Essai Clinique

Généré le 17 mai 2024 à partir de

Titre	Étude d'expansion de phase Ib sur le CX-5461 chez des patients présentant une tumeur solide et une mutation du gène BRCA2 et/ou PALB2
Protocole ID	CX-5461-04
ClinicalTrials.gov ID	NCT04890613
Type(s) de cancer	Tumeurs solides
Phase	Phase I
Type étude	Clinique
Médicament	CX-5461
Institution	CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL
Ville	
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Statut	Actif en recrutement
But étude	This is an open-label, multi-center, phase 1b study designed to determine a tolerable dose of CX-5461 administered by IV infusion on Day 1 and Day 8 of a 28-day cycle in patients with selected solid tumours and associated mutations for future Phase II trials. The safety and tolerability of CX-5461, preliminary evidence of antitumor effect and the effect of CX-5461 on the Health-Related Quality of Life (HRQoL) will also be evaluated. The study will also evaluate the predictive value of mutational signatures and explore the significance of dynamic changes in ctDNA levels and plasma DNA methylome profiling in this study's exploratory cohort.

Critères d'éligibilité	Main study cohort:
	• Histologically or cytologically confirmed malignancy of the pancreas, prostate, breast, or ovary.
	• Documented evidence of pathogenic or likely pathogenic germline mutation in BRCA2 and/or PALB2 as indicated in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory report. The report must be submitted to and approved by study sponsor prior to registration. Patients with somatic BRCA2 and/or PALB2 mutation are allowed provided that these patients also have corresponding germline pathogenic or likely pathogenic BRCA2 and/or PALB2 mutation.
	• Patients must have measurable disease as per RECIST 1.1.
	
	Exploratory cohort:
	• Histologically confirmed ovarian, fallopian tube or primary peritoneal cancer, with a high grade serous or high grade endometrioid histology subtype.
	• Documented evidence of pathogenic or likely pathogenic germline mutation or a clinically actionable somatic mutation in BRCA1 and/or other HRD-associated mutation, as indicated in a CLIA-certified laboratory report. The report must be submitted to and approved by study sponsor prior to registration.
	• Patients must have measurable disease as per RECIST 1.1.
	• Meet one of the following criteria:
	  • Platinum Sensitive with no evidence of disease progression within 6 months of the last dose of platinum-based chemotherapy (n=10 patients); OR
	  • Platinum Resistant with disease progression within 6 months of the last dose of a platinum-based chemotherapy.
	
	All participants:

	• Age ≥ 18 years.
	• Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 within 14 days of registration.
	• Radiographically documented disease progression within 28 days of registration and evaluable as per RECIST v1.1.
	• Patients must have adequate bone marrow, renal and hepatic function per local laboratory reference ranges as follows within 14 days of registration:
	  • Absolute Neutrophil Count ≥ 1.5 x 10^9/L
	  • Platelets ≥ 100 x 10^9/L
	  • Hemoglobin ≥ 9 g/dL (blood transfusion ≤ 7 days of screening not permitted).
	  • Calculated creatinine clearance > 51mL/min (Cockcroft-Gault formula)
	  • AST/ALT ≤ 2.5× the upper limit of normal (ULN). Subjects with liver metastasis may have AST, ALP, and ALT ≤ 5.0 X ULN.
	  • Bilirubin ≤ 1.5×ULN. This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only at the discretion of the Study Investigator.
	  • INR/PT and aPTT ≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.
	  • Albumin ≥3.0 g/dL
	• Patients are willing to undergo tumour biopsy pre-treatment and at time of progression on treatment. If a biopsy at the time of progression on prior therapy is available and can be submitted to the Central Lab for this study, this procedure does not need to be repeated. Patients who consent but have tumour that is not amenable to safe biopsy will be allowed to enter the trial and continue therapy as per protocol if this has been addressed and permission is granted from the sponsor prior to registration.
	• Life expectancy of greater than 3 months from the date of registration.
	• Able to provide written informed consent.
	• Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
	• Female patients of childbearing potential must have a negative serum pregnancy test within 14 days prior to registration. (Note: a negative urine/serum pregnancy test is required on Cycle 1, Day 1 prior to treatment unless the screening pregnancy test was done within 48hrs of registration).
	• Female patients of childbearing potential and male patients who are sexually active must agree to practice true abstinence or at least two effective methods of contraception (ie: condoms with spermicide, hormonal methods such as oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs), non-hormonal IUDs, such as ParaGard, bilateral tubal ligation, vasectomy, complete abstinence) within 14 days prior to registration, and agree to continue using such precautions while on treatment with CX-5461 (including dose interruptions) and for 6 months following the last dose of CX-5461.
	• There is no minimum or maximum number of lines of prior therapy and prior PARP inhibitor therapy is allowed.

Critères d'exclusion	• For pancreatic cancer; non-adenocarcinoma histology is excluded from this study. • Patients with malignant bowel obstruction. • Patients with a history of spinal cord compression. • Untreated, unstable brain or meningeal metastases or tumor. Patients with radiological evidence of stable brain metastases are eligible provided that they are asymptomatic and either do not require corticosteroids or have been treated with corticosteroids, with clinical and radiological evidence of stabilization at least 10 days after discontinuation of steroids. • Unresolved toxicity > CTCAE grade 1 from previous anti-cancer therapy (including radiotherapy) except hematological toxicity and alopecia. • Any evidence of severe or uncontrolled diseases such as but not limited to active infection, unstable or uncompensated respiratory, cardiac, neurological, hepatic, renal disease or psychiatric illness/social situations, which in the opinion of the investigator, would limit compliance with study requirements. • Treatment with an investigational (non-registered - other than PARP inhibitor) agent within 30 days and treatment with PARP inhibitor within 14 days prior to the first dose of study medication. • Immuno-compromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV), patients with known active hepatitis (i.e., hepatitis B or C). Note: Patients with a prior history of treated HBV infection who are antigen-negative or patients with a prior history of treated HCV infection who are HCV RNA-undetectable may be enrolled. Patients who are known to be serologically positive for human immunodeficiency virus (HIV) can enroll if their CD4+ T-cell (CD4+) counts ≥ 350 cells/uL. • Patients who have had recent (within 14 days of registration, or until any wound has completely healed) major thoracic or abdominal surgery prior to study start, or a surgical incision that is not fully healed. • No concurrent systemic anti-cancer therapy, biological therapy or other novel agent is to be permitted. Palliative radiotherapy may be allowed. If radiotherapy is required due to disease progression, patient will be considered off study. If radiotherapy is be used to treat non-target lesions and patients may benefit from continuing on study treatment, CX-5461 may re-commence 14 days after completion of radiotherapy. Any continuation on study treatment must be discussed with and approved by study sponsor. • Patients may be potentially eligible where the current tissue diagnosis is confirmed histologically

from biopsy of a target lesion, and the patient has had no evidence of active second malignancy which requires treatment or would confound interpretation of safety, tolerability and efficacy of CX-5461. These cases must be discussed with the medical monitor prior to confirm eligibility.

- Presence of known photosensitivity disorders (xeroderma pigmentosa, porphyria etc.). Strict adherence to protocol-defined sun-protection measures is essential for the duration of study. Patients who do not agree to follow these measures are not eligible. Patients who do not agree to use sunglasses and sun blocker (with SPF50 to UVB and a high degree of protection against UVA) if exposed to sunlight during the course of the study and for 3 months after the last dose are not eligible. Patients who plan to use sunbeds or tanning booths during the course of the study and within 3 months after the last dose are not eligible.
- Female patients who are pregnant or nursing.
- Patients who have a positive COVID-19 test within 14 days of starting study treatment. Patients that test positive can re-test after the 14-day exclusion and may be eligible if the re-test is negative.
- Ophthalmological: active ocular surface disease at baseline (based on an ophthalmological evaluation).
- History of cicatricial conjunctivitis (as evaluated by an ophthalmologist).
- Has had radiotherapy with a limited field for palliation within 1 week of the first dose of study drug, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study drug.
- A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 ms).
- A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of long QT syndrome).
- The use of concomitant medications that prolong the QT/QTc interval.
- Patients with the use of strong CYP3A4 inhibitor or inducer.
- Other malignancies within 5 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin, or ductal carcinoma in situ of the breast that has been surgically cured. Cancer patients with incidental histologic findings of prostate cancer (tumour/node/metastasis stage T1a or T1b or prostate-specific antigen <10 ng/mL) who have not received hormonal treatment may be included, pending a discussion with the Study Sponsor.