AVANZAR

# A phase iii, randomised, open-label, multicentre, global study of datopotamab deruxtecan (dato-dxd) in combination with durvalumab and carboplatin versus pembrolizumab in combination with platinum-based chemotherapy for the first-line treatment of patients with locally advanced or metastatic nsclc without actionable genomic alterations (d926nc00001; avanzar)

Promoteur(s) : **AstraZeneca**

Recrutement : partiellement ouvert

Centres participants 4 0

Dernière modification : 2024-02-11

## DESCRIPTION DE L'ÉTUDE

Donnée non renseignée

## RECRUTEMENT

### Profil des participants

#### Sexe(s) des participants

Femmes

Hommes

#### Aptitude des participants

Majeurs aptes

### Condition médicale (spécialité visée)

#### Domaine de recherche

Recherche avec prédominance d’une aire thérapeutique :

Cancérologie / Radio-oncologie/ tumeurs solides

#### Stades de cancer

Métastatique

Avancé

**Biomarqueur**

ROS1

PD-L1

EGFR

ALK

Autre :

TROP2

## Critères de sélection

**Critères d'inclusion**

STUDY POPULATION
The target population of interest in this study is participants with locally advanced or metastatic NSCLC without actionable genomic alterations (ie, alterations in genes with approved therapies available) who have received no prior chemotherapy or other systemic therapy for first-line Stage IIIB, IIIC or IV metastatic NSCLC.
Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.
Participants who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.
5.1 Inclusion Criteria
Participants are eligible to be included in the study only if all of the following criteria apply:
Age
1 Participant must be ≥ 18 years at the time of screening.
Type of Participant and Disease Characteristics
2 Histologically or cytologically documented NSCLC that:
(a) Is Stage IIIB or IIIC disease not amenable for surgical resection or definitive chemoradiation, or Stage IV metastatic NSCLC disease at the time of randomisation who have not received prior chemotherapy or other systemic therapy for first-line Stage IIIB, IIIC or IV NSCLC. Participants who have received prior platinumcontaining adjuvant, neoadjuvant, or definitive chemoradiation for early stage disease (Stage I to IIIA) are eligible, provided that progression has occurred > 6 months from the last dose of checkpoint inhibitor, chemotherapy, or other systemic anti-cancer therapy.
(b) Lacks sensitising EGFR tumour tissue mutation (eg, exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation), as well as ALK and ROS1 rearrangements.
(c) Has no documented tumour genomic alteration results in NTRK, BRAF, RET, MET or any other actionable driver oncogenes for which there are locally approved and available targeted first-line therapies.
Note: Participants whose tumours harbour KRAS mutations are eligible for the study.
3 ECOG PS of 0 or 1 with no deterioration over the previous 2 weeks prior to day of first dosing.
FFPE tumour sample collected prior to signing of informed consent, ie, the start of screening (see Section 8.6.1.1 and the Laboratory Manual for further details).
5 Tumour PD-L1 status defined as TC < 1%, TC 1% to 49%, or TC ≥ 50%, determined using the VENTANA PD-L1 (SP263) IHC Assay by a central laboratory. Participants with unknown central PD-L1 status are not eligible for the study.
6 TROP2 biomarker status as determined retrospectively using the VENTANA TROP2 IHC + QCS Assay (clinical trial assay), or prospectively once a TROP2 IHC + QCS assay is validated in a CAP/CLIA laboratory. Participants with unknown central TROP2 biomarker status are not eligible for the study once prospective testing is implemented.
7 At least 1 lesion, not previously irradiated, that qualifies as a target lesion (TL) per RECIST 1.1 at baseline and can be accurately measured at baseline as ≥ 10 mm in the

longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with CT or MRI and is suitable for accurate repeated measurements.
8 Adequate bone marrow reserve and organ function within 7 days before randomisation defined as:
˜ Haemoglobin ≥ 9.0 g/dL (red blood cell/plasma transfusion is not allowed within 1 week prior to screening assessment).
˜ Absolute neutrophil count ≥ 1.5 × 109/L (granulocyte colony stimulating factor administration is not allowed within 1 week prior to screening assessment).
˜ Platelet count ≥ 100 × 109/L (platelet transfusion is not allowed within 1 week prior to screening assessment).
˜ International normalised ratio/prothrombin time and either partial thromboplastin time or activated partial thromboplastin time ≤ 1.5 × ULN.
˜ TBL ≤ 1.5 × ULN or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.
˜ ALT and AST ≤ 3 × ULN (< 5 × ULN in participants with liver metastases).
˜ Calculated CrCL > 40 mL/min as determined by Cockcroft-Gault (using actual body weight).
Males:
CrCL = Weight (kg) × (140 – Age [years])
(mL/min) 72 × serum creatinine (mg/dL)
Females:
CrCL = Weight (kg) × (140 – Age [years]) × 0.85
(mL/min) 72 × serum creatinine (mg/dL)
9 Minimum life expectancy of 12 weeks.
Sex
10 Male and/or female.
Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Reproduction
11 Negative pregnancy test (serum) for women of childbearing potential who are sexually active with a non-sterilised male partner.
12 Female participants must be 1 year postmenopausal, surgically sterile, or using 1 highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). For women who are on HRT please refer to Appendix G. Women of childbearing potential who are sexually active with a non-sterilised male partner must agree to use 1 highly effective method of birth control (see Appendix G for complete list of highly effective birth control methods). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to use it throughout the total duration of the drug treatment and the drug washout period (see Appendix G).
13 Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or using a highly effective method of contraception (see Appendix G) from the time of screening throughout the total duration of the study and the drug washout period (see Appendix G) to prevent pregnancy in a partner. Male participants must not freeze or donate sperm during this same time period.
Informed Consent
14 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

**Critères d'exclusion**

5.2 Exclusion Criteria
Participants are excluded from the study if any of the following criteria apply:
Medical Conditions
1 As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, including active bleeding diseases, active infection, active ILD/pneumonitis, serious chronic gastrointestinal conditions associated with diarrhoea, psychiatric illness/social situations or significant cardiac conditions), or history of allogenic organ transplant, which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the

protocol.
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 intervention and of low potential risk for recurrence, adequately resected basal cell carcinoma of the skin or squamous cell carcinoma of the skin, lentigo maligna that has undergone potentially curative therapy or adequately treated in situ disease without evidence of disease.
3 Mixed small-cell lung cancer and NSCLC histology; sarcomatoid variant of NSCLC.
4 Persistent toxicities caused by previous anti-cancer therapy, excluding alopecia or vitiligo, not yet improved to Grade ≤ 1 or baseline. Note: participants may be enrolled with some chronic, stable Grade 2 toxicities (defined as no worsening to > Grade 2 for at least 3 months prior to randomisation and managed with SoC treatment) which the investigator deems related to previous anti-cancer therapy, including (but not limited to):
˜ Chemotherapy-induced neuropathy.
˜ Fatigue.
Participants with irreversible toxicity that is not reasonably expected to be exacerbated by study intervention may be included (eg, hearing loss) after consultation with the AstraZeneca study clinical lead.
5 Active or prior documented autoimmune, connective tissue or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis, systemic lupus erythematosus, Sjögren's syndrome, sarcoidosis (granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.), autoimmune pneumonitis and autoimmune myocarditis. The following are exceptions to this criterion:
˜ Participants with vitiligo or alopecia.
˜ Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
˜ Any chronic skin condition that does not require systemic therapy.
˜ Participants without active disease in the last 5 years may be included but only after consultation with the study clinical lead.
˜ Participants with coeliac disease controlled by diet alone.
6 Spinal cord compression or brain metastases unless asymptomatic, stable, and not requiring steroids for at least 7 days prior to randomisation. Participants with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants must have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of radiotherapy and study enrolment.
7 History of leptomeningeal carcinomatosis.
Clinically significant corneal disease.
9 Known active or uncontrolled hepatitis B or C virus infection. Participants are eligible if they:
(a) Have been curatively treated for hepatitis C virus infection as demonstrated clinically and by viral serologies.
(b) Have received hepatitis B virus vaccination with only anti-hepatitis B virus surface antibody positivity and no clinical signs of hepatitis.
(c) Are hepatitis B surface antigen-negative and anti-hepatitis B core antibody-positive (ie, those who cleared hepatitis B virus after infection) and meet conditions i to iii below:
(d) Are hepatitis B surface antigen-positive with chronic hepatitis B virus infection (lasting 6 months or longer) and meet conditions i to iii below:
(i) Hepatitis B virus DNA viral load < 2000 IU/mL.
(ii) Have normal transaminase values, or if liver metastases are present, abnormal transaminases, with a result of AST/ALT < 3 × ULN, which are not attributable to hepatitis B virus infection.
(iii) Start or maintain antiviral treatment if clinically indicated as per the investigator.
10 Uncontrolled infection requiring i.v. antibiotics, antivirals or antifungals; suspected infections (eg, prodromal symptoms); or inability to rule out infections (participants with localised fungal infections of skin or nails are eligible).
11 Known HIV infection that is not well controlled. All of the following criteria are required to define an HIV infection that is well controlled: undetectable viral RNA, CD4+ count ≥ 350, no history of acquired immune deficiency syndrome-defining opportunistic

infection within the past 12 months, and stable for at least 4 weeks on the same anti-HIV medications (meaning there are no expected further changes in that time to the number or type of antiretroviral drugs in the regimen). If an HIV infection meets the above criteria, monitoring of viral RNA load and CD4+ count is recommended and should be performed per local SoC (eg, every 3 months) in order to determine whether the infection is controlled and whether the participant is eligible for inclusion into the study. Participants must be tested for HIV if acceptable by local regulations or an IRB/EC.

12 Known to have active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice).

13 Mean resting QTcF > 470 ms, regardless of gender obtained from triplicate 12-lead ECGs performed at screening.

14 Uncontrolled or significant cardiac disease including myocardial infarction or uncontrolled/unstable angina within 6 months prior to randomisation, congestive heart failure (New York Heart Association Class II to IV), cardiac arrhythmia requiring treatment, or uncontrolled hypertension (resting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg). Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted upon discussion with the study clinical lead.

15 History of non-infectious ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or has suspected ILD/pneumonitis that cannot be ruled out by imaging at screening.

16 Clinically severe pulmonary function compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (eg, pulmonary emboli within 3 months of the study enrolment, severe asthma, severe COPD, restrictive lung disease, pleural effusion, etc.).

Prior/Concomitant Therapy

17 Prior exposure to:

(a) Durvalumab.

(b) Any agent including ADC containing a chemotherapeutic agent targeting topoisomerase I.

(c) Chemotherapy or any other systemic therapy for first-line Stage IIIB, IIIC or IV NSCLC.

(d) TROP2-targeted therapy.

(e) Chloroquine/hydroxychloroquine without an adequate treatment washout period of > 14 days prior to randomisation.

18 Participants who have received prior anti-PD-1, anti-PD-L1, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) in the adjuvant or neoadjuvant setting:

(a) Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.

(b) All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.

(c) Must not have experienced a Grade ≥ 3 immune-related AE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy. Note: Participants with an endocrine AE of Grade ≤ 2 are permitted to enrol if they are stably maintained on appropriate replacement therapy and are asymptomatic.

(d) Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require doses of > 10 mg prednisone or equivalent per day.

19 Current or prior use of immunosuppressive medication within 14 days before the first dose of study intervention. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids or local steroid injections (eg, intra-articular injection).
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
- Steroids as premedication for hypersensitivity reactions or as an anti-emetic (eg, CT scan premedication).
- Use of steroids for known central nervous system metastases and/or carcinomatous meningitis (see exclusion criterion 6).

20 Receipt of live attenuated vaccine within 30 days prior to the first dose of study intervention (see Appendix I 2).
21 Any concurrent anti-cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, HRT) is acceptable.
22 Palliative radiotherapy with a limited field of radiation within ≤ 2 weeks or with wide field of radiation to chest or to more than 30% of the bone marrow within ≤ 4 weeks before the first dose of study intervention.
23 Major surgical procedure or significant traumatic injury within ≤ 3 weeks of the first dose of study intervention or an anticipated need for major surgery during the study. Note: Local surgery of isolated lesions for palliative intent is acceptable.
Prior/Concurrent Clinical Study Experience
24 Previous randomisation/treatment in the present study or a previous clinical study of Dato-DXd and/or durvalumab regardless of treatment group assignment.
25 Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 4 weeks prior to randomisation or concurrent enrolment in another clinical study unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
26 Participants with a known hypersensitivity to study intervention or any of the excipients of these products including but not limited to polysorbate 80 or other mAbs.
Other Exclusions
27 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
28 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.
29 Currently pregnant (confirmed with positive pregnancy test), breastfeeding or planning to become pregnant.

**Intervention**

Dato-DXd in combination with durvalumab and carboplatin

**Cohortes**

**Centre intégré universitaire de santé et de services sociaux du Nord-de-l'Île-de-Montréal**
Donnée non disponible
**Centre intégré universitaire de santé et de services sociaux de l'Est-de-l'Île-de-Montréal**
Donnée non disponible
**Centre intégré de santé et de services sociaux des Laurentides**
Donnée non disponible
**Centre universitaire de santé McGill**
Donnée non disponible

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## LOCALISATION ET CONTACTS

**Centre principal**

**CENTRE INTÉGRÉ UNIVERSITAIRE DE SANTÉ ET DE SERVICES SOCIAUX DE L'EST-DE-L'ÎLE-DE-MONTRÉAL**
MONTRÉAL, QUÉBEC
Recrutement local: INCONNU

**Centres au Québec**

**CENTRE UNIVERSITAIRE DE SANTÉ MCGILL**

MONTRÉAL, QUÉBEC
Recrutement local: POSSIBLEMENT OUVERT
**Coordonnées pour le recrutement**
Donnée non disponible
**Chercheurs**
Donnée non disponible

**CENTRE INTÉGRÉ DE SANTÉ ET DE SERVICES SOCIAUX DES LAURENTIDES**
SAINT-JÉRÔME, QUEBEC
(450) 431-
6571
Recrutement local: OUVERT
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**CENTRE INTÉGRÉ UNIVERSITAIRE DE SANTÉ ET DE SERVICES SOCIAUX DU NORD-DE-L'ÎLE-DE-MONTRÉAL**
MONTRÉAL, QUÉBEC
Recrutement local: À VENIR

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