Essai Clinique

Généré le 18 mai 2024 à partir de

Titre	A Phase 3, Open-label, Randomised Study of Datopotamab Deruxtecan (Dato-DXd) Versus Investigator's Choice of Chemotherapy in Patients Who Are Not Candidates for PD-1/PD-L1 Inhibitor Therapy in First-line Locally Recurrent Inoperable or Metastatic Triple-negative Breast Cancer
Protocole ID	TROPION Breast02
ClinicalTrials.gov ID	NCT05374512
Type(s) de cancer	Sein
Phase	Phase III
Stade	Métastatique
Type étude	Clinique
Médicament	Datopotamab Deruxtecan versus une chimiothérapie au choix de l'investigateur
Institution	CIUSSS DU CENTRE-OUEST-DE-L'ILE-DE-MONTREAL HOPITAL GENERAL JUIF SIR MORTIMER B.DAVIS 3755 rue de la Côte Ste. Catherine, Montréal, QC, H3T 1E2
Ville	
Investigateur principal	Dr Khashayar Esfahani
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Statut	Actif en recrutement
Date d'activation	01-01-2024
But étude	This is a Phase III, randomised, open-label, 2 arm, multicentre, international study assessing the efficacy and safety of Dato-DXd compared with ICC in participants with locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy.The primary objectives of the study are to demonstrate superiority of Dato-DXd relative to ICC by assessment of PFS in participants with locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy, per BICR and to demonstrate superiority of Dato-DXd relative to ICC by assessment of OS in participants with locally recurrent inoperable or metastatic TNBC who are not candidates for PD-1/PD-L1 inhibitor therapy.
Critères d'éligibilité	1. Participant must be ≥ 18 years at the time of screening. 2. Histologically or cytologically documented locally recurrent inoperable or metastatic TNBC. TNBC is defined as: • Negative for ER with < 1% of tumour cells positive for ER on IHC. • Negative for progesterone receptor with < 1% of tumour cells positive for progesterone receptor on IHC. • Negative for HER2 with 0 or 1+ intensity on IHC or 2+ intensity on IHC and negative by in situ hybridisation per the ASCO-CAP HER2 guideline 3. No prior chemotherapy or targeted systemic therapy for metastatic or locally recurrent inoperable breast cancer. 4. Not a candidate for PD-1/PD-L1 inhibitor therapy, defined as: • Participants whose tumours are PD-L1-negative, or • Participants whose tumours are PD-L1-positive and have: 1. relapsed after prior PD-1/PD-L1 inhibitor therapy for early-stage breast cancer, 2. comorbidities precluding PD-1/PD-L1 inhibitor therapy, or 3. no regulatory access to pembrolizumab [participant's country does not have

regulatory approval at the time of screening]).

5. At least 1 measurable lesion not previously irradiated that qualifies as a RECIST 1.1 TL 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 computed tomography (CT) or magnetic resonance imaging (MRI), and is suitable for accurate repeated measurements.
6. ECOG PS 0 or 1 with no deterioration over the previous 2 weeks prior to baseline or day of first dosing.
7. Eligible for one of the chemotherapy options listed as ICC (paclitaxel, nab-paclitaxel, capecitabine, carboplatin, or eribulin), per investigator assessment.
8. Has had an adequate treatment washout period before Cycle 1 Day 1, defined as:
    - Major surgery: ≥ 3 weeks.
    - Radiation therapy including palliative radiation to chest: ≥ 4 weeks (palliative radiation therapy to other areas ≥ 2 weeks).
    - Corticosteroid therapy for central nervous system metastatic disease: > 3 days.
    - Anti cancer therapy including hormonal therapy: ≥ 3 weeks (for small molecule targeted agents: ≥ 2 weeks or 5 half-lives, whichever is longer).
    - Antibody-based anti cancer therapy: ≥ 4 weeks with the exception of receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (eg, denosumab for the treatment of bone metastases).
    - Chloroquine/hydroxychloroquine: > 14 days.
9. Written confirmation of tumour sample needs to be available prior to enrolment and tumour samples should be available prior to randomisation. All participants must have a FFPE metastatic (excluding bone) or locally recurrent inoperable tumour sample (block preferred, or a minimum of 20 freshly cut slides) available, collected ≤ 3 months prior to screening. If neither an adequate FFPE block nor the minimum of 20 slides are available from the most recent biopsy, or if a biopsy is not feasible for safety reasons, and this is clearly documented, an archival tumour specimen obtained before the diagnosis of locally recurrent inoperable or metastatic breast cancer may be submitted, pending approval by the Global Study Team.
10. Participants with a history of previously treated neoplastic spinal cord compression or clinically inactive brain metastases, who require no treatment with corticosteroids or anticonvulsants may be included in the study, if they have recovered from acute toxic effects of radiotherapy. A minimum of 2 weeks must have elapsed between the end of radiotherapy and study enrolment. A minimum of 3 days must have elapsed between the end of corticosteroid therapy for central nervous system metastatic disease and study enrolment.
11. Adequate organ and bone marrow function within 7 days before day of first dosing as follows:
    - 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 × 10^9/L (granulocyte colony stimulating factor administration is not allowed within 1 week prior to screening assessment).
    - Platelet count ≥ 100 × 10^9/L (platelet transfusion is not allowed within 1 week prior to screening assessment).
    - Total bilirubin (TBL) ≤ 1.5 × upper limit of normal (ULN) if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN for AST/ALT (< 5 × ULN in participants with liver metastases).
    - Calculated CrCL ≥ 30 mL/minute as determined by Cockcroft Gault
    - International normalised ratio (INR) or prothrombin time, and either partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT): ≤ 1.5 × ULN.
12. Minimum life expectancy of 12 weeks.
13. Male 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.
14. Negative pregnancy test (serum) for women of childbearing potential.
15. Female participants must be at least 1 year post-menopausal, surgically sterile, or using at least 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.) Women of childbearing potential who are sexually active with a non sterilised male partner must agree to use at least 1 highly effective method of birth control. They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue for at least 7 months after the last dose. Female participants must refrain from egg cell donation and breastfeeding while on study and for at least 7 months after the last dose of study drug. Any non sterilised male partner of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period.
16. Male participants who intend to be sexually active with a female partner of childbearing potential must be surgically sterile or use an acceptable method of contraception from the time of screening throughout the total duration of the study and the drug washout period (at least 4 months after the last dose of study intervention) to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Not engaging in heterosexual activity (sexual abstinence) for the duration of the study and drug washout period is an acceptable practice, if this is the preferred usual lifestyle of the participant. Periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
17. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
18. Provision of signed and dated written Optional Genetic Research Information informed consent

	prior to collection of sample for optional genetic research that supports Genomic Initiative.
Critères d'exclusion	Medical Conditions 1. As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, uncontrolled hypertension, history of allogeneic organ transplant, and active bleeding diseases, ongoing or active infection, or significant cardiac or psychological conditions) 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. 2. 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 (per investigator assessment). Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that have undergone potentially curative therapy, adequately resected non-melanoma skin cancer, curatively treated in situ disease, or other solid tumours curatively treated. 3. Persistent toxicities caused by previous anti cancer therapy, excluding alopecia, not yet improved to Grade ≤ 1 or baseline. 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 sponsor study clinical lead or designee. Note: per the discretion of the investigator after consultation with the sponsor study clinical lead or designee, 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 first dosing and managed with SoC treatment) which the investigator deems related to previous anti cancer therapy. 4. Uncontrolled infection requiring IV 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). 5. Known active or uncontrolled hepatitis B or C virus infection; or is positive for hepatitis B or C virus, based on the evaluation of tests for hepatitis B (hepatitis B virus surface antigen, anti-hepatitis B virus surface antibody, and anti hepatitis B virus core antibody, or hepatitis B virus DNA) or hepatitis C (hepatitis C antibody or hepatitis C virus ribonucleic acid [RNA]) infection at screening. Participants who have received hepatitis B vaccination with only anti-hepatitis B virus surface antibody positivity and no clinical signs of hepatitis, and participants who have been curatively treated for hepatitis C infection (as demonstrated clinically and by viral serologies) are eligible. 6. Known human immunodeficiency virus (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 load, cluster of differentiation (CD)4+ count > 250 cells/mm3, no history of an 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. 7. Uncontrolled or significant cardiac disease including: • Myocardial infarction or uncontrolled/unstable angina within 6 months prior to Cycle 1 Day 1 • Congestive heart failure (New York Heart Association Class II to IV), or • Uncontrolled or significant cardiac arrhythmia, or • Uncontrolled hypertension (resting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg). 8. Investigator judgment of any one of the following: • Mean resting corrected QT interval corrected by Fridericia's formula (QTcF) > 470 ms regardless of gender, obtained from triplicate 12-lead electrocardiograms (ECGs) performed at screening. • History of QT prolongation associated with other medications that required discontinuation of that medication, or any current concomitant medication known to prolong the QT interval and/or cause Torsades de Pointes. • Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives. 9. Uncontrolled hypercalcaemia: > 1.5 mmol/L (> 6 mg/dL) ionised calcium, or serum calcium (uncorrected for albumin) > 3 mmol/L (> 12 mg/dL), or corrected serum calcium > ULN, or clinically significant (symptomatic) hypercalcaemia. 10. 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 11. Clinically severe pulmonary function compromise resulting from intercurrent clinically significant pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months of first dosing, severe asthma, severe chronic obstructive pulmonary disease (COPD), restrictive lung disease, pleural effusion, etc.) or any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc.) where there is documented or suspected pulmonary involvement at the time of screening. 12. Leptomeningeal carcinomatosis. 13. Clinically significant corneal disease. 14. Known active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with local practice). Prior/Concomitant Therapy 15. Prior exposure to: • Any treatment (including ADC) containing a chemotherapeutic agent targeting topoisomerase I • TROP2-targeted therapy

- Prior treatment with same ICC agent
- Chloroquine/hydroxychloroquine without an adequate treatment washout period of > 14 days prior to randomisation.

16. Any concurrent anti cancer treatment.
17. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy [HRT], except topical).
18. Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 3 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.
19. Receipt of live, attenuated vaccine within 30 days prior to the first dose of study treatment.
20. Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs (inhaled steroids or intra articular steroid injections are permitted in this study)Prior/Concurrent Clinical Study Experience
21. Previous treatment in the present study.
22. Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 4 weeks prior to first dose of study intervention, randomisation into a prior T-DXd or Dato DXd study regardless of treatment assignment, 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.
23. Participants with a known severe hypersensitivity to Dato DXd or any of the excipients of the product, including but not limited to polysorbate 80.
24. Known history of severe hypersensitivity reactions to other monoclonal antibodies. Other Exclusions
25. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
26. 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.
27. Currently pregnant (confirmed with positive pregnancy test) or breast feeding or planning to become pregnant.