Essai Clinique

Généré le 16 mai 2025 à partir de

Titre	Essai clinique de phase I du PCLX-001 dans le lymphome non hodgkinien à cellules B récidivant/réfractaire et dans les tumeurs solides avancées.
Protocole ID	PCLX-001-01
ClinicalTrials.gov ID	NCT04836195
Type(s) de cancer	Lymphome non-hodgkinien (LNH) Tumeurs solides
Phase	Phase I
Stade	Récidivant/réfractaire (2ième ligne de traitement et plus)
Type étude	Clinique
Médicament	PCLX-001
Institution	CENTRE HOSPITALIER DE L'UNIVERSITE DE MONTREAL
Ville	
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Statut	Actif en recrutement
But étude	This is a phase I dose-escalation study of oral PCLX-001, conducted in a multicenter, non-randomized, open-label, non-controlled design. The study is comprised of two parts: Part A (single-agent dose escalation) and Part B (single-agent expansion cohorts)For Part A dose-escalation, patients will be accrued in cohorts of 3 to 6 patients to each dose level. A new dose level cannot open to accrual until toxicity has been determined in the preceding dose level (i.e. all patients have completed their first cycle of therapy and data for all patients in that dose level have been reviewed at a safety cohort review meeting). Six patients will be treated at the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D). If required, the MTD cohort may be expanded by an additional 10 patients for further toxicity and response assessment. The MTD cohort expansion may be restricted to B-cell lymphoma or advanced solid tumours to ensure there is proper distribution during dose escalation.For Part B (single agent expansion cohorts), two expansion cohorts (N=20 each) will be opened to determine the preliminary clinical activity of PCLX-001 at the RP2D: • Expansion Cohort A: Participants with advanced solid malignancies showing preclinical sensitivity or molecular markers of sensitivity to PCLX-001. This includes breast, nonsmall cell lung (NSCLC), small-cell lung (SCLC), colorectal (CRC), and bladder cancers • Expansion Cohort B: Participants with relapsed/refractory (R/R) B-cell lymphoma: diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and Burkitt lymphoma. Transformed large B-cell lymphoma will also be included.
Critères d'éligibilité	• Ability to understand and the willingness to sign a written informed consent. A signed informed consent must be obtained before any study-specific procedures are performed. • Male or female patients aged ≥ 18 years • Dose Escalation Dose Expansion Cohort A: Participants with histologically-confirmed advanced breast, NSCLC, SCLC, colorectal, and bladder cancers who have failed at least one prior therapy and/or are not eligible for therapies expected to provide clinical benefit.Cohort B: Participants with histologically-confirmed R/R B-cell lymphomas that are expected to express CD20 including DLBCL, HGBL, FL (grades 1-3a), FL (grade 3b), MCL, and Burkitt lymphoma who have failed at least two prior therapies and/or are not eligible for therapies expected to provide clinical benefit. Transformed large B-cell lymphoma patients are eligible. FL patients

should meet criteria for requiring treatment.
    - Participants with histologically-confirmed advanced solid tumor who have failed at least one prior therapy and/or are not eligible for therapies expected to provide clinical benefit.
    - Histologically-confirmed B-cell lymphomas that are expected to express CD20 including DLBCL, HGBL, FL (grades 1 to 3b), MCL, and Burkitt lymphoma who have failed at least two prior therapies and/or are not eligible for therapies expected to provide clinical benefit (including autologous stem cell transplantation). Transformed large B-cell lymphoma patients are eligible. FL patients should meet criteria for requiring treatment.
- Patients must have evaluable or measurable disease (as per Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST 1.1], or the Lugano lymphoma classification.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Appendix A).
- Life expectancy of at least 12 weeks
- Patients must have adequate bone marrow function as assessed by the following laboratory tests to be conducted within 7 (±3) days before the first dose of study drug:
    - Hemoglobin ≥ 85 g/L
    - Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
    - Platelet count ≥ 100 x 109/L for Dose Escalation and ≥ 75 x 109/L for Dose Expansion NOTE: For Dose Expansion, patient who do not meet the above hematological criteria, because of bone marrow suppression from prior therapies and/or extensive tumour involvement in the marrow, may be considered for enrollment in the trial after consultation with the Medical Monitor.
- Patients must have adequate liver function as assessed by the following laboratory tests to be conducted within 7 (±3) days before the first dose of study drug:
    - Total bilirubin ≤ 1.5 times the upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times ULN or ≤ 5 times ULN for patients with malignant liver involvement
- Patients must have adequate kidney function, as assessed by the estimated glomerular filtration rate (eGFR) >50 mL/min within 7 (±3) days before the first dose of study drug (eGFR to be calculated by the Cockcroft-Gault formula) or creatinine ≤ 1.5 times the ULN
- Patients must have adequate coagulation, as assessed by the following laboratory tests to be conducted within 7 (±3) days before the first dose of study drug:
    - Prothrombin time/International normalized ratio (PT/INR) ≤ 1.5 for patients not on anticoagulation
    - Activated partial thromboplastin time (aPTT) ≤ 1.5 times ULN for patients not on anticoagulation Note: Patients on anticoagulation with an agent such as heparin (eg. enoxaparin, dalteparin, etc.) will be allowed to participate if no prior evidence of underlying abnormality in coagulation parameters exists.
- Adequate cardiac function per institutional normal measured by echocardiography or multigated acquisition (MUGA) scan (LVEF ≥ 50%)
- Women of childbearing potential must have a negative serum beta human chorionic gonadotropin (β-HCG) pregnancy test obtained within 7 (±3) days before the start of administration of study drugNote: A woman is of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy.
- Women of childbearing potential and fertile men must agree to use adequate contraception when sexually active from signing of the informed consent form for the full study until at least 6 months after the last study drug administration. Patients must agree to utilize 2 reliable and acceptable methods of contraception simultaneously. A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy. Men being treated with PCLX-001 are advised not to father a child during and up to 6 months after treatment; prior to treatment, advice should be sought for conserving sperm due to the chance of irreversible infertility as a consequence of treatment with PCLX-001. Female partners of childbearing potential from male study participants have to use adequate contraception / birth control between signing of the informed consent and 6 months after the last administration of the study drug if the male study participant is not sterilized.
- The investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control. Highly effective (failure rate of less than 1% per year) contraception methods, when used consistently and correctly, include:
- Combined (estrogen and progestin containing: oral, intravaginal transdermal and progestin-only (oral, injectable, implantable) hormonal contraception associated with inhibition of ovulation.
- Intra-uterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion or vasectomized partner (provided that partner is the sole sexual partner and has received medical assessment of the surgical success).
- Sexual abstinence (reliability to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient).
- Male patients with a female partner of reproductive potential must use a condom and ensure that an additional form of contraception is also used during treatment and until 6 months after last study drug administration. Patients must agree to utilize reliable and acceptable methods of contraception simultaneously

Critères d'exclusion	• Known hypersensitivity to the study drugs or excipients of the preparations or any agent given in association with this study
	• History of cardiac disease: congestive heart failure New York Heart Association (NYHA) class > II, unstable angina (angina symptoms at rest), new-onset angina (within the past 6 months before study entry), myocardial infarction within the past 6 months before study entry, or uncontrolled cardiac arrhythmias
	• Uncontrolled arterial hypertension despite optimal medical management (per investigator's opinion)
	• Moderate or severe hepatic impairment, i.e. Child-Pugh class B or C
	• Patients with known human immunodeficiency virus (HIV) infection
	• Patients who have an active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection requiring treatment. Patients with chronic HBV or HCV infection are eligible at the investigator's discretion provided that the disease is stable and sufficiently controlled under treatment.
	• Infections of CTCAE Grade 2 not responding to therapy or active clinically serious infections of CTCAE Grade > 2
	• Symptomatic metastatic brain or meningeal tumors unless the patient is > 3 months from definitive therapy, has a stable imaging study within 4 weeks prior to the first dose of study drug and is clinically stable with respect to the tumor at the time of study entry. Patients with asymptomatic brain metastases must not be on steroid therapy. Patients with neurological symptoms should undergo a CT / MRI scan of the brain to exclude new or progressive brain metastases.
	• Current or past history of central nervous system (CNS) lymphoma
	• Uncontrolled seizure disorder requiring therapy (e.g. strong CYP3A4 inducers such as carbamazepine and phenytoin)
	• History of organ allograft transplantation or autologous stem cell transplantation ≤ 3 months prior to the first dose of study drug. Patients who received prior CAR-T or other T-cell targeting treatment (approved or investigational) ≤ 4 weeks prior to study drug administration
	• Evidence or history of bleeding disorder, i.e. any hemorrhage / bleeding event of CTCAE Grade > 2 within 4 weeks before the first dose of study drug
	• Serious, non-healing wound, ulcer, or bone fracture
	• Previous or concurrent cancer that is distinct in primary site or histology from the cancer being evaluated in this study, with the exception of the following previous or concurrent cancer types:
	  • Curative treatment for localized cancer completed without signs of recurrence and treatment-related toxicity and low risk of recurrence as assessed by the investigator,
	  • In-situ prostate cancer, Gleason Score <7, prostate-specific antigen <10 ng/mL (very low risk and low risk, according to therapy guidelines, e.g. the National Comprehensive Cancer Network guideline; active surveillance / observation is a recommended option).
	• Any clinical condition that is considered unstable or might jeopardize the safety of the patient and his / her compliance in the study
	• Inability to swallow oral medications
	• Any malabsorption condition
	• Breastfeeding. Female patients must not breastfeed during treatment and until 4 months after last study drug administration.
	• Treatment with anticancer chemotherapy or immunotherapy during the study or within 3 weeks before the first dose of study drug. For small-molecule drugs, a period of at least 3 half-lives before the first dose of study drug is acceptable. Mitomycin C or nitrosoureas should not be given within 6 weeks before the first dose of study drug.
	• Treatment with systemic steroids (prednisone dose ≥10 mg/day or equivalent dose).
	• Acute toxic effects (CTCAE Grade ≥2) of previous anticancer chemotherapy or immunotherapy that have not yet stabilized or if significant post-treatment toxicities have been observed. (Note however that toxic effects of previous anticancer therapy considered as chronic, such as chemotherapy-induced neuropathy, fatigue, alopecia, or anorexia of CTCAE Grade <2, for which further resolution is not expected, do not prevent participation in this study.)
	• Radiotherapy for target lesions during study or within 3 weeks before the first dose of study drug. Palliative radiotherapy is allowed for non-target lesions.
	• Major surgery or significant trauma within 4 weeks before the first dose of study drug
	• Previous assignment to treatment during this study
	• Concomitant participation in another clinical study with investigational medicinal product(s)
	• Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results
	• Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
	• Use of strong CYP3A4 inhibitors and inducers from 14 days prior to first administration of study drug. Strong CYP3A4 inhibitors and inducers are prohibited during the study and until the active FU visit.
	• Clinically relevant findings in the ECG such as a second- or third-degree atrioventricular block, prolongation of the QRS complex > 120 ms (except for bundle branch block pattern), or prolongation of the of the QTc interval (Fridericia) over 450 ms unless agreed otherwise between the investigator and the sponsor's medically responsible person