dato-DXd
Primary endpoint	PFS per RECIST v1.1 by BICR
Key secondary endpoints	OS CNS PFS per modified RECIST v1.1 by BICR PFS per RECIST v1.1 by investigator
Secondary efficacy endpoints	ORR and DoR per RECIST v1.1 by BICR and investigator Neuro-radiologist assessments according to CNS RECIST v1.1 PFS2 PFS by investigator by plasma *EGFR* mutation status Pharmacokinetics of Dato-DXd Immunogenicity of Dato-DXd
Safety endpoints	AEs graded by CTCAE version 5.0

PFS is defined as time from randomization until progression per RECIST v1.1 as assessed by BICR, or death due to any cause, regardless of whether the patient withdraws from study therapy, receives other anticancer therapy, or clinically progresses. OS is defined as the time from randomization until the date of death due to any cause. CNS PFS is defined as time from randomization to BICR-confirmed progression in the CNS or death due to any cause (in the absence of CNS progression), regardless of whether the patient withdraws from study therapy or receives other anticancer therapy. PFS is defined as time from randomization until progression per RECIST v1.1 as assessed by the investigator, or death due to any cause, regardless of whether the patient withdraws from study therapy, receives other anticancer therapy, or clinically progresses. ORR is defined as the proportion of patients with a confirmed CR or PR, as determined by BICR per RECIST v1.1. DoR is defined as the time from the date of first documented response until the date of documented progression per RECIST v1.1, as assessed by BICR (and investigator) or death due to any cause. PFS2 is defined as the time from randomization to the earliest instance of a progression event (following initial investigator-assessed progression) after the first subsequent therapy, or death.
AEs, adverse events; BICR, blinded independent central review; CNS, central nervous system; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; *EGFR*, epidermal growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second PFS; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

received at least 12 months prior to the development of recurrent disease. For patients enrolled in the randomization period, it is mandatory to provide an unstained, archival tumor tissue sample to allow for central confirmation of the *EGFR* mutation status, and a baseline plasma sample for retrospective plasma *EGFR* testing. Patients with stable brain metastases after completion of definitive therapy, who are not on steroids, and have a stable neurological status for ⩾2 weeks after completion of definitive therapy and steroids can be enrolled. Patients with unstable spinal cord compression and/or brain metastases are ineligible. Patients with asymptomatic untreated brain metastases can be eligible for inclusion if, in the opinion of the investigator, immediate definitive treatment is not indicated.

Endpoints

Endpoints for the study are presented in Table 3. The primary endpoint is PFS by BICR for osimertinib in combination with Dato-DXd versus osimertinib alone. PFS is defined as time from randomization until progression per RECIST v1.1 as assessed by BICR, or death due to any cause, regardless of whether the patient withdraws from study therapy, receives other anticancer therapy, or clinically progresses prior to BICR-confirmed RECIST v1.1 progression. 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 assessed by CNS BICR, defined as the time from randomization to CNS BICR-confirmed progression in CNS or death due to any cause (in absence of CNS progression), regardless of whether the patient withdraws from study therapy or received other anticancer therapy. Other secondary endpoints include: PFS by investigator, defined as time from randomization until progression per RECIST v1.1 as assessed by investigator; ORR and duration of response per RECIST v1.1 by BICR; effectiveness of osimertinib in combination with Dato-DXd in the prevention of CNS metastases, by neuro-radiological assessment per CNS modified RECIST v1.1 to determine the presence/absence of CNS lesions at progression in

patients without CNS metastases at baseline; and 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. The pharmacokinetics of osimertinib in combination with Dato-DXd and the immunogenicity of Dato-DXd will be also 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, WHO PS, and ophthalmologic assessments.

Study procedures and assessments

Tumor assessments per RECIST v1.1 will be undertaken at Week 7, Week 13, and every 12 weeks thereafter until radiologic progression by investigator assessment using computed tomography (CT, preferred), or MRI scans. Screening/baseline imaging should be performed as close as possible to, and prior to, the first dose of study intervention and no more than 28 days before randomization. All patients will undergo a brain scan MRI (preferred) or brain CT with contrast at baseline and at the time of radiologic progression (using the same modality) for evaluation of CNS PFS per RECIST v1.1. If brain metastases are not detected at baseline, a brain MRI will be performed every 24 weeks from randomization until disease progression per RECIST v1.1.

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. Collected information will include WHO PS, vital signs, body weight, and physical examinations; laboratory assessments, ophthalmologic assessments, and cardiac testing will also be performed. If new or worsening pulmonary symptoms or radiological abnormality suggestive of ILD or pneumonitis is observed, an interruption to osimertinib is recommended, Dato-DXd will be delayed, and a full investigation will be required.

A daily oral care plan for stomatitis prophylaxis will be given to all patients; a steroid-containing mouthwash (dexamethasone, or an alternative per local guidelines) is highly recommended for patients randomized to treatment including 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

The full analysis set population, comprising all patients randomized to study intervention, will be used for all efficacy analyses. The safety analysis set will comprise all randomized patients who received any amount of any study treatment, regardless of treatment group assignment.

PFS will be based on the BICR assessment of disease progression by RECIST v1.1 and will be analyzed using a log-rank test stratified by *EGFR* mutation type (Ex19del or L858R), WHO PS (0 vs 1), and CNS metastasis status as assessed by the investigator at baseline (Yes or No). A stratified Cox proportional hazard model will be used to estimate the HR, associated CIs, and p value. Kaplan–Meier estimates of PFS will be presented graphically by treatment group. Safety and other data will be summarized descriptively.

The study is powered to demonstrate the superiority of Dato-DXd in combination with osimertinib versus osimertinib in terms of PFS per RECIST v1.1 by BICR in the full analysis set. To preserve the overall type 1 error a multiple testing procedure will be implemented for the primary and key secondary endpoints.

Discussion

Osimertinib is a third-generation, irreversible, CNS-active, *EGFR*-TKI that is SoC in the *EGFR*-mutated advanced or metastatic NSCLC setting; however, treatment resistance is common. Dato-DXd has demonstrated efficacy in patients with *EGFR*-mutated NSCLC, as a monotherapy and in combination with osimertinib in patients who had previously progressed on 1L osimertinib.[14–16,20] The promising efficacy demonstrated by osimertinib in combination with Dato-DXd in the phase II ORCHARD study provides rationale for evaluating the combination of osimertinib with Dato-DXd in TROPION-Lung14 and TROPION-Lung15.[20] TROPION-Lung14 is a phase III trial assessing the efficacy and safety of 1L osimertinib in combination with Dato-DXd versus osimertinib alone in patients with *EGFR*-mutated advanced or metastatic NSCLC. Osimertinib in combination with Dato-DXd is also being investigated in the phase III

TROPION-Lung15 study (NCT06417814), versus platinum doublet chemotherapy in patients with *EGFR*-mutated locally advanced or metastatic NSCLC who experienced disease progression on prior osimertinib.[25] In summary, TROPION-Lung14 aims to build upon previous studies assessing Dato-DXd as a monotherapy and those assessing Dato-DXd in combination with other agents and may provide a new treatment option for patients with *EGFR*-mutated NSCLC in the 1L setting.

Author's note

Shengmei Feng: affiliation at the time of manuscript development.

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

Shun Lu: Conceptualization; Investigation; Writing – review & editing.

Mariano Provencio Pulla: Investigation; Writing – review & editing.

Eldsamira Mascarenhas: Investigation; Writing – review & editing.

Junko Tanizaki: Investigation; Writing – review & editing.

Hye Ryun Kim: Investigation; Writing – review & editing.

Yinglei Liu: Writing – review & editing.

Shengmei Feng: Writing – review & editing.

Biao Zhang: Writing – review & editing.

Laurence Toms: Writing – review & editing.

James Chih-Hsin Yang: Writing – review & editing.

Sarah B. Goldberg: Conceptualization; Investigation; Writing – review & editing.

Acknowledgements

The authors would like to thank Prof. Ying Cheng (who was unable to participate in publication activities when this article was prepared). Medical writing support, under the direction of the authors, was provided by Lydia Hallam, MPhil, of Ashfield MedComms (London, UK), an Inizio company, in accordance with Good Publication Practice (GPP) guidelines (http://www.ismpp.org/gpp-2022), and funded by AstraZeneca. The details of this study protocol were previously presented at the American Society of Clinical Oncology Annual Meeting 2025 and the European Conference on Lung Cancer 2025.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: TROPION-Lung14 study (NCT06350097; https://clinicaltrials.gov/study/NCT06350097, date of registration April 5, 2024) is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialization collaboration with AstraZeneca for Dato-DXd.

Competing interests

S.B.G.: Consultant or advisor for: AstraZeneca, Lilly, Daiichi Sankyo, Johnson & Johnson, Summit Therapeutics, Merck, Regeneron, Bayer, Synthekine, and Tubulis. Research funding from: AstraZeneca, Boehringer Ingelheim, Mirati, and Adela. M.P.P.: Advisory Board: Bristol Myers Squibb, Merck Sharp & Dohme, Bayer, Lilly, Roche, Takeda, Janssen; Consulting, support for attending meetings and/or travel, honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events: Bristol Myers Squibb, AstraZeneca, Merck Sharp & Dohme, Roche, Takeda, Lilly, Roche, Janssen, Pfizer, Amgen, Boehringer Ingelheim, Pierre Fabre Pharmaceuticals; Financial Interests: Institutional; Coordinating PI: AstraZeneca, Bristol Myers Squibb, Takeda, Merck Sharp & Dohme, Roche; Non-Financial Interests, Leadership Role, President of Spanish Lung Cancer Group: President; Non-Financial Interests, Leadership Role, Instituto Investigación

Sanitaria Puerta de Hierro: Director; Non-Financial Interests, Leadership Role, President: Grupo Oncológico para el Tratamiento de las Enfermedades Linfoides. E.M.: Consultant or advisor for: AstraZeneca, Roche, Pfizer, and Daiichi Sankyo; Speaker for: AstraZeneca, Roche, Pfizer, Daiichi Sankyo, Janssen; PI for Roche, Janssen, Amgen; Steering Committee Member for: AstraZeneca. J.T.: Honoraria for: lecture from AstraZeneca K.K., AbbVie GK, Boehringer Ingelheim Japan Inc., Bristol Myers Squibb Co. Ltd, Chugai Pharmaceutical Co., Ltd, Daiichi Sankyo Co. Ltd, Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Merck Sharp & Dohme K.K., Nihon Medi-Physics Co. Ltd, Nippon Kayaku Co. Ltd, Ono Pharmaceutical Co. Ltd, Pfizer Japan Inc., Taiho Pharmaceutical Co. Ltd K., and Takeda Pharmaceuticals. H.R.K.: Research funding: AbbVie (Inst), ABL Bio (Inst), AstraZeneca (Inst), Bayer (Inst), BiGene (Inst), Boehringer Ingelheim (Inst), Boryung (Inst), Bristol Myers Squibb (Inst), F. Hoffmann-La Roche Ltd/Genentech, Inc., Hanmi (Inst), Genmab (Inst), GSK (Inst). Merck & Co. Inc. (Inst), Mythic (Inst), Pfizer (Inst), Regeneron (Inst), Samsung Bioepis (Inst), Seagen (Inst), Takeda (Inst), and Yuhan (Inst); Speakers' Bureau: AstraZeneca, MSD, Takeda, Yuhan; Advisory Board: AstraZeneca, Daiichi, Janssen, and Takeda. Y.L.: Employee of AstraZeneca. S.F.: Employee of AstraZeneca. B.Z.: Employee of AstraZeneca. L.T.: Employee of AstraZeneca. J.C.-H.Y.: Honoraria: Amgen (Inst), AstraZeneca/MedImmune (Inst), Boehringer Ingelheim (Inst), Daiichi Sankyo/AstraZeneca (Inst), Merck Sharp & Dohme Oncology (Inst), Pfizer (Inst), Roche/Genentech (Inst), Takeda (Inst); Consulting or Advisory Role: AbbVie (Inst), Amgen (Inst), ArriVent Biopharma (Inst), AstraZeneca (Inst), Daiichi Sankyo (Inst), Daiichi Sankyo/AstraZeneca (Inst), Janssen Oncology (Inst), Lilly (Inst), Merck Sharp & Dohme Oncology (Inst), Takeda (Inst); Research Funding: AstraZeneca (Inst); Travel, Accommodations, Expenses: AstraZeneca, Dizal Pharma, Takeda. S.L.: Leadership: Innovent Biologics, Inc., Shanghai Fosun, Simcere Zaiming; Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, GenomiCare, Hutchison MediPharma, InventisBio Co. Ltd, Menarini, Pfizer, Roche, Simcere, Yuhan, Zai Lab; Speakers' Bureau: AstraZeneca, Hansoh Pharma, Hengrui Therapeutics, Roche; Research Funding: AstraZeneca (Inst), BeiGene (Inst), Bristol Myers Squibb (Inst), Hansoh (Inst), Hengrui Therapeutics (Inst), Hutchison MediPharma (Inst), Lilly Suzhou Pharmaceutical Co. (Inst), Roche (Inst).

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/our-member/astrazeneca/.

ORCID iDs

Shun Lu https://orcid.org/0000-0001-8833-7262

Hye Ryun Kim https://orcid.org/0000-0002-1842-9070

Supplemental material

Supplemental material for this article is available online.

References

1. 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.
2. 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.
3. 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: 629–640.
4. 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.
5. Cross DAE, 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.
6. 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.

7. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023; 34: 339–357.
8. Remon J, Soria JC, Peters S, et al. 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.
9. 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.
10. Gomatou G, Syrigos N and Kotteas E. Osimertinib resistance: molecular mechanisms and emerging treatment options. *Cancers* 2023; 15: 841.
11. Tan AC and Tan DSW. Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. *J Clin Oncol* 2022; 40: 611–625.
12. Planchard D, Jänne PA, Kobayashi K, et al. PL02.06 First-line osimertinib + chemotherapy versus osimertinib monotherapy in EGFRm advanced NSCLC: FLAURA2 final overall survival. *J Thorac Oncol* 2025; 20: S1.
13. 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.
14. 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: 260–272.
15. 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.
16. 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.
17. 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: 1669–1682.
18. US Food and Drug Administration (FDA). DATROWAY® (datopotamab deruxtecan-dlnk) for injection, for intravenous use. Initial U.S. Approval 2025. *Highlights of prescribing information*, https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761464s000lbl.pdf (2025, accessed 19 November 2025).
19. 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.
20. 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.
21. Goto Y, Su W-C, Levy BP, et al. TROPION-Lung02: datopotamab deruxtecan (Dato-DXd) plus pembrolizumab (pembro) with or without platinum chemotherapy (Pt-CT) in advanced non-small cell lung cancer (aNSCLC). *J Clin Oncol* 2023; 41: 9004.
22. Cuppens K, Papadopoulos KP, Nishio M, et al. 8O First-line (1L) datopotamab deruxtecan (Dato-DXd) + durvalumab ± carboplatin in advanced or metastatic non-small cell lung cancer (a/mNSCLC): results from TROPION-Lung04 (cohorts 2 and 4). *ESMO Open* 2025; 10: 104164.
23. Chan A-W, Boutron I, Hopewell S, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. *BMJ* 2025; 389: e081477.
24. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017; 67: 93–99.
25. Tan DS, Nadal E, Cheema P, et al. 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; 17.