TROPION-Lung10: Phase 3 study of datopotamab deruxtecan plus rilvegostomig in non-squamous advanced or metastatic non-small cell lung cancer with high PD-L1 expression and without actionable genomic alterations

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Plain language summary

Why are we performing this research?

- Non-small cell lung cancer (NSCLC) is the most common type of lung cancer.[1] For patients with NSCLC that has spread to nearby tissue or lymph nodes (advanced) or from its original site (metastatic), and who have expression of a protein called PD-L1 on at least 50% of their tumour cells, 1L treatment options include immunotherapy, given with or without chemotherapy.[2–6]
- Immunotherapy targets the immune system to help the body fight cancer. However, some patients don't respond to immunotherapy, or the treatment stops working, and new treatment options are needed.[7]
- 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.[8] Dato-DXd has shown promising efficacy in previous studies in patients with advanced or metastatic NSCLC, either when given alone or in combination with immunotherapy and/or chemotherapy.[9–12]
- Rilvegostomig is a drug that blocks proteins called PD-1 and TIGIT on the surface of immune cells, which helps the immune system kill cancer cells.[13]
- TROPION-Lung10 is evaluating if the combination of Dato-DXd and rilvegostomig can improve outcomes for patients with advanced or metastatic NSCLC.

How are we performing this research?

Approximately 675 patients will be randomised to receive either Dato-DXd in combination with rilvegostomig, rilvegostomig alone, or pembrolizumab, which is the current standard of care treatment.

Who will participate in this study?

Eligible patients:

- Have a type of NSCLC called non-squamous that is advanced or metastatic
- Do not have tumours with genetic changes for which there are approved targeted therapies
- Have tumours that express a protein called PD-L1 on at least 50% of tumour cells
- Have not received any treatment for advanced or metastatic NSCLC

Where can I access more information?

For more information about TROPION-Lung10, please visit https://clinicaltrials.gov/study/NCT06357533. You may also speak to your doctor about clinical studies.

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Background

- 1L immunotherapy targeting the PD-1/PD-L1 pathway, with or without chemotherapy, has improved outcomes for patients with advanced/metastatic NSCLC without AGAs;[1–5] however, some patients may not respond or may develop resistance, meaning new treatment strategies and approaches to identifying patients who may respond are needed.[4,6]
- TROP2 is a transmembrane glycoprotein that is highly expressed in several solid tumours, including lung cancers.[7–11]
- Dato-DXd is a TROP2-directed ADC composed of a humanised anti-TROP2 IgG1 monoclonal antibody conjugated to a highly potent topoisomerase I inhibitor payload via a plasma-stable tetrapeptide-based tumour selective cleavable linker.[7]
- Dato-DXd alone or in combination with anti-PD-1/PD-L1 therapy ± chemotherapy has shown activity as 1L+ treatment in patients with advanced or metastatic NSCLC.[12–15]
  - In the phase 3 TROPION-Lung01 study, Dato-DXd monotherapy significantly improved PFS compared with docetaxel (median PFS: 4.4 vs 3.7 months; HR 0.75 [95% CI: 0.62–0.91]) in patients with pretreated advanced/metastatic NSCLC with and without AGAs, which was driven by patients with non-squamous histology.[12]
  - In an exploratory analysis of TROPION-Lung01, the use of a computational pathology-based approach showed that patients receiving Dato-DXd who had TROP2 QCS-NMR-positive tumours had increased ORR and longer PFS than those with TROP2 QCS-NMR-negative tumours.[13]
  - In the phase 1b TROPION-Lung02 study in patients who received doublet and triplet combinations of 1L Dato-DXd plus pembrolizumab ± chemotherapy, ORRs were 52% and 56%, DCRs were 88% and 89%, and median DoRs were NE and 12.9 months, respectively.[14]
  - In the phase 1b TROPION-Lung04 study, 1L Dato-DXd demonstrated promising efficacy in combination with durvalumab ± carboplatin, with no new safety signals identified, in patients with advanced or metastatic NSCLC (ORR: 50% and 77%; DCR: 93% and 92%, respectively)[15] and is also being investigated in combination with rilvegostomig.[16]
- Rilvegostomig (AZD2936) is an Fc-reduced, monovalent, bispecific, humanised monoclonal IgG1 antibody targeting both PD-1 and TIGIT receptors.[17]
- Rilvegostomig has shown preliminary efficacy, with an ORR of 62%, and an acceptable safety profile in patients with advanced/metastatic NSCLC with ≥50% PD-L1 expression on tumour cells and who were naïve to immune checkpoint inhibitors.[17]
- TROPION-Lung10 (NCT06357533) is evaluating the potential of the directed cytotoxicity of Dato-DXd, combined with the immune checkpoint inhibition of rilvegostomig as 1L treatment for patients with advanced/metastatic non-squamous NSCLC versus the current standard of care pembrolizumab.

TROPION-Lung10 (NCT06357533): A phase 3, randomised, open-label, global study

Treatment-naïve adults with stage IIIB/C or IV NSCLC
Non-squamous histology
High PD-L1 expression (≥50% of tumour cells)
No AGAs
ECOG PS 0 or 1

→ **N≈675 Randomised 2:1:2**

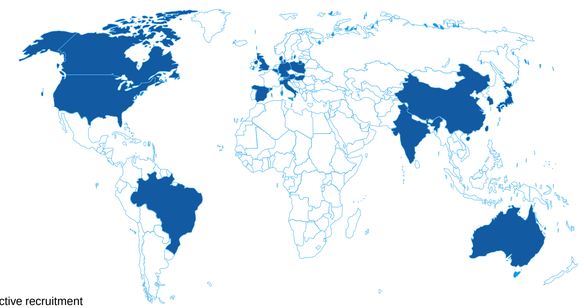
Stratified by:
- Smoking history (yes vs no)
- Geography (Asia vs other geographic regions)
- TROP2 biomarker status (positive vs negative)

→
- **Dato-DXd** 6 mg/kg Q3W + **Rilvegostomig** 750 mg Q3W
- **Rilvegostomig*** 750 mg Q3W
- **Pembrolizumab** 200 mg Q3W for up to 35 cycles or 24 months

Treatment will continue until PD, unacceptable toxicity, end of treatment (pembrolizumab only), or until other discontinuation criteria are met.

*The rilvegostomig monotherapy arm will be used to assess the contribution of components of the experimental arm.

Enrolment start: April 2024 | Enrolment is ongoing



Planned/active recruitment

Countries and regions with participating study sites

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

Key inclusion criteria

- Age ≥18 years
- Histologically or cytologically documented non-squamous NSCLC
- Stage IIIB/C or stage IV NSCLC (based on the AJCC edition 8) not amenable to curative surgery or definitive chemoradiation
- Absence of sensitising *EGFR* mutations, *ALK* and *ROS1* rearrangements and negative results for any other known genomic alteration for which there are locally approved and available targeted 1L therapies
- ≥50% PD-L1 expression on tumour cells
- No prior chemotherapy or other systemic therapy for stage IIIB, IIIC or IV NSCLC
- Measurable disease per RECIST version 1.1
- ECOG PS 0 or 1
- Provision of a tumour sample to determine PD-L1 status, TROP2 status and other biomarkers prior to randomisation

Key exclusion criteria

- History of another primary malignancy within 3 years
- Severe or uncontrolled systemic diseases, including active bleeding diseases, active infection, and cardiac disease, or active or prior documented autoimmune or inflammatory disorders
- Clinically significant third-space fluid retention not amenable to repeated drainage
- History of non-infectious ILD/pneumonitis that required steroids, or current or suspected ILD/pneumonitis
- Significantly compromised pulmonary function
- Spinal cord compression, or brain metastases unless treated, no longer symptomatic and radiologically stable
- History of leptomeningeal carcinomatosis
- Clinically significant corneal disease
- Active infection with TB, HBV, HCV, HAV, or uncontrolled HIV infection
- History of active primary immunodeficiency

Key study endpoints

1° Dual-primary endpoints:

PFS* and OS in the TROP2 QCS-NMR-positive population for Dato-DXd + rilvegostomig vs pembrolizumab.

2°

		Dato-DXd + rilvegostomig vs pembrolizumab	Rilvegostomig monotherapy vs pembrolizumab	Dato-DXd + rilvegostomig vs rilvegostomig monotherapy
Secondary Endpoints	TROP2+ population	ORR* DoR* PFS2 Patient-reported outcomes	PFS* OS ORR* DoR*	
	Full analysis set	PFS* OS ORR* DoR* PFS2 Patient-reported outcomes		
	Safety analysis set	Safety and tolerability		-
		PK and immunogenicity of Dato-DXd + rilvegostomig and rilvegostomig monotherapy		

*Assessed by BICR per RECIST v1.1.

TROP2 biomarker status will be assessed using the TROP2 QCS-NMR assay. The full analysis set will include all randomised patients. The safety analysis set will include all randomised patients who have received ≥1 dose of study intervention and for whom any post-dose data are available. PK and immunogenicity analysis will be conducted in those in the safety analysis set who have ≥1 reportable PK concentration or ≥1 non-missing Dato-DXd or rilvegostomig ADA result at any time, respectively.

Mobile-friendly poster

Poster

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Abbreviations

1L, first line; ADA, anti-drug antibody; ADC, antibody-drug conjugate; AGA, actionable genomic alterations; AJCC, American Joint Committee on Cancer; ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HAV/HBV/HCV, hepatitis A/B/C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IgG1, immunoglobulin G1; ILD, interstitial lung disease; NE, not evaluable; NMR, normalised membrane ratio; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, disease progression; PD-(L)1, programmed cell death (ligand) 1; PFS, progression-free survival; PFS2, second PFS; PK, pharmacokinetics; PS, performance status; QCS, quantitative continuous scoring; Q3W, every 3 weeks; RECIST v1.1; Response Evaluation Criteria in Solid Tumors version 1.1; TB, tuberculosis; TIGIT, T cell immunoglobulin and ITIM domain; TROP2, trophoblast cell surface antigen-2.

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Disclosures

Thomas Newsom-Davis reports advisory board participation with AbbVie, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, EQRx, Gilead, GlaxoSmithKline, Janssen, Lilly, Merck, Merck Sharpe Dohme, Novartis, Novocure, Pfizer, Regeneron, Roche, Sanofi and Takeda, has been an invited speaker for Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, EQRx, Gilead, GlaxoSmithKline, Janssen, Lilly, Novartis, Roche and Takeda and a steering committee member for AstraZeneca, Merck Sharpe Dohme and Roche. For co-author disclosures, please refer to the abstract.

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