TROPION-Lung17: A randomised phase 3 study of datopotamab deruxtecan (Dato-DXd) vs docetaxel in patients with previously-treated TROP2 NMR positive advanced/metastatic non-squamous non-small cell lung cancer (NSCLC) without actionable genomic alterations (AGA)

Jacob Sands,[1] Hidetoshi Hayashi,[2] Shun Lu,[3] Clarissa Mathias,[4] Sandip P. Patel,[5] Elvire Pons-Tostivint,[6] Michael Thomas,[7,8,9] Alexandra Tyulyandina,[10] Ellie Grainger,[11] Paula G. Fraenkel,[12] Marina C. Garassino[13]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Kindai University Hospital, Osaka, Japan; [3]Shanghai Chest Hospital, Shanghai, China; [4]NOB/Grupo Oncoclinicas, Salvador, Brazil; [5]UC San Diego Moores Cancer Center, San Diego, CA, USA; [6]University Hospital of Nantes, Nantes, France; [7]Dept. of Thoracic Oncology, Thoraxklinik, Heidelberg University Hospital, Heidelberg, Germany; [8]National Center for Tumor Diseases (NCT), a partnership between DKFZ and Heidelberg University Hospital, Heidelberg, Germany; [9]Translational Lung Research Center Heidelberg (TLRC-H), German Center for Lung Research (DZL), Heidelberg, Germany; [10]Oncology R&D, AstraZeneca, Barcelona, Spain; [11]Oncology R&D, AstraZeneca, Cambridge, United Kingdom; [12]Oncology R&D, AstraZeneca, Waltham, MA, USA; [13]University of Chicago Medicine & Biological Sciences, Chicago, IL, USA

Poster 145TiP

Plain language summary

Why are we performing this research?

For patients with non-small cell lung cancer (NSCLC) that has spread to nearby tissue or lymph nodes (advanced disease) or from its original site (metastatic), their cancer often returns after treatment (known as recurrence). When this happens, treatment options are limited and may include chemotherapy such as docetaxel.[1–3]

- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of an antibody (datopotamab) that recognises and attaches to cells with a specific protein called human trophoblast cell surface antigen 2 (TROP2), and an anticancer drug (DXd), joined via a cleavable linker.[4] Dato-DXd has received regulatory approval for patients with previously-treated locally advanced or metastatic *EGFR*-mutated NSCLC.
- We previously found that patients with a specific type of NSCLC (non-squamous) whose tumours did not have certain genetic changes (or actionable genomic alterations) responded better to treatment with Dato-DXd if they were positive for a marker called TROP2 normalised membrane ratio (NMR), which was measured using a method called quantitative continuous scoring.[5]
- TROPION-Lung17 will compare Dato-DXd versus docetaxel in patients with advanced or metastatic NSCLC with TROP2 NMR positive tumours that lack genetic changes (such as *EGFR*, *ALK* and/or *ROS1* mutations) whose disease has worsened after prior treatment.

How are we performing this research?

Approximately 400 patients will be randomised to receive either Dato-DXd or docetaxel (the current standard of care treatment) until their disease progresses, side effects become unacceptable, or patients choose to leave the study. The objective of the study is to assess how long patients remain alive overall (known as overall survival) or alive without their cancer growing or spreading (known as progression-free survival).

Who will participate in this study?

We are recruiting patients with previously-treated advanced or metastatic TROP2 NMR positive non-squamous NSCLC that lacks genetic changes for which there are approved targeted therapies.

Where can I access more information?

For more information about TROPION-Lung17, please visit https://clinicaltrials.gov/study/NCT07291037. You may also speak to your doctor about clinical studies.

1. Velcheti V, et al. JAMA Netw Open 2025;8:e2514527; 2. Divan HA, et al. Lung Cancer 2023;179:107177; 3. Messori A, et al. Curr Oncol 2025;32:46; 4. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40; 5. Garassino MC, et al. J Thorac Oncol 2024;19:S2–S3.

Background

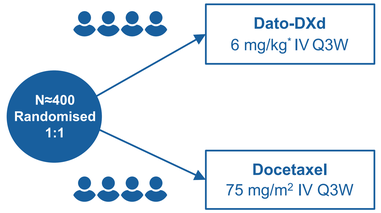
- Treatment options remain limited for patients with advanced NSCLC without AGA following progression on platinum-based chemotherapy +/- immune checkpoint inhibitors.[1–3]
  - Docetaxel is commonly used in this setting; yet survival outcomes remain poor, with a median real-world PFS of 2.3 months and median real-world OS of 6.1 months.[2]
- Dato-DXd is an ADC composed of a humanised anti-TROP2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor payload via a plasma-stable tetrapeptide-based tumour-selective cleavable linker.[4]
- Data from TROPION-Lung05 (NCT04484142),[5] supported by findings from TROPION-Lung01 (NCT4656652),[6] led to the regulatory approval of Dato-DXd for the treatment of adult patients with locally advanced or metastatic *EGFR*-mutated NSCLC who have received prior EGFR-directed therapy and platinum-based chemotherapy.
  - In the phase 3 TROPION-Lung01 study, among patients with non-squamous tumours without AGA, median PFS was 5.1 versus 4.0 months with Dato-DXd versus docetaxel (HR: 0.71; 95% CI: 0.56–0.91); median OS was 13.6 months versus 12.3 months (HR: 0.89; 95% CI: 0.70–1.13).[6]
- QCS, a fully supervised computational approach that precisely quantifies target expression in tumour cells and subcellular compartments, was used to measure TROP2 expression in the membrane relative to the cytoplasm of tumour cells, producing an NMR.[7]
  - Assay optimisation was performed in the biomarker-evaluable subset of patients in TROPION-Lung01.[7]
- Following assay development, a retrospective analysis of TROPION-Lung01 evaluated clinical outcomes by TROP2 NMR status and showed prolonged median PFS with Dato-DXd in patients with TROP2 NMR positive tumours (63% of patients) compared with TROP2 NMR negative tumours (6.9 versus 2.9 months).[7]
  - The greatest PFS benefit was observed in TROP2 NMR positive patients with non-squamous NSCLC without AGA (median PFS: 7.2 months; HR: 0.52 [95% CI: 0.35–0.78 versus docetaxel]), supporting further investigation of Dato-DXd in this population.[7]

TROPION-Lung17 is evaluating the efficacy and safety of Dato-DXd versus docetaxel in patients with prospectively selected TROP2 NMR positive non-squamous advanced/metastatic NSCLC without AGA whose disease has progressed after prior platinum-based chemotherapy and anti-PD-(L)1 therapy.

TROPION-Lung17 (NCT07291037): A phase 3, randomised, open-label, sponsor-blind, global study

Patients

- Aged ≥18 years
- Pathologically documented non-squamous NSCLC (stage IIIB, IIIC, or IV, per AJCC Staging Manual, 9th Edition) without AGA
  - Negative for *EGFR*, *ALK*, and *ROS1* mutations
  - No known AGAs including *KRAS* G12C, *NTRK*, *BRAF*, *MET* exon14 skipping, *RET*, or *HER2* mutations
- TROP2 NMR positive
- Prior receipt of platinum-based chemotherapy and anti-PD-(L)1 monoclonal antibodies
- ≥1 measurable lesion per RECIST v1.1
- ECOG PS 0 or 1
- Stable or asymptomatic brain metastases permitted



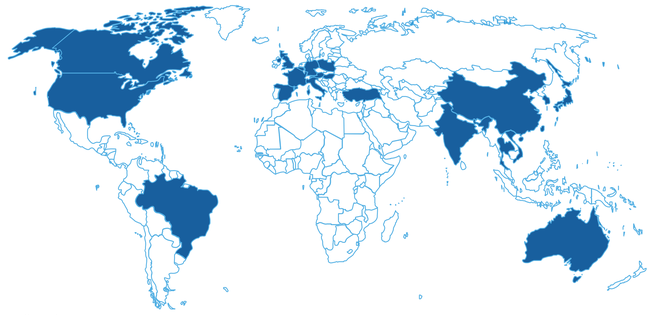
Stratified by:
- Duration of prior anti-PD-(L)1 therapy (<6 months vs ≥6 months)
- Geographical region (US, Europe, Canada vs other geographic regions)

Dual primary endpoints:
- PFS by BICR
- OS

Treatment will continue until investigator assessed radiological progression per RECIST v1.1, unacceptable toxicity, withdrawal of consent, or any other discontinuation criterion is met

*Up to a maximum of 540 mg for patients ≥90 kg

Enrolment start: October 2025 | Enrolment is ongoing



Planned/active recruitment

Countries with participating study sites

Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Italy, Japan, Poland, Republic of Korea, Spain, Taiwan, Thailand, Türkiye, United Kingdom, United States, Vietnam

Key inclusion criteria

- Aged ≥18 years
- Pathologically documented stage IIIB, IIIC, or IV non-squamous NSCLC without AGA, per AJCC Staging Manual, 9th Edition
  - Negative test results for sensitising *EGFR* mutations, *ALK* or *ROS1* genomic alterations
  - No known actionable tumour genomic alterations (e.g. *NTRK*, *BRAF*, *RET*, *MET* exon 14 skipping, *KRAS* [G12C only], *HER2*)
- TROP2 NMR positive tumour
  - Provision of an FFPE tumour sample for prospective assessment of TROP2 NMR by central laboratory testing
- Radiographic disease progression on or following treatment for advanced or metastatic NSCLC
- Prior receipt of platinum-based chemotherapy and anti-PD-(L)1 monoclonal antibody therapy (concurrently as 1L therapy, or sequentially as the only 2 prior lines of therapy) as the only prior lines of therapy
- ECOG PS of 0 or 1
- At least one measurable lesion per RECIST v1.1
- Life expectancy ≥3 months
- Adequate bone marrow reserve and organ function within 7 days prior to randomisation

Key exclusion criteria

- Squamous, mixed NSCLC, or SCLC histology
- NSCLC disease eligible for definitive therapy alone
- Treatment with any agent, including an ADC, containing a chemotherapeutic targeting topoisomerase, TROP2-targeted therapy, or docetaxel
- History of another primary malignancy within 3 years
- Persistent toxicities from previous anti-cancer therapy
- Spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring treatment with corticosteroids or anticonvulsants for at least 7 days prior to randomisation
- Clinically significant corneal disease
- Significant third-space fluid retention
- Active or uncontrolled HBV, HCV, uncontrolled HIV, uncontrolled infection requiring IV antimicrobials, suspected infection, an inability to rule out infection, or active tuberculosis
- Uncontrolled or significant cardiac disease, or resting electrocardiogram with clinically abnormal findings
- History of non-infectious ILD/pneumonitis, including radiation pneumonitis requiring steroid treatment or any evidence of current/suspected ILD
- Severe pulmonary function compromise

Study endpoints

1° Dual primary endpoints
- PFS per RECIST v1.1 by BICR
- OS

2° Secondary endpoints
- ORR per RECIST v1.1 by BICR
- DoR per RECIST v1.1 by BICR
- PFS2
- Pharmacokinetics
- Immunogenicity
- Patient-reported time to deterioration in pulmonary symptoms per NSCLC-SAQ
- Patient-reported time to deterioration in physical functioning per PROMIS Short Form
- Patient-reported GHS/QoL per EORTC IL172
- Correlation of TROP2 expression with clinical efficacy outcomes (including PFS, OS, ORR, and DoR)
- Diagnostic development
- Safety

Poster

Abbreviations

1L, first line; ADC, antibody-drug conjugate; AJCC, American Joint Committee on Cancer; AGA, actionable genomic alterations; BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EORTC IL172, European Organisation for research and Treatment of Cancer item library 172; FFPE, formalin-fixed paraffin-embedded; GHS, global health status; HBV/HCV, hepatitis B/C virus; HIV, human immunodeficiency virus; HR, hazard ratio; ILD, interstitial lung disease; IV, intravenously; NMR, normalised membrane ratio; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death-(ligand) 1; PFS, progression-free survival; PFS2, time to second progression or death; PROMIS, Patient Reported Outcomes Measurement Information System; PS, performance status; Q3W, every three weeks; QCS, quantitative continuous scoring; QoL, quality of life; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1, SAQ; symptom assessment questionnaire; SCLC, small-cell lung cancer; TROP2, trophoblast cell surface antigen 2.

Acknowledgements

This study (NCT07291037) is sponsored by AstraZeneca. In July 2020, Daiichi-Sankyo entered into a global development and commercialisation collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd). Medical writing support, under the direction of the authors, was provided by Claire Bellis, PhD, of Ashfield MedComms (Cape Town, South Africa), an Inizio Company, in accordance with Good Publication Practice (GPP) guidelines (http://www.ismpp.org/gpp-2022), and funded by AstraZeneca.

Disclosures

Jacob Sands reports consulting or advisory for AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Curadev, Daiichi Sankyo Inc, Fosun, Genentech, Gilead, Jazz Pharmaceuticals, Lilly, Merck, Novartis, Pfizer, PharmaMar, Sanofi; and research funding from Amgen, Novartis. For co-author disclosures, please refer to the abstract.

References

1. Velcheti V, . JAMA Netw Open 2025;8:e2514527.
2. Divan HA, et al. Lung Cancer 2023;179:107177.
3. Messori A, et al. Curr Oncol 2025;32:46.
4. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40.
5. Sands J, et al. J Clin Oncol 2025;43:1254–65.
6. Ahn MJ, et al. J Clin Oncol 2025;43:260–72. Supplementary material available online. DOI: 10.1200/JCO-24-01544.
7. Garassino MC, et al. J Thorac Oncol 2024;19:S2–S3.

Poster presented at the European Lung Cancer Congress (ELCC) 2026; Copenhagen, Denmark; 25–28 March 2026 by Jacob Sands.
Corresponding author email address: jacob_sands@dfci.harvard.edu