# AVANZAR: Phase III study of datopotamab deruxtecan (Dato-DXd) + durvalumab + carboplatin as first-line treatment of advanced/metastatic non-small-cell lung cancer

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## Plain language summary

**Why are we performing this research?**

- Lung cancer is the leading cause of cancer-related deaths worldwide.[1] Non-small-cell lung cancer (NSCLC), a group of lung tumors that originate from specific cells found in the lung, is responsible for over 80% of all lung cancer diagnoses.[2]
- Datopotamab deruxtecan (Dato-DXd) is a drug that consists of two parts: datopotamab (an antibody) and DXd (an anticancer drug), which are connected via a linker. Dato-DXd binds to a protein called trophoblast cell surface antigen 2 (TROP2), which is often overexpressed on lung cancer tumors. Once bound, Dato-DXd is taken inside the tumor cell where the linker breaks, releasing DXd to kill the tumor. By binding to cancer cells before releasing DXd, treatment is directed to the site of action, potentially reducing side effects in the rest of the body.
- In the ongoing Phase 1 TROPION-PanTumor01 and TROPION-Lung02 trials, Dato-DXd showed promising antitumor activity in patients with advanced or metastatic NSCLC, when either given alone or in combination with immunotherapy (treatments that target the immune system to help the body fight cancer) with or without chemotherapy.[3,4]
- The AVANZAR study aims to see if Dato-DXd, in combination with durvalumab (immunotherapy) and carboplatin (chemotherapy), can delay the length of time to when cancer grows, spreads, or gets worse (progression-free survival) and lengthen the time participants are alive (overall survival).

**Who will participate in this study and how are we performing this research?**

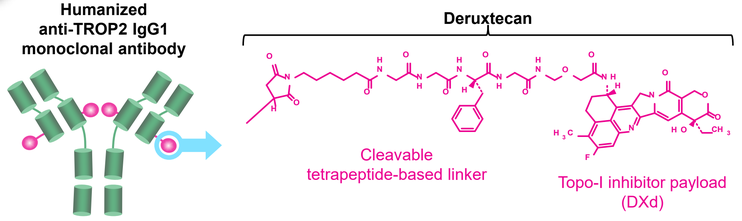
- We are aiming to recruit approximately 1000 patients who have:
  - NSCLC that has spread to nearby tissue or lymph nodes (locally advanced), or spread from its original site (metastatic)
  - Tumors without alterations in genes that have approved molecular-targeted therapies in the first-line setting
  - Not received any prior first-line treatment for locally advanced or metastatic NSCLC
- Eligible patients will be randomly assigned to an initial treatment group in equal numbers:
  - Dato-DXd in combination with durvalumab and carboplatin
  - Pembrolizumab (immunotherapy) in combination with histology-specific chemotherapy
- Each patient will generally continue to receive their designated treatments as long as the tumor is controlled by the drugs, there are no unacceptable side effects, or the patient doesn't choose to stop treatment.

[1]https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed 3 Aug 2023; [2]Casal-Mouriño A, et al. Transl Lung Cancer Res 2021;10:506–18; [3]Shimizu T, et al. J Clin Oncol 2023;10.1200/JCO.23.00059:ePub. [4]Goto Y, et al. Oral 9004. Presented at ASCO 2023.

## Background

- First-line treatment with immunotherapies targeting the PD-1/PD-L1 pathway, administered with or without chemotherapy, have improved survival outcomes of patients with metastatic NSCLC without actionable genomic alterations.[1–3]
- Despite the improved survival seen in this setting, median OS at 5 years remains low.
  - For example, the KEYNOTE-189 (non-squamous NSCLC; N=410)[2] and KEYNOTE-407 (squamous NSCLC; N=278)[3] trials of pembrolizumab (PD-1 inhibitor) + platinum-based chemotherapy reported a median OS of 22.0 months (95% CI, 19.5–24.5) and 17.2 months (95% CI, 14.4–19.7), respectively, after 5 years of follow-up.
  - These results underline the unmet need for new therapeutic strategies in metastatic NSCLC.
- TROP2 is a transmembrane glycoprotein that is broadly expressed on the cell surface of many epithelial tumors, including lung cancers, and represents a promising antigen for TROP2-directed therapies.[4–6]
- Dato-DXd is an ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase-I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker (**Figure 1**).[6]
- Dato-DXd has shown encouraging early clinical efficacy and safety in patients with advanced/metastatic NSCLC.
  - The Phase 1 TROPION-PanTumor01 study (NCT03401385) reported a confirmed ORR of 26% (95% CI, 14.6–40.3) and median DoR of 10.5 months (95% CI, 5.6–26.5) with Dato-DXd monotherapy 6 mg/kg (N=50) in heavily pre-treated NSCLC.[7]
  - The Phase 1 TROPION-Lung02 study (NCT04526691) reported a combined (confirmed + pending) ORR of 50% (95% CI, 32–68) and 57% (95% CI, 42–70) in doublet (N=34) and triplet (N=53) combination cohorts, respectively, with first-line Dato-DXd + pembrolizumab ± platinum-based chemotherapy.[8]
  - The Phase 3 TROPION-Lung01 study (NCT04656652) demonstrated a statistically significant improvement in PFS with Dato-DXd monotherapy 6 mg/kg versus docetaxel in previously treated advanced/metastatic NSCLC.[9]
- Durvalumab is an anti-PD-L1 monoclonal antibody that has demonstrated notable efficacy in the treatment of NSCLC,[10] as well as early clinical efficacy and safety in combination with Dato-DXd in first-line locally advanced/metastatic TNBC.[11]
  - Cohorts 1–4 of the TROPION-Lung04 study (NCT04612751) are investigating Dato-DXd + durvalumab ± carboplatin in advanced/metastatic NSCLC; initial results will be presented by Papadopoulos et al. at this meeting (Oral OA05.06).
- The addition of a TROP2-directed ADC to anti-PD-1/PD-L1 immunotherapy and chemotherapy may improve outcomes for patients with advanced/metastatic NSCLC.

## Figure 1. Structure of Dato-DXd[12]




Payload mechanism of action: Topo-I inhibitor

High-potency payload

Optimized drug to antibody ratio ≈4

Payload with short systemic half-life

Stable linker-payload

Tumor-selective cleavable linker

Bystander antitumor effect

## AVANZAR (NCT05687266): an ongoing Phase 3, multicenter, open-label, randomized study

**Patients with Stage IIIB, IIIC, or IV (metastatic) NSCLC**

**Squamous or non-squamous histology (Lacks sensitizing *EGFR* mutation and *ALK* and *ROS1* rearrangements)**

**ECOG PS 0 or 1**

**N=1000 Randomized 1:1**

Stratified by:
- PD-L1 status (TC <1%, TC 1–49%, TC ≥50%)
- Histology (squamous vs. non-squamous)
- Smoking status (never vs. ever)
- TROP2 biomarker status* (positive vs. negative)

**Dato-DXd 6 mg/kg + durvalumab 1120 mg + carboplatin AUC 5 IV Q3W for 4 cycles followed by Dato-DXd 6 mg/kg + durvalumab 1120 mg IV Q3W†**

**Histology-specific chemotherapy + pembrolizumab IV Q3W†‡**

**Dual primary endpoints**
PFS (by BICR per RECIST v1.1) and OS in the TROP2-positive population

*When ready/available; †Treatment with Dato-DXd and/or durvalumab will continue until investigator-assessed radiological progression (per RECIST v1.1), unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met. Treatment with pembrolizumab will continue for a maximum of 35 cycles or 2 years (whichever occurs first); ‡Squamous: Pembrolizumab 200 mg + paclitaxel 200 mg/m$^2$ + carboplatin AUC 5 or 6 for 4 cycles, followed by pembrolizumab 200 mg; non-squamous: Pembrolizumab 200 mg + pemetrexed 500 mg/m$^2$ + either cisplatin 75 mg/m$^2$ or carboplatin AUC 5 for 4 cycles, followed by pembrolizumab 200 mg ± pemetrexed 500 mg/m$^2$.

## Study endpoints

***Dual primary endpoints***

1°
- PFS by BICR per RECIST v1.1 in the TROP2-positive population
- OS in the TROP2-positive population

***Secondary endpoints***

2°
- PFS by BICR per RECIST v1.1 in the ITT and TROP2-negative populations
- OS in the ITT and TROP2-negative populations
- ORR and DoR by BICR and investigator assessment per RECIST v1.1 in the ITT and TROP2-positive populations
- PFS by investigator assessment per RECIST v1.1 in the ITT and TROP2-positive populations
- PFS2 in the ITT and TROP2-positive populations
- Pharmacokinetics and immunogenicity
- Safety and tolerability

## Key inclusion criteria

- Adults (≥18 years) with histologically or cytologically documented Stage IIIB or IIIC NSCLC not amenable for surgical resection or definitive chemoradiation, or Stage IV (metastatic) NSCLC.
- No prior first-line chemotherapy or other systemic therapy for Stage IIIB, IIIC, or IV NSCLC.
- Lacks sensitizing *EGFR* mutation and *ALK* and *ROS1* rearrangements and has no documented tumor genomic alterations in *NTRK*, *BRAF*, *RET*, *MET* or other actionable driver oncogenes with approved and currently available targeted therapies.
- ECOG PS of 0 or 1.
- Archival tumor tissue.
- Adequate bone marrow and organ function.

## Key exclusion criteria

- History of another primary malignancy except for malignancy treated with curative intent with no known active disease <3 years before the first study dose (additional exceptions may apply).
- Mixed small-cell lung cancer and NSCLC histology; sarcomatoid variant of NSCLC.
- Prior exposure to durvalumab, TROP2-targeted therapy, or any agent (including an ADC) containing a chemotherapeutic agent targeting topoisomerase I.
- Spinal cord compression or clinically active brain metastases (unless asymptomatic, stable, not requiring steroids for ≥7 days prior to randomization, and ≥2 weeks have elapsed between the end of radiotherapy and study enrollment).
- History of leptomeningeal carcinomatosis.
- Clinically significant corneal disease.
- Active or uncontrolled hepatitis B or C virus infections or uncontrolled HIV infection.
- Current or suspected non-infectious ILD/pneumonitis or history of non-infectious ILD/pneumonitis that required steroids.

## Study status

- Enrollment began in December 2022. Approximately 230 study locations in an estimated 24 countries are planned.
- The estimated study completion is planned for May 2027.

Poster

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**Abbreviations**

ADC, antibody-drug conjugate; AUC, area under the curve; BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Ig, immunoglobulin; ILD, interstitial lung disease; ITT, intention-to-treat; IV, intravenous; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PFS2, time to second progression or death; Q3W, once every three weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TC, tumor cell; TNBC, triple-negative breast cancer; Topo-I, topoisomerase I; TROP2, trophoblast cell surface protein 2.

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