TROPION-Lung15: A phase 3 study of datopotamab deruxtecan ± osimertinib vs platinum-doublet chemotherapy in patients with *EGFR*-mutated locally advanced or metastatic non-small cell lung cancer and disease progression on prior osimertinib

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Plain language summary

Why are we performing this research?

- Osimertinib is an anticancer drug that blocks the activity of a protein called epidermal growth factor receptor (EGFR) on cancer cells and prevents their growth.[1] It is the recommended first treatment for people with *EGFR*-mutated advanced non-small cell lung cancer (NSCLC), for those with *EGFR*-mutated NSCLC where the cancer has been removed by surgery, and for *EGFR*-mutated NSCLC that cannot be removed by surgery and whose disease has not got worse during or after chemoradiotherapy.[2–6] Unfortunately, osimertinib eventually stops working in many people, and the cancer returns.[7] Studies are therefore looking for new therapy combinations that might overcome resistance to osimertinib. Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of an antibody (datopotamab) and an anticancer drug (DXd), joined via a stable cleavable linker.[8] Dato-DXd has shown promising antitumour efficacy in previous studies in patients with advanced or metastatic NSCLC, including patients with *EGFR*-mutated NSCLC, when given alone or in combination with immunotherapy and/or chemotherapy.[9,10]
- This study, known as TROPION-Lung15, will compare Dato-DXd ± osimertinib versus standard chemotherapy in patients with *EGFR*-mutated advanced NSCLC whose disease has progressed after previously taking osimertinib.

How are we performing this research?

- Eligible patients will be randomly assigned to receive Dato-DXd + osimertinib, Dato-DXd alone, or conventional chemotherapy. Patients will continue to receive treatment until their disease progresses, 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 remain alive without their cancer growing or spreading (referred to as progression-free survival) compared with patients in the chemotherapy group.

Who will participate in this study?

- We are planning to enrol about 630 adults with *EGFR*-mutated advanced NSCLC whose cancer has progressed after previously taking osimertinib.

Where can I access more information?

The first results are expected to be available in mid-2026, with the study expected to end in 2027. For more information about TROPION-Lung15, please visit https://clinicaltrials.gov/study/NCT06417814. You may also speak to your doctor about clinical studies.

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Background

- Osimertinib, a third-generation, irreversible, CNS-active EGFR-TKI,[1–7] is recommended as 1L treatment for *EGFR*-mutated advanced NSCLC,[8,9] as adjuvant treatment for resected stage IB–IIIA *EGFR*-mutated NSCLC[10,11] and for patients with unresectable *EGFR*-mutated stage III NSCLC without progression during or after chemoradiotherapy.[12]
  - The 1L recommendation for *EGFR*-mutated NSCLC is based on the results of the phase 3 FLAURA study, which demonstrated significant improvements in both PFS and OS with osimertinib versus first-generation EGFR-TKIs (gefitinib or erlotinib) in patients with previously untreated locally advanced or metastatic NSCLC whose tumours had *EGFR* exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations.[3,4]
- Disease progression on osimertinib is common, can be due to multiple different resistance mechanisms, and the mechanism of resistance is unknown in up to 50% of cases.[13]
- Combining osimertinib with therapies with broad antitumour activity, such as an ADC, following disease progression may have the potential to overcome osimertinib resistance, regardless of the mechanism, while maintaining suppression of *EGFR*-mutant clones and continued protection from new CNS metastases or progression of existing CNS metastases.
- Dato-DXd, an ADC, is composed of a humanised anti-TROP2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor.[14]
  - Dato-DXd binds to its antigen (TROP2), which is highly expressed on the cell surface of several solid tumours, including NSCLC[15] and is internalised leading to the release of the cytotoxic drug (DXd).[14] This selective payload delivery minimises systemic exposure while achieving a sustained response.[14]
- The efficacy and tolerability of Dato-DXd have been demonstrated in several studies in NSCLC, including in patients with previously treated advanced NSCLC and actionable genomic alterations.[16–20]
  - In the phase 3 TROPION-Lung01 study, Dato-DXd significantly improved PFS versus docetaxel in patients with pretreated advanced/metastatic NSCLC. 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 to 0.60).[16]
  - In the phase 2 TROPION-Lung05 study 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 ORR was 44% (95% CI 32, 55), 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) in patients with *EGFR*-mutated tumours.[19]
  - In a pooled analysis of patients with *EGFR*-mutated NSCLC from TROPION-Lung05 and TROPION-Lung01, the confirmed ORR by BICR was 42.7%, median DoR was 7.0 months and disease control rate was 86.3%.[17]
- Data from the ORCHARD study, osimertinib in combination with Dato-DXd in patients with *EGFR*-mutated advanced NSCLC whose disease progressed on 1L osimertinib, will be presented at ELCC 2025.

TROPION-Lung15 is evaluating the efficacy and safety of Dato-DXd ± osimertinib versus platinum-doublet chemotherapy in patients with *EGFR*-mutated advanced NSCLC who have disease progression on prior osimertinib

TROPION-Lung15 (NCT06417814): a phase 3, randomised, open-label, sponsor-blind study

Patients

- Aged ≥18 years
- Histologically or cytologically confirmed non-squamous, locally advanced or metastatic NSCLC
- Documented EGFR-TKI-sensitive mutations
- Extracranial radiological progression on prior osimertinib monotherapy (in adjuvant, locally advanced or metastatic setting)
- ≤2 prior lines of EGFR-TKIs
- ≥1 measurable lesion per RECIST 1.1
- WHO/ECOG PS of 0 or 1

N=~630 Randomised 1:1:1

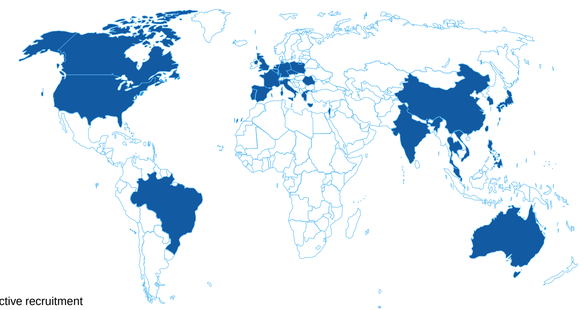
Stratified by:
- Brain metastases (yes vs no)
- Prior osimertinib therapy (adjuvant vs post-CRT/1L vs 2L)
- Race (Chinese Asian vs non-Chinese Asian vs non-Asian)

- **Dato-DXd 6 mg/kg IV Q3W***
- **Dato-DXd 6 mg/kg IV Q3W + osimertinib 80 mg PO QD***
- **Platinum-doublet CT*†**

Dual Primary Endpoints:
PFS by BICR (Dato-DXd vs CT)
PFS by BICR (Dato-DXd + osimertinib vs CT)

*Treatment will continue until RECIST 1.1-defined radiological 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 + carboplatin AUC5 or cisplatin 75 mg/m^2 IV Q3W × 4 cycles, followed by pemetrexed 500 mg/m^2 IV Q3W as maintenance.

Enrolment start: October 2024 | Enrolment is ongoing



Planned/active recruitment

Countries and regions with participating study sites (~280 sites)

Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Greece, Hong Kong, India, Israel, Italy, Japan, Malaysia, Netherlands, Philippines, Poland, Portugal, Romania, Singapore, Republic of Korea, Spain, Taiwan, Thailand, UK, USA, Vietnam

Key inclusion criteria

- Age ≥18 years
- Histologically or cytologically confirmed, non-squamous NSCLC
- ≥1 documented EGFR-TKI-sensitive mutation (eg 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 (adjuvant, post-CRT, locally advanced [stage IIIB/IIIC not amenable to curative therapy] or metastatic [stage IVA/IVB] disease) per the IASLC Cancer Staging Manual in Thoracic Oncology Version 9
- ≤2 prior lines of EGFR-TKIs in the advanced or metastatic setting
- No more than 28 days off osimertinib prior to randomisation
- ECOG / WHO PS of 0 or 1
- ≥1 measurable lesion per RECIST 1.1, not previously irradiated
- Life expectancy >12 weeks
- Tumour biopsy or archival tissue for retrospective evaluation of exploratory biomarkers
- Adequate bone marrow reserve and organ function

Key exclusion criteria

- History of another primary malignancy
- 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
- Prior treatment with a third-generation EGFR-TKI other than osimertinib
- 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 IV 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
- Any other anticancer therapy in the metastatic setting
- Platinum-based CT in the non-metastatic setting within 12 months prior to randomisation

Key study endpoints

	Dato-DXd versus CT	Dato-DXd + Osimertinib versus CT	Dato-DXd + Osimertinib versus Dato-DXd
Primary Endpoint	PFS per RECIST 1.1 by BICR		–
Key Secondary Endpoints	OS CNS PFS, per modified RECIST 1.1 by BICR		–
Secondary 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; pharmacokinetics and immunogenicity; safety and tolerability		PFS OS CNS PFS ORR and DoR

PFS, defined as time from randomisation 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 progression. OS, defined as time from randomisation until date of death due to any cause. CNS PFS, defined as time from randomisation 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. PFS2, defined as time from randomisation to earliest progression event (following initial investigator-assessed progression), after first subsequent therapy or death.

Dato-DXd and osimertinib clinical programme

Dato-DXd and osimertinib are also being investigated in the ongoing, phase 3 TROPION-Lung14 study (NCT06350097); osimertinib in combination with Dato-DXd versus osimertinib alone as 1L treatment for patients with *EGFR*-mutated (Ex19del or L858R) locally advanced or metastatic NSCLC

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Abbreviations

1L/2L, first/second line; ADC, antibody–drug conjugate; AUC, area under the curve; BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CRT, chemoradiotherapy; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HBV/HCV, hepatitis B/C virus; HIV, human immunodeficiency virus; IASLC, International Association for the Study of Lung Cancer; ILD, interstitial lung disease; IV, intravenous; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression or death; PO, oral; PS, performance status; Q3W, every 3 weeks; QD, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor; TROP2, trophoblast cell surface antigen 2; WHO, World Health Organization.

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