PCLX-001-01

Phase I Trial of PCLX-001 in Relapsed/Refractory B-cell Non-Hodgkin Lymphoma and Advanced Solid Malignancies

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Test Product:	PCLX-001	
Sponsor:	Pacylex Pharmaceutics, Inc. 4000, 10230 Jasper Avenue Edmonton, Alberta, CANADA T5J 4P6	
Sponsor's Medical Advisor:	John Mackey, MD; CMO, Pacylex Pharmaceuticals, Inc. 4000, 10230 Jasper Avenue Edmonton, Alberta, CANADA T5J 4P6 Phone: (780) 616-9020	
Principal Investigator:	Randeep Sangha, MD, FRCPC Cross Cancer Institute 11560 University Avenue Edmonton, Alberta, CANADA T6G 1Z2 Phone: (780) 432-8248 | Fax: (780) 432-8888 Email: Randeep.Sangha@ahs.ca	

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Confidential

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Sponsor's Agreement to Protocol version 3.0, dated 5 Jan 2023

Name of Authorized Personnel

(Print) _____

Title of Authorized Personnel

(Print) _____

Signature of Authorized Personnel: _____

Date of Approval: _____

DD-MMM-YYYY

Protocol Acceptance Form

By signing below, the Principal Investigator (PI) agrees to adhere to the protocol in the conduct of this study. Any change in the study must be reviewed by a formal protocol amendment procedure and the Principal Investigator will submit all changes, amendments and revisions to their Research Ethics Board. Any change to the protocol that affects patient selection, safety, or changes in the conduct of the trial will require written approval from the REB and Health Canada (HC) / the U.S. Food and Drug Administration (FDA) (as applicable) before implementing the change.

The Investigator will provide access to this protocol for personnel at the study center who are involved in this clinical study and will ensure that study personnel understand the protocol and have knowledge of the investigational medicinal product or intervention.

The Investigator will keep all study documents in confidence.

The Investigator(s) also agree(s) to conduct the study in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines on Good Clinical Practice (ICH GCP).

The Principal Investigator also thereby agrees that the REB will approve all patient informed consent forms (ICF) before the study is initiated. The investigator will obtain informed consent and document this process for all patients enrolled on this study.

_____	_____	_____
Principal Investigator (Print)	Signature	Date (dd/mmm/yyyy)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviations	Definitions
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AML	Acute myelogenous leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARA	Acid Reducing Agents
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BCR	B-cell receptor
BL	Burkitt lymphoma
CK	Creatine kinase
CL	Clearance
C_{max}	Maximum observed drug concentration
CRC	Colorectal cancer
CT	Computed tomography
CTA	Clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
DL1	Dose level 1
DL-1	Dose level minus 1
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
DSMB	Data Safety Monitoring Board

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
FDA	Food and Drug Administration
FL	Follicular lymphoma
FLIPI	Follicular lymphoma International Prognostic Index
FSH	Follicle stimulating hormone
FU	Follow-up
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HC	Health Canada
HCV	Hepatitis C virus
HCG	Human chorionic gonadotropin
HED	Human equivalent dose
hERG	Human Ether-à-go-go-Related-gene
HGBL	High grade B-cell lymphoma
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH-GCP	International Conference of Harmonization-Good Clinical Practice
IEC	Independent Ethics Committee
IP	Intraperitoneal
IPI	International Prognostic Index

IRB	Institutional Review Board
IUD	Intra-uterine device
IUS	Intra-uterine hormone-releasing system
IV	Intravenous
LVEF	Left ventricular ejection fraction
MCL	Mantle cell lymphoma
MIPI	Mantle Cell Lymphoma International Prognostic Index
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition
NHL	Non-Hodgkin lymphoma
NMT	N-myristoyltransferase
NOL	No Objection Letter
NYHA	New York Heart Association
NSCLC	Non-small cell lung cancer
OTC	Over the counter
PDX	Patient derived xenograft
PD	Pharmacodynamic
PET	Positron emission tomography
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PPI	Proton Pump Inhibitor
PT/INR	Prothrombin time / International normalized ratio
PTT	Partial thromboplastin time
REB	Research ethics board
RECIST	Response Evaluation Criteria in Solid Tumours

RP2D	Recommended phase II dose
R/R	Relapsed/refractory
SAE	Serious adverse event
SC	Subcutaneous
SCLC	Small-cell lung cancer
SFK	Src family kinases
TLS	Tumour lysis syndrome
TPD	Therapeutic Products Directorate
TSH	Thyroid stimulating hormone
V_d	Volume of distribution

PROTOCOL SYNOPSIS

PROTOCOL TITLE	Phase I Trial of PCLX-001 in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma and Advanced Solid Malignancies
PROTOCOL NUMBER	PCLX-001-01
TEST PRODUCT	PCLX-001
PHASE OF DEVELOPMENT	I
NUMBER OF PARTICIPANTS	Part A - Dose Escalation: At least 9 and up to 52 participants Part B – Dose Expansion: 40 participants
STUDY DURATION	24 months

RATIONALE

Myristoylation, the N-terminal modification of proteins with the fatty acid myristate, is critical for membrane targeting and cell signaling. Because cancer cells often have increased NMT expression, NMTs are proposed as anti-cancer agents. PCLX-001 is an oral small molecule NMT inhibitor that potently and selectively inhibits the growth of a wide spectrum of cultured cancer cells in vitro, with particularly pronounced effects in cells derived from hematological cancers including B-cell lymphomas. Pre-clinical models also show notable activity of PCLX-001 in vivo and support further clinical development.

OBJECTIVES

The primary objectives of this study are to:

- Assess safety and tolerability of oral PCLX-001 in patients with B-cell lymphoma and advanced solid tumours
- Determine the maximum tolerated dose (MTD) and / or recommended Phase II dose (RP2D) of PCLX-001 in patients with B-cell lymphomas and advanced solid tumours
- Evaluate the pharmacokinetics (PK) of PCLX-001 in patients with B-cell lymphomas and advanced solid tumours

The secondary objective of the study is to:

- Evaluate the preliminary single agent anti-tumour activity of PCLX-001 in the patient populations studied

The exploratory objective of this study is to:

- Assess the pharmacodynamic (PD) effects of PCLX-001 in patients with B-cell lymphomas and advanced solid tumours

STUDY DESIGN

This is a dose-escalation, safety and tolerability study of oral PCLX-001 in patients with B-cell lymphoma and advanced solid malignancies. This study will be conducted in a multicenter, non-randomized, open-label, non-controlled design. There are two parts to study, Part A dose escalation and Part B dose expansion.

Part A dose-escalation will determine the MTD and RP2D. Patient will be accrued in a standard 3+3 design based on toxicities experienced during the first cycle. For each dose-escalation cohort, treatment with the first dose of PCLX-001 will be staggered such that the second participant enrolled in the cohort will receive PCLX-001 at least two weeks after the first participant and all subsequent participants at least one week after the previous participant.

PCLX will be administered as an oral daily dose on a 28-day cycle as per the dose level schedule below.

Dose Level Escalation Schedule (1 cycle = 28 days)

Dose Level**	**Daily Oral Dose (mg)**	**Number of Capsules**	
		10 mg	70 mg
-1	10	1	0
1 (starting dose)*	20	2	0
2	40	4	0
3	70	0	1
4	100	3	1
5	140	0	2
6	210	0	3
7	280***	0	4

* Trial will start at Dose Level 1 and will de-escalate to Dose Level -1 if DLT is observed.
** If ≥ 2 out of 6 DLTs are observed in Dose Level -1, 1 or 2 then consideration will be given to changing dosing schedule (eg. 28-day schedule with each week comprising 4 days on medication and 3 days off medication).
*** If DLT is not observed at the dose of 280 mg, the dose will be considered the MTD. If required, the MTD cohort may be expanded by an additional 10 patients for further toxicity and response assessment.

Part B dose expansion Cohort A will occur once MTD and RP2D has been determined. Part B dose expansion Cohort B will occur once dose escalation has achieved a dose that has both acceptable safety and achieves drug exposures predicted to have activity in R/R B-cell lymphomas.

Two expansion cohorts of 20 patients will be opened to determine preliminary clinical activity of PCLX-001.

- Expansion Cohort A will be patients with advanced breast, NSCLC, SCLC, CRC, and bladder cancer.
- Expansion Cohort B will be patients with R/R B-cell lymphomas. These will include patients with DLBCL, HGBL, FL, MCL, and BL.

STUDY POPULATION

The following eligibility criteria apply to ALL patients (Part A and Part B as specified).

Select Inclusion Criteria (refer to protocol for full criteria)

1. 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.
2. Male or female patients aged ≥ 18 years
3. **Dose Escalation**
   a. Participants with histologically-confirmed advanced solid tumor (non-breast cancer) who have failed at least one prior therapy and/or are not eligible for therapies expected to provide clinical benefit.
   b. Participants with histologically-confirmed metastatic breast cancer with known hormone receptor status meeting the therapy requirements as listed below (just prior to criterion #4).
   c. 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. These histologic subtypes are based on WHO 2016 criteria.

   Dose Expansion

   Cohort A: Participants with histologically-confirmed advanced 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. Participants with histologically-confirmed

metastatic breast cancer with known hormone receptor status meeting the therapy requirements as listed below (just prior to criterion #4).

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. These histologic subtypes are based on WHO 2016 criteria.
Therapy requirements and stratification factors for histologically-confirmed metastatic breast cancer participants in either the dose escalation or dose expansion phases are dependent upon hormone receptor status as follows:

i. **Estrogen Receptor positive and/ or Progesterone Receptor positive, and HER 2 negative disease.**
Prior treatment with:
- Two or more lines of endocrine therapy in the adjuvant or metastatic setting including the following: Selective Estrogen Receptor Modulators (eg. tamoxifen), Aromatase Inhibitors (eg. letrozole, anastrozole, exemestane), Selective Estrogen Receptor Downregulators (fulvestrant), and CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in combination or monotherapy, and
- at least three lines of cytotoxic chemotherapy given in the adjuvant, neoadjuvant, or metastatic setting including an anthracycline, a taxane, and capecitabine.

ii. **Estrogen Receptor and Progesterone Receptor and HER2 negative disease.**
- Prior treatment with at least three lines of cytotoxic chemotherapy in the adjuvant or metastatic setting including the following agents: anthracyclines, taxanes, platinum (carboplatin or cisplatinum), and
- if known BRCA1 or BRCA2 mutated disease, prior PARP inhibitor therapy is required if available to the patient.

iii. **HER2 positive disease with negative Estrogen receptors.**
- Prior treatment with three or more lines of HER2-directed therapy in the adjuvant, neoadjuvant, or metastatic setting including at least three of the following HER2 directed agents: trastuzumab, trastuzumab emtansine, trastuzumab deruxtecan, pertuzumab, lapatinib, neratinib, tucatinib.

iv. **HER2 positive disease with positive Estrogen receptors.**
Prior treatment with:
- three or more lines of HER2-directed therapy in the adjuvant, neoadjuvant, or metastatic setting including at least three of the following HER2 directed agents: trastuzumab, trastuzumab emtansine, trastuzumab deruxtecan, pertuzumab, lapatinib, neratinib, tucatinib, and
- two or more lines of endocrine therapy in the adjuvant or metastatic setting including the following: Selective Estrogen Receptor Modulators (eg. tamoxifen), Aromatase Inhibitors (eg. letrozole, anastrozole, exemestane), Selective Estrogen Receptor Downregulators (fulvestrant), and CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in combination or monotherapy, and
- at least three lines of cytotoxic chemotherapy given in the adjuvant, neoadjuvant, or metastatic setting including an anthracycline, a taxane, and capecitabine.

4. 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.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
6. Life expectancy of at least 12 weeks
7. 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:
   a. Hemoglobin ≥ 85 g/L
   b. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   c. Platelet count ≥ 100 x 10^9/L Platelet count ≥ 100 x 10^9/L for Dose Escalation and ≥ 75 x 10^9/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.

8. Patients must have adequate kidney function, as assessed by both: a) 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), and b) creatinine ≤ 1.5 times the ULN.
9. 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:
   a. Prothrombin time/International normalized ratio (PT/INR) ≤ 1.5 for patients not on anticoagulation
   b. 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.
10. Adequate cardiac function per institutional normal measured by echocardiography or multigated acquisition (MUGA) scan (LVEF ≥ 50%)
11. 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 drug.
12. 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.

<u>Select Exclusion Criteria</u> (refer to protocol for full criteria)

1. Known hypersensitivity to the study drugs or excipients of the preparations or any agent given in association with this study
2. 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 enrollment date, or uncontrolled cardiac arrhythmias
3. Uncontrolled arterial hypertension despite optimal medical management (per investigator's opinion)
4. Moderate or severe hepatic impairment, i.e. Child-Pugh class B or C
5. Patients with known human immunodeficiency virus (HIV) infection
6. 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.
7. Patients with significantly impaired 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), and/or
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥ 3 times ULN or ≥ 5 times ULN for patients with malignant liver involvement.
8. Infections of CTCAE Grade 2 not responding to therapy or active clinically serious infections of CTCAE Grade > 2
9. 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.
10. Current or past history of central nervous system (CNS) lymphoma
11. Uncontrolled seizure disorder requiring therapy (e.g. strong CYP3A4 inducers such as carbamazepine and phenytoin)

12. 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
13. 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
14. Serious, non-healing wound, ulcer, or bone fracture
15. 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).
16. Any clinical condition that is considered unstable or might jeopardize the safety of the patient and his / her compliance in the study
17. Inability to swallow oral medications
18. Any malabsorption condition
19. Breastfeeding. Female patients must not breastfeed during treatment and until 4 months after last study drug administration.
20. 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.
21. Treatment with systemic steroids (prednisone dose ≥10 mg/day or equivalent dose).
22. 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.)
23. Radiotherapy to target lesions in the 21 days before starting the first dose of study drug. Palliative radiotherapy is allowed to non-target lesions at any time before starting the first dose of study drug.
24. Major surgery or significant trauma within 4 weeks before the first dose of study drug
25. Previous assignment to treatment during this study
26. Concomitant participation in another clinical study with investigational medicinal product(s)
27. Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results
28. 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)
29. 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.
30. Use of Proton Pump Inhibitors (PPIs) must be discontinued at least 48 hours prior to initiation of study drug.
    Note: If a potential participant is on a PPI and requires some form of Acid Reducing Agent(s) (ARAs), the investigator should consider alternatives for the duration of the trial, including Famotidine, or oral antacid drugs such as calcium carbonate.
31. 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.

1. INTRODUCTION

1.1 Myristoylation and Cancer

Myristoylation, the N-terminal modification of proteins with the fatty acid myristate, is critical for membrane targeting and cell signaling (Beauchamp *et. al*, 2020). Up to 600 proteoforms in humans are myristoylated and the proper membrane targeting and functions of these proteins require myristoylation. Src-family kinases (SFK), Abl, Gα subunits, Arf GTPases, caspase truncated (ct-) Bid, and ct-PAK2 are examples of myristoylated proteins that critically regulate cell growth and apoptosis.

In humans, protein myristoylation is mediated by two ubiquitously expressed N-myristoyl-transferases (NMT), NMT1 and NMT2. Aberrant myristoylation has been identified in human cancer cells including non-Hodgkin lymphoma (NHL) and solid tumours. Increased NMT expression and activity is needed for the localization and function of over-expressed myristoylated oncogenes, such as c-Src which must be localized to the plasma membrane in order to phosphorylate downstream targets. Hence, inhibition of myristoylation represents a novel anticancer treatment strategy.

1.2 PCLX-001 Overview

NMTs are essential for the viability of parasites, and small molecule inhibitors such as DDD85646 were developed in the Dundee Drug Development program as a *Trypanosoma brucei* NMT inhibitor to treat African sleeping sickness. However, these compounds were not pursued further because of a lack of brain penetration required for effective management of advanced African trypanosomiasis.

PCLX-001 is an orally bioavailable derivative of the NMT inhibitor DDD85646, and is more selective and potent towards human NMTs. Preclinical data show that PCLX-001 inhibits the viability and growth of hematological cancer cells and other solid cancers. It has been selected from other analogs for the treatment of human cancer because of its high affinity for human NMTs, high bioavailability, and drug like pharmacokinetic properties.

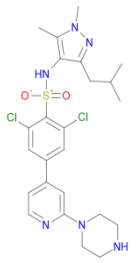
1.2.1 PCLX-001 Mechanism of Action and Properties

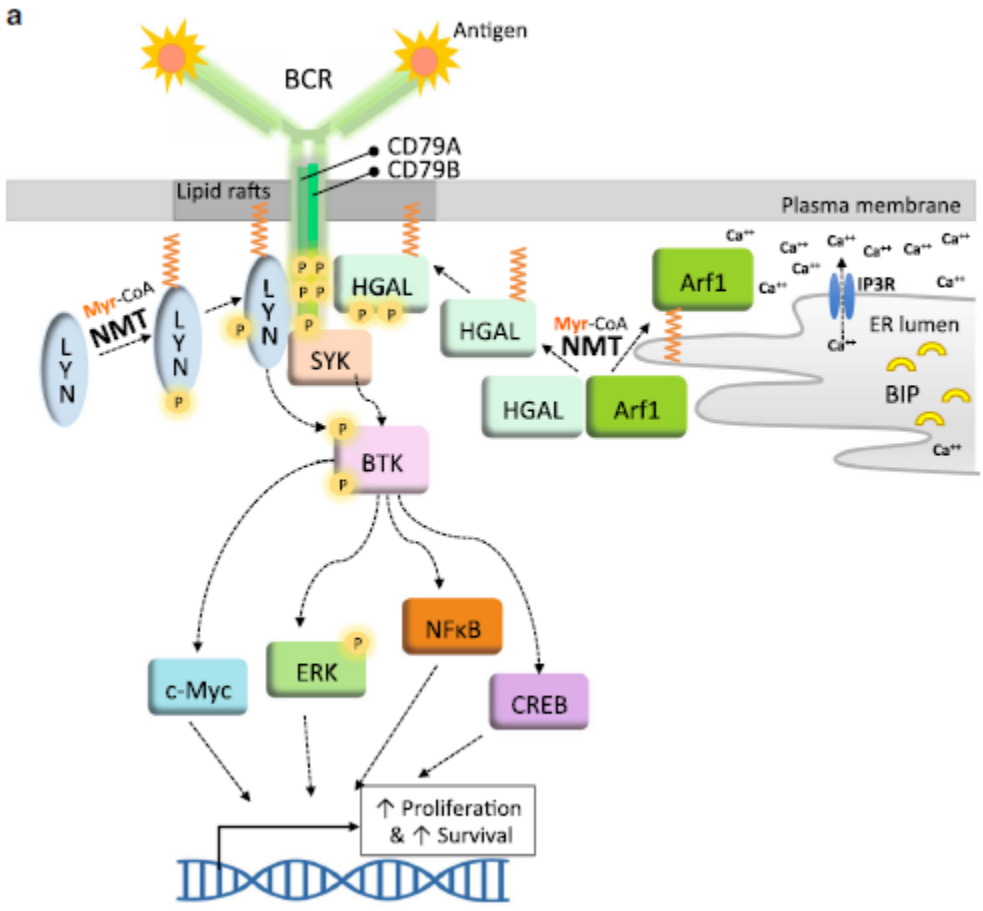
Mechanism of Action:

PCLX-001 inhibits both NMT1 and NMT2 with an IC_{50} of 5nM and 8nM, respectively (Table 1). It completely abrogates myristoylation in cultured human cells within 15 minutes. Given that cancer cells are selectively killed at concentrations lower than required to kill and inhibit the proliferation of normal cells, PCLX-001 offers a therapeutic window to support development of PCLX-001.

In cultured human lymphoma cells, PCLX-001 inhibits B-cell receptor signaling and also induces apoptosis. Figure 1 demonstrates a model depicting the proposed mechanism of action in B-cell lymphoma.

Table 1: PCLX-001 Drug Substance

Property	
Chemical Name	2,6-dichloro-N-(3-isobutyl-1,5-dimethyl-1H-pyrazol-4-yl)-4-(2-(piperazin-1-yl)pyridin-4-yl)benzenesulfonamide
Empirical Formula	$C_{24}H_{30}Cl_2N_6O_2S$
Chemical Structure	
Molecular Weight	537.5 daltons (free base)



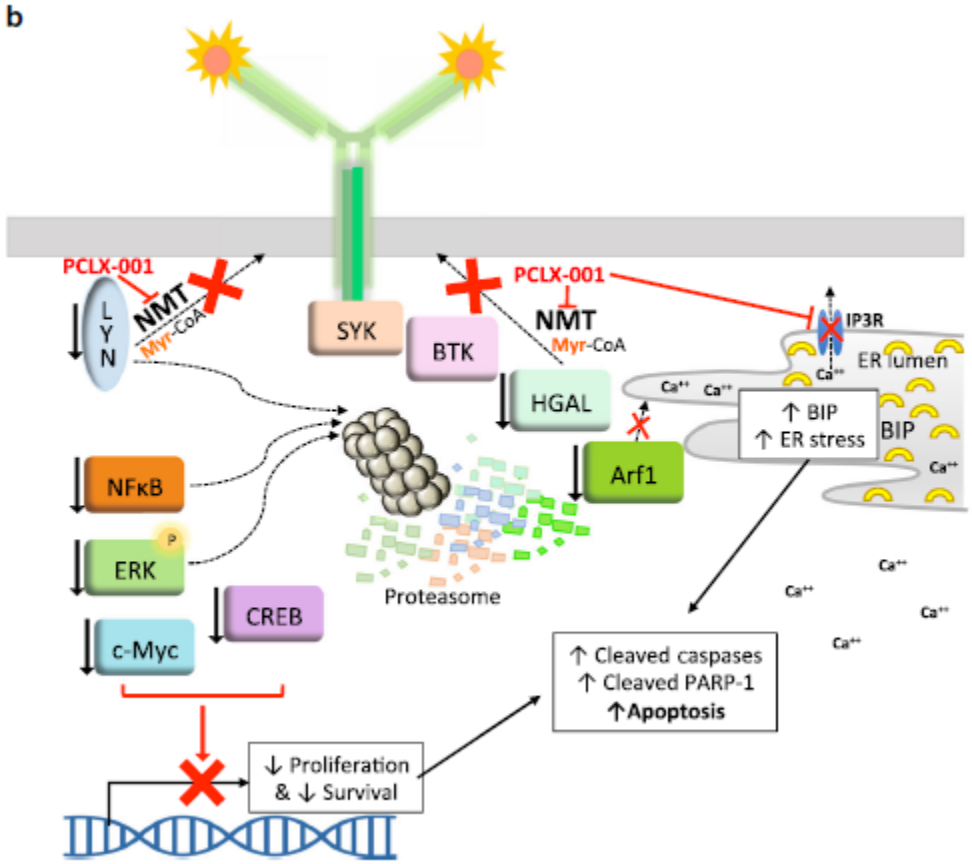


Figure 1: Model depicting proposed PCLX-001 mechanism of action in B cell lymphoma. a Upon BCR activation, first the myristoylated SFK Lyn is recruited to the lipid raft domains of the plasma membrane containing the BCR, dephosphorylated Lyn at Y507 leads to its activation and autophosphorylation at Y396. This leads to the phosphorylation and activation of BTK at Y551 and Y223. Second, myristoylated HGAL is also recruited to the plasma membrane and phosphorylated thereby enhancing BCR signaling by stimulating SYK, BTK and the release of Ca++ ions from the endoplasmic reticulum via the inositol-3-phosphate ion channel receptor (IP3R). Altogether these early signaling events lead to transcription activation by c-Myc, P-ERK, NFκB, and CREB. **b** The NMT inhibitor PCLX-001 prevents the myristoylation of Lyn-SFK (as well as other SFKs not shown in this model), HGAL and Arf1 thereby impeding the proper membrane targeting and function of these proteins. PCLX-001 treatment impedes calcium homeostasis by reducing the BCR mediated Ca++ release from the ER and increasing basal Ca++ levels in cells in addition to promote the degradation of both myristoylated (Lyn, HGAL, Arf1) and, surprisingly, non-myristoylated proteins (NFκB, P-ERK, c-Myc and CREB), some via the ubiquitin-proteasome pathway thereby further abrogating downstream BCR signaling and increasing ER stress leading to apoptosis and cell death.

1.2.2 Preclinical Studies

In vitro Efficacy in Cultured Human Cancer Cells

PCLX-001 was studied using 68 cell lines on the Horizon (St. Louis, MO) platform and recapitulated using a 101 cell line Oncolines™ screen. Drug sensitivity varied across lines, but was significantly higher in cells of hematologic cancer origin. However, high sensitivity and cell kill was also seen in solid tumour lines derived from lung, pancreas, breast, colon, and bladder carcinomas as well as melanoma (Figure 2).

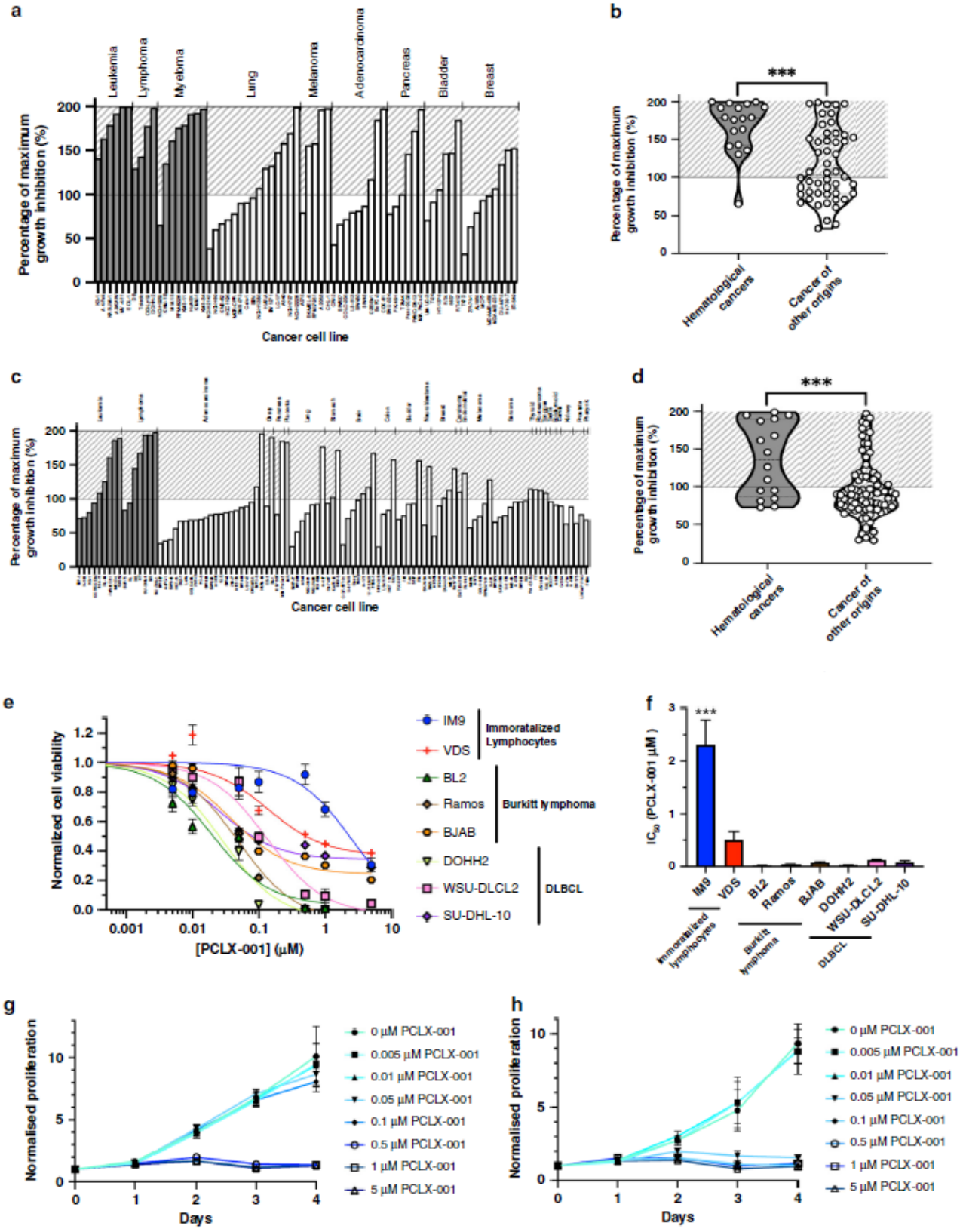


Figure 2: PCLX-001 selectively kills hematological and solid cancer cell lines. Percentage of maximum growth inhibition of various cell lines following 96 h treatment with 1.2 µM PCLX-001 as determined using a Horizon cell line screen (**a, b**), or following 72 h treatment with 1 µM of PCLX-001 using

a OncolinesTM cell line screen (**c, d**). Cell lines are arranged according to tumor cell type. Cross-hatched zone represents cytotoxic effect. Hematological cancer cell lines are depicted in gray while all other types of cancer cell lines are depicted in white. Corresponding violin graphs compare the average PCLX-001-mediated growth inhibition on hematological cancer cell lines to cancer cell lines of other origins combined as calculated from the Horizon (**b**) and OncolinesTM (**d**) cell screens (Unpaired t test, two-tailed P < 0.0001). Quartiles are separated by dotted lines. Error bars represent standard deviation within each group. Normalized cell viability curves of immortalized lymphocyte (IM9, VDS), BL (BL2, Ramos, BJAB), and DLBCL (DOHH2, WSU-DLCL2, SU-DHL-10) cell lines treated with 0.001–5 μM of PCLX-001 for 96 h as determined by CellTiter Blue Viability Assay (**e**). Corresponding histograms of absolute IC50 (and SD) values calculated from a log(inhibitor) vs response (three parameters) equation cell viability curves plotted in e (**f**). ***Indicates a significant difference (P ≤ 0.001) in IC50 between IM9 cells and all other cell lines tested (Ordinary oneway Anova, Tukey's multiple comparisons test, P < 0.0001). Normalized proliferation of IM9 (**g**) and BL2 (**h**) cells reated with 0–5 μM of PCLX-001 for 96 h as determined by cell count. Values are mean ± s.e.m. of three independent experiments

In vivo Efficacy with Cell Line Derived Xenografts (CDX)

PCLX-001 mitigates tumor progression *in vivo* in two lymphoma cell line derived subcutaneous tumor xenograft models. These models were developed by injecting 1 x 10^7 DOHH2 (DLBCL: diffuse large B-cell lymphoma) or BL2 (BL: Burkitt lymphoma) NMT2-deficient cells subcutaneously in the flank of NOD/SCID mice (10 mice per group). PCLX-001 was injected subcutaneously once a day into the opposite flank. In mice bearing DOHH2 tumors (125–200 mm^3), PCLX-001 had a significant, tumoricidal effect at 20 mg/kg daily or 50 mg/kg every other day (P<0.001). When injected daily at 50 mg/kg, PCLX-001 shrank tumors by 70% from their original size (average tumor size at day 7 = 44.0 ± 8.1 mm^3). Similarly, in mice bearing BL2 xenografts, PCLX-001 showed partial total growth inhibition (TGI) at 20 mg/kg reaching 42.5% by day 9 (P=0.016) (Figure 3). PCLX-001 given at 50 or 60 mg/kg for 13 consecutive days caused 100% tumor regression in 9 of 9 and 7 of 7 surviving mice, respectively. Therefore, the optimal biological dose appears to be 50 mg/kg in NOD/SCID mice.

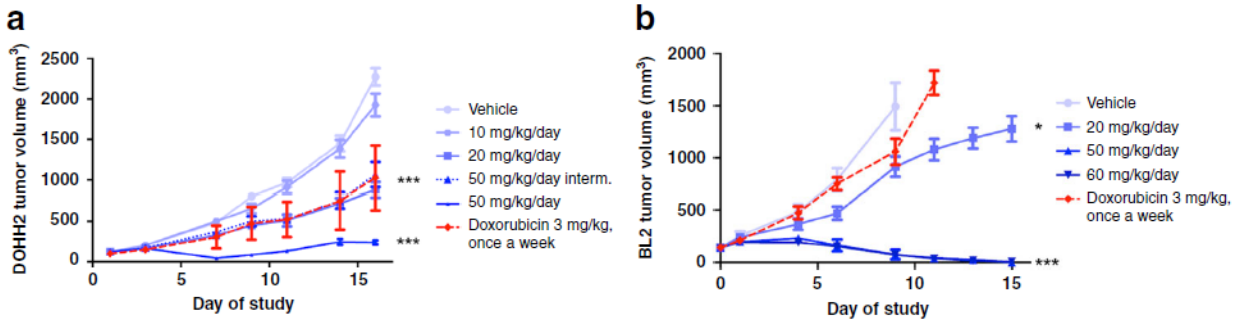


Figure 3: PCLX-001 inhibited tumor growth of DOHH2 and Burkitt lymphoma murine xenografts. DOHH2 (a) and BL2 cells (b) were injected subcutaneously (sc) into the flanks of 10 NOD/SCID mice per group. PCLX-001 was injected sc once daily into the opposite flank at 20-60 mg/kg/day. Survival was significantly improved compared to vehicle: * p0.01; *** p< 0.0001

In vivo Efficacy with Patient Derived Xenografts

Since cell line derived xenografts lack the complexity of human tumours, PCLX-001 was studied in a patient derived xenograft model (PDX). This was established from patient "DLBCL3" whose cancer was refractory to multiple lines of chemotherapy [R-CHOP (Rituxumab, Cyclophosphamide, Hydroxydaunorubicin, Vincristine, Prednisone); R-ICE (Rituximab, Ifosfamide, Carboplatin, Etoposide); DHAP (Dexamethasone, Cytarabine, Cisplatin)] and propagated in NODscid mice. The mean initial "DLBCL3" tumor volume was 240 mm^3. PCLX-001 treatment regimens were assessed in groups of 8 mice each. At a 20 mg/kg subcutaneous daily dose for 21 days, PCLX-001 caused a TGI of 66% (P<0.001). At 50 mg/kg subcutaneously daily for two 9-day periods separated by a 3-day treatment suspension, PCLX-001 caused the tumors to regress completely in 6 of 7 surviving mice at day 13; one mouse with no detectable tumor died at day 7. In surgically removed control and PCLX-001-treated PDX tumors, there was confirmation of concentration-dependent reduction in tumor size. In the only remaining tumor from the 50 mg/kg treatment, PCLX-001 effectively induced apoptosis and reduced malignant cell proliferation.

1.2.3 PCLX-001 Pharmacokinetics and Pharmacology

Mouse Pharmacokinetics

PCLX-001 was dosed as a bolus solution intravenously at 3 mg free base/kg (5% DMSO; 95% sterile water) or by gavage orally as a solution at 10 mg free base/kg (5% DMSO; 40% PEG400; 55% sterile water) to female NMRI mice (n=3/dose route). Blood samples (10 µL) were taken from each mouse at 5 (IV only), 15, 30 minutes, 1, 2, 4, 6 and 8 hours post-dose, mixed with two volumes of distilled water and stored frozen until analysis.

Following intravenous administration at 3 mg free base/kg, PCLX-001 mean blood clearance was low at 3mL/min/kg (~3% liver blood flow), mean volume of distribution (V_{ss}) was low at 0.4 L/kg, resulting in a moderate mean half-life at 1.6 hours. Mean $AUC_{0\text{-}8}$ was 1,119,500 ng.min/mL.

Following oral administration at 10 mg free base/kg, PCLX-001 had a mean C_{max} of 11,200ng/mL and median t_{max} at 2 hours. Mean $AUC_{0\text{-}8}$ was 3,400,810 ng.min/mL and mean bioavailability recorded at 91%.

PCLX-001 was not brain penetrant in mouse models (B:B ratio following a 1 mg/kg IV dose is 0.04 at 5- and 30-minutes post-dose).

Rat Pharmacokinetics

PCLX-001 was dosed as a bolus solution intravenously at 1 mg free base/kg (5% DMSO; 95% saline) or by gavage orally as a solution at 3 mg free base/kg (5% DMSO; 95% sterile water) to male Sprague Dawley rat (n=2 IV; n=3 PO). Blood samples (10 µL) were taken from each rat at 5 (IV only), 15, 30 minutes, 1, 2, 4, 6 and 8 hours post-dose, mixed with two volumes of distilled water and stored frozen until analysis.

Following intravenous administration at 1 mg free base/kg, PCLX-001 mean blood clearance was low at 15 mL/min/kg (~18% liver blood flow), mean volume of distribution (V_{ss}) was moderate at 1.3 L/kg, resulting in a moderate mean half-life at 1 hour. Mean $AUC_{0\text{-}8}$ was 67,230 ng.min/mL. Blood clearance was well aligned to hepatic extraction (E_H) at 16%, determined from a separate male Sprague Dawley rat hepatic portal vein study following oral dosing at 3 mg free base/kg.

Following oral administration at 3 mg free base/kg, PCLX-001 had a mean C_{max} of 170ng/mL and median t_{max} at 4 hours. Mean $AUC_{0\text{-}8}$ was 52,868 ng.min/mL and mean bioavailability 26%.

Dog Pharmacokinetics

PCLX-001 was dosed as a bolus solution intravenously at 1 mg free base/kg (in saline) or by gavage orally as a solution at 10 mg free base/kg (in saline) to male beagle dog (n=3/dose route). Blood samples (10 µL) were taken from each dog at 5, 15, 30 minutes, 1, 2, 4, 6, 8 and 24 hours post-dose, mixed with two volumes of distilled water and stored frozen until analysis.

Following intravenous administration at 1 mg free base/kg, PCLX-001 mean blood clearance was moderate at 22 mL/min/kg (~58% liver blood flow), mean volume of distribution (V_{ss}) was moderate at 4.3 L/kg, resulting in a moderate mean half-life at 2.3 hours. Mean $AUC_{0\text{-}24}$ was 42,140 ng.min/mL.

Following oral administration at 10mg free base/kg, PCLX-001 had a mean C_{max} of 1229ng/mL and median t_{max} at 1.7 hours. Mean $AUC_{0\text{-}24}$ is 560,220 ng.h/mL and mean bioavailability was 133%.

Pharmacokinetics Interpretation

The low volume of distribution observed in mouse (less than body water) appeared to be a mouse specific phenomenon. Improved efficacy may be seen in higher volume species through better distribution to the target such that there is no net change in potential therapeutic index.

In vitro ADME Profile

PCLX-001 (0.5 µM) has low intrinsic clearance (Cl_{int}) in mouse, rat and human when incubated with liver microsomes, with Cl_{int} of <0.5, 1.0 and 0.7 mL/min/g respectively (using 52.5 mg microsomal protein/g liver). *Cl*i in mouse and rat is consistent with the low *in vivo* Cl_B observed. Blood:plasma ratio was 0.59, 0.56, 0.69 and 0.50 in mouse, rat, dog and human respectively.

PCLX-001 has high (>99%) plasma protein binding in mice, rat, dog, and human plasma after 4 hour incubation at 5 µM.

The cytochrome P450 enzymes (CYP) are a super family of hemethiolate enzymes responsible for the metabolic clearance of a wide variety of drugs. To characterize the metabolic clearance of PCLX-001, the relative contribution of CYP450 enzymes to the overall elimination process and the identification of the enzymes responsible for oxidative reactions were studied using native recombinant human CYP enzymes. These studies showed that PCLX-001 directly inhibited CYP3A4 (IC_{50} of 12.1 µM), CYP1A2 (40.6 µM), CYP2B (63.02 µM), CYP2C9 (52.3 µM), and CYP2C19 (60.7 µM). There was no inhibition of CYP2D6, CYP2E1, CYP2A6, or CYP2C8 (all with IC_{50} > 100µM).

PCLX-001 is a substrate for P-glycoprotein, as demonstrated by efflux studies in CaCo2 cells. It is not a substrate for or OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2K or BRCP. Overall, PCLX-001 shows a low probability for drug-drug interaction.

PCLX-001 was not mutagenic in the Ames test.

In vitro hERG Testing

A non-GLP study was done by a group developing a proprietary system for human ether-á-go-go-related (hERG) analysis (https://www.achlys-inc.com/Cardiomyocytes). The negative controls were acetylsalicylic acid and chloramphenicol and the positive control (determined IC_{50} of 0.9 µM) was Thioridazine Hydrochloride. PCLX-001 had a determined IC_{50} of 9.9 µM. This concentration was well above that expected to be achieved in a human phase I trial and suggests that PCLX-001 is likely not to be cardiotoxic.

KINOMEscan

PCLX-001 is a small molecule inhibitor that theoretically could also have the ability to inhibit kinases, and cause unexpected off-target effects. PCLX-001 was screened *in vitro* at concentrations of 0.5, 10, and 100 µM (269, 5380, and 53,800 ng/mL) for its ability to inhibit the activity 468 human kinases. PCLX-001 at concentrations up to 10 µM (5380 ng/mL) did not inhibit any kinase. PCLX-001 at 100 µM (53,800 ng/mL), a concentration ~4000 x greater than the EC50 of PCLX-001 for BL2 cells, produced meaningful inhibition of only three kinases: MRCKA, PIP5K2B, and SRPK1. Based on these results, PCLX-001 is unlikely to produce adverse effects in patients due to off-target kinase inhibition and appears to be NMT-specific.

1.2.4 PCLX-001 Toxicology and Safety Profile

Non-GLP Toxicity and Safety Profile:

Tissue of control and PCLX-001 treated (with doses up to 50 mg/kg subcutaneous daily injection) NOD/SCID mice were studied after formalin fixation and paraffin-embedding, followed by immunohistochemical staining. There was no morphologic evidence of toxicity of PCLX-001 on small intestine, kidney, liver, or bone marrow. Blood counts and standard biochemical testing of blood from treated and untreated mice revealed no evidence of marrow, renal, or hepatic toxicity.

PCLX-001 is >90% orally bioavailable in mice and dogs and 26% in rats, has a half-life from oral dosing of 10 mg/kg of 5.7 hours in mice and 3.9 hours in dogs, and is well-tolerated by mice, rats, and dogs with a maximum tolerated dose in 14-day repeat dose toxicity studies of >75 mg/kg in rats and 4 mg/kg in dogs. Based on a body surface area scaling of the 50 mg/kg dose that resulted in complete tumor remission in most mouse xenografts of hematologic malignancies (BL, DLBCL, AML), the effective human dose is projected to be ~4 mg/kg daily (250 mg for a 70 kg individual).

GLP Non-Clinical Safety Testing:

PCLX-001 was evaluated for safety in 4-week oral toxicity studies with 2-week recovery periods in rats at 50, 125, and 300 mg/kg/day and dogs at 2, 4, 8, and 12 mg/kg/day, performed to GLP standards (Weickert *et al*, 2020). The highest non-severely toxic dose levels (HNSTDs) were 125 mg/kg/day for male rats, 300 mg/kg/day for female rats, and 4 mg/kg/day for dogs of both sexes. At higher dose levels, dose-limiting toxicity occurred within the first few days, was similar in both species, and was attributed to GI mucosal damage and decreased hematopoiesis, with secondary complications such as dehydration and inflammation.

In dogs, systemic exposure to PCLX-001 increased more-than-proportionally with dose level after the first dose and did not change with repeated daily dosing. After the last dose at the HNSTD, C_{max} averaged 651 ng/mL and 24-hour AUC averaged 3,760 h*ng/mL. In rats, systemic exposure to PCLX-001 after the first dose increased approximately proportionally with dose level and was much greater in males than females at all dose levels. With repeated daily dosing, exposure decreased dramatically in male rats but less so in female rats. As a result, exposure to PCLX-001 was similar in rats of both sexes after the last dose. After the last dose at the HNSTD in males and females, C_{max} was 1650 and 8510 ng/mL, respectively, and 24-hour AUC averaged 6470 and 7590 h*ng/mL, respectively. When expressed on the basis of body surface area, the HNSTDs in male rats, female rats, and dogs were 750, 1800, and 80 mg/m^2, respectively.

As recommended in the ICH S9 Guidance, the starting human dose level of 20 mg/m^2 would be appropriate since this approximates 1/6th of the HNSTD in dogs

In rat and dog GLP studies, there were no coagulation toxicities noted with PCLX-001. Similarly, no significant cardiac findings were elicited in dogs. ECGs at baseline were similar to those after 4 weeks of dosing or at the end of the recovery period.

1.3 Study Rationale

1.3.1 Rationale for Patient Selection in Dose Escalation

Patients selected for study have relapsed/refractory B-cell lymphomas and advanced solid tumors who have failed or are not eligible for therapies expected to provide clinical benefit. This protocol will not include patients with leukemia for which an independent phase I study is planned.

Given the strong *in vitro* and *in vivo* single-agent antitumor activity and tolerability of PCLX-001, it is hypothesized that in this first-in-human trial, PCLX-001 will be safe, tolerable and demonstrates preliminary clinical activity in human patients with specified relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) and advanced solid malignancies.

Pacylex Pharmaceuticals, Inc. will not study PCLX-001 in a pediatric population in this initial phase I study. As this is a novel agent and target, Pacylex Pharmaceuticals, Inc. will consider pediatric and adolescent patients once safety has been adequately established in adult patients.

1.3.2 Rationale for Patient Selection in Dose Expansion

PCLX-001 has been studied in a number of pre-clinical studies, and these data provide justification for the selected patient population.

<u>Solid tumors: Selected by pre-clinical sensitivity in cell lines</u>

Three large tumor cell line robotic screens have been performed with PCLX-001, as well as several cell line derived murine xenograft studies as well as patient derived murine xenograft studies. In aggregate, these data suggest sensitivity in breast, non-small cell lung, small-cell lung, colorectal, and bladder cancers (Figure 4).

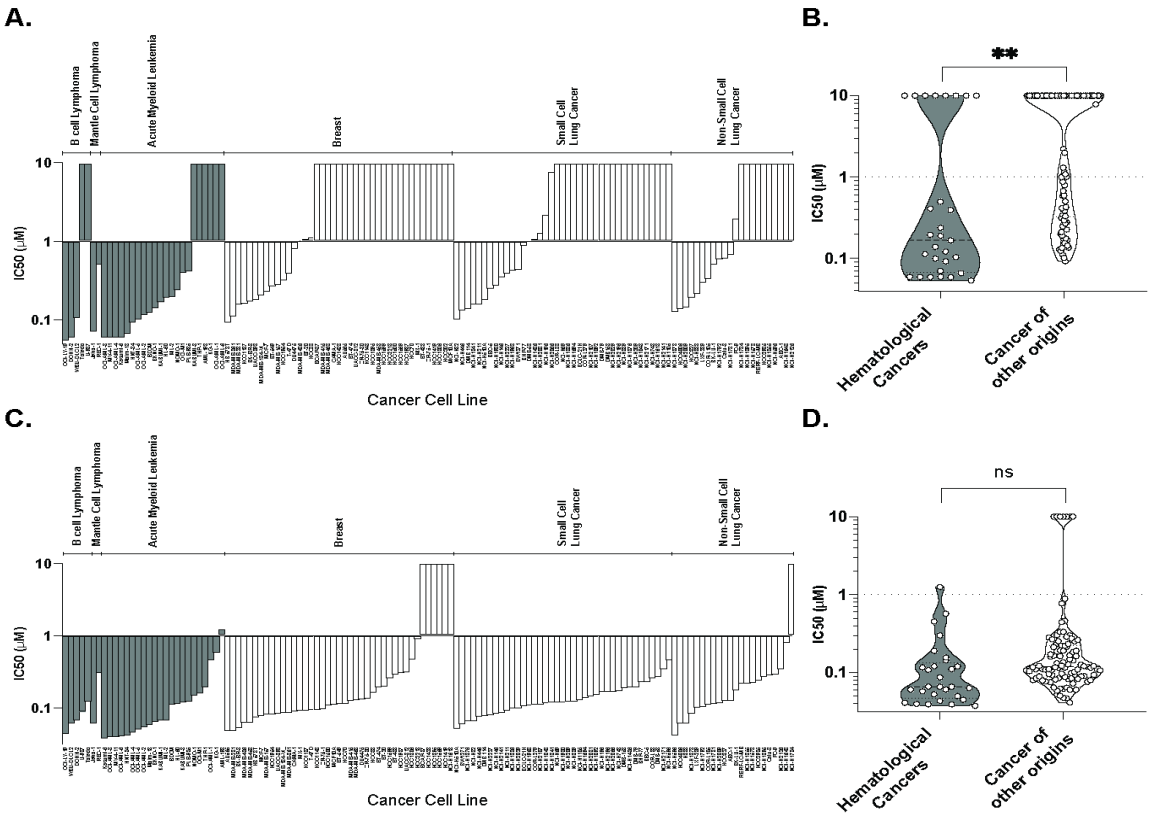


Figure 4. Breadth of efficacy screen demonstrates that PCLX-001 is active against various other cancer cell lines including those derived from solid tumors. Absolute IC_{50} values of various cell lines treated for 3 days (A, B) or 6 days (C, D) with 0.0005 - 10μM PCLX-001. Cell lines are arranged according

cancer type. Individual bars represent a single cancer cell line derived from B cell lymphoma and Mantle Cell Lymphoma, Acute Myeloid Leukemia (AML), Breast, Small-cell lung carcinoma (SCLC), Non-small-cell lung carcinoma (NSCLC). ChemPartner robotic platform determined cell viability using Cell Titer Blue viability assay.

Further evidence of solid tumor activity is provided by murine models of human lung and breast cancers (Figure 5).

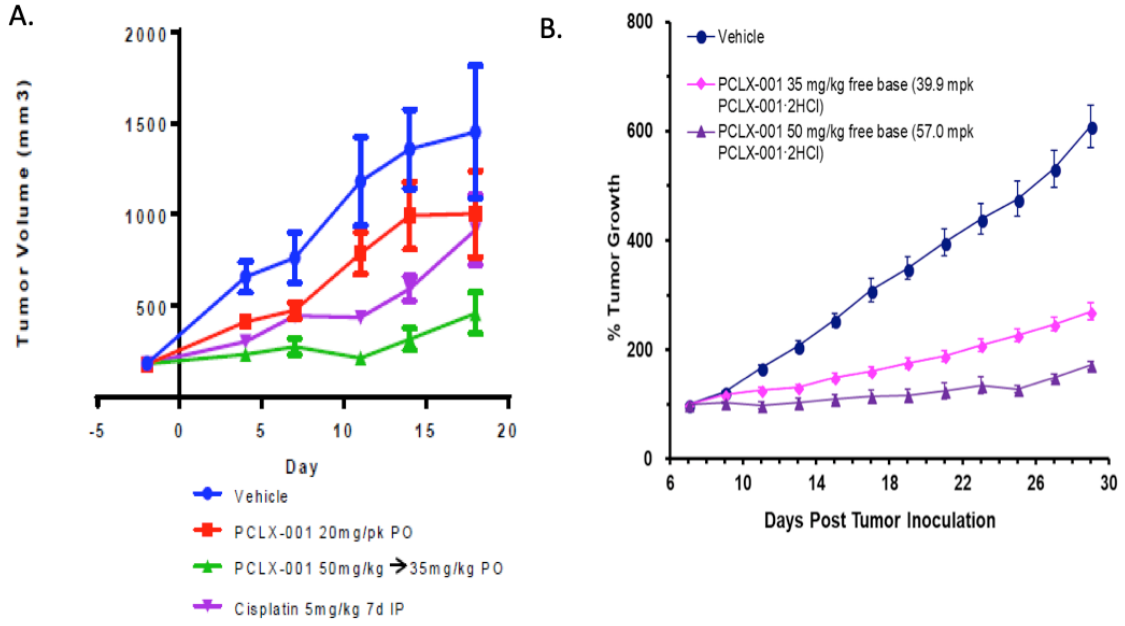


Figure 5. PCLX-001 inhibits tumor growth in patient derived small cell lung cancer and breast cancer xenograft models. Established tumor in patient derived xenografts grown in immunodeficient mice were treated with daily PCLX. Panel A shows oral therapy of a small-cell lung cancer patient derived xenograft, showing efficacy superior to that of cisplatin. Panel B shows the efficacy of subcutaneous PCLX-001 in a cell line derived breast cancer model.

B-cell Lymphomas

In three large tumor cell line robotic screens, PCLX-001 potently and preferentially inhibited the growth of hematological cell lines, including B-cell lymphomas, in comparison to other types of cancer cell lines. Moreover, PCLX-001 selectively killed lymphoma cells while sparing normal cells *in vitro*, as well as in three human lymphoma xenograft models including a patient-derived, drug-resistant tumor. The global myristoylation of lymphoma cell proteins, including that of the protein tyrosine kinase Src, was found to be especially sensitive to PCLX-001 treatment. This was accompanied by the loss of Src localization to the cell membrane and the targeting of Src, as well as other SFKs, for degradation by the proteasome. Without functional SFKs (especially Lyn-SFK), pro-survival signaling downstream of the B-cell receptor (BCR) was profoundly attenuated in all B-cell lymphoma cell lines, resulting in apoptosis.

Of potential therapeutic relevance, the effects of PCLX-001 on BCR signaling and lymphoma cell survival were more potent than those of dasatinib and ibrutinib, two clinically approved drugs. By inhibiting critical signaling processes immediately downstream of the BCR, PCLX-001 mediated NMT inhibition may provide an effective, selective and novel therapeutic approach for treatment of B-cell lymphoma.

NMT1 and NMT2 Expression

NMT1 number of transcripts is about eight times the number of *NMT2* transcripts in all cell lines. As well, there is a heterogeneous but significant reduction of *NMT2* expression or low levels of NMT2 protein in cancer cell lines, and particularly in hematological cancers. This may account for these tumours being more sensitive to PCLX-001.

NMT2 deficiency has been identified in a high proportion of human tumors interrogated with immunohistochemistry using a NMT2 mAb. Normal breast epithelial elements in 10 normal breast mammoplasty specimens were universally NMT2 positive (1-2+) on a 0-3 scale (scored as 0 – absent; 1+ weak staining; 2+ moderate staining; 3+ strong staining). Primary breast adenocarcinoma samples from participants in the BCIRG 001 clinical trial were studied using 1.0 mm tissue microarrays with triplicate samples for each tumor. NMT2 immunohistochemistry status in malignant cells was scored as 0 absent; 1+ weak staining; 2+ moderate staining; 3+ strong staining. NMT2 status was generally homogeneous within each core and concordant across triplicates. 509 of the 706 breast cancer adenocarcinomas were NMT2 negative. Using identical techniques, 157 of 214 (73%) of non-small cell lung carcinomas, and 23 of 23 colon cancers were NMT2 deficient by immunohistochemistry. Preliminary data from a series of bladder urothelial carcinomas show a significant proportion lack detectible NMT2 protein.

Altogether, the reduction in NMT2 expression in hematological cancer cell line and the solid tumours described may be more prone to growth inhibition.

Populations for Expansion Cohorts

Based on the pre-clinical sensitivity in cell lines and molecular markers associated with PCLX-001 sensitivity, it is hypothesized that an expansion cohort of solid tumors of breast, non-small cell lung, small-cell lung, colorectal, and bladder origin would be particularly susceptible. These patients will comprise Expansion Cohort A.

Also, an expansion cohort of relapsed/refractory B-cell lymphomas will be studied. Patients with diffuse large B-cell lymphoma (including transformed DLBCL), high grade B-cell lymphoma (HGBL), follicular lymphoma, mantle cell lymphoma, and Burkitt lymphoma would similarly be expected to be sensitive to PCLX-001. These patients will comprise Expansion Cohort B.

2. OBJECTIVES

The primary objectives of this study are to:

- Assess safety and tolerability of oral PCLX-001 in patients with B-cell lymphoma and advanced solid tumours
- Determine the maximum tolerated dose (MTD) and / or recommended Phase II dose (RP2D) of PCLX-001 in patients with B-cell lymphomas and advanced solid tumours
- Evaluate the pharmacokinetics (PK) of PCLX-001 in patients with B-cell lymphomas and advanced solid tumours

The secondary objective of the study is to:

- Evaluate the preliminary single agent anti-tumour activity of PCLX-001 in the patient populations studied

The exploratory objective of this study is to:

- Assess the pharmacodynamic (PD) effects of PCLX-001 in patients with B-cell lymphomas and advanced solid tumours

3. STUDY DESIGN

3.1 Overview of Study Design

This is a phase I dose-escalation, safety and tolerability 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. The Part B dose expansion Cohort A will occur once MTD and RP2D has been determined. Part B dose expansion Cohort B will occur once dose escalation has achieved a dose that has both acceptable safety and achieves drug exposures predicted to have activity in R/R B-cell lymphomas.

Expansion Cohort A: Participants with advanced solid malignancies showing preclinical sensitivity or molecular markers of sensitivity to PCLX-001. This includes breast, non-small 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.

3.1.1 Selection of Starting Dose Level and Dosing Considerations

As recommended by the ICH S9 Guidance, the starting dose level is 1/6th the highest non-severely toxic dose (HNSTD) from GLP studies in the most sensitive of tested non-rodent species. The HNTSD was 4 mg/kg/day for dogs of both sexes and, when expressed as body surface area, this calculates to 80 mg/m^2. Consequently, the starting dose level in humans would be approximately 20 mg/m^2. To ensure maximal safety in this first-in-human trial, the starting dose level was chosen to be 20 mg daily. PCLX-001 will be supplied as 10 mg and 70 mg capsules which provides the range of doses required for dose escalation.

3.2 Definition of Dose Limiting Toxicity and Maximum Tolerated Dose

Toxicities are to be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 5.0). A copy of the CTCAE version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

Dose Limiting Toxicity (DLT) for Part A, dose-escalation, is defined as any of the following AEs related to PCLX-001 treatment occurring in Cycle 1:

Hematologic

- Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)
- Grade ≥ 3 thrombocytopenia (platelet count < 50 x 10^9/L) associated with any major bleeding, and/or requirement for transfusion
- Grade 4 neutropenia (ANC < 0.5 x 10^9/L) for ≥ 7 days[a]
- Febrile neutropenia. (Per NCI CTCAE, ANC < 1.0 x 10^9/L and fever ≥ 38.3^{o}C or a

sustained temperature of ≥ 38°C for more than one hour). Febrile neutropenia is by definition a grade ≥3 toxicity.

[a] Detection of CTCAE Grade 4 neutropenia (only in Cycle 1) will trigger twice-weekly white blood cell counts to be performed, and will be considered a DLT if drug interruption lasts ≥ 7 days.

Non-hematologic

Any non-hematological toxicity of CTCAE Grade ≥ 3 is considered a DLT, excluding the following:

- Grade ≥3 nausea, vomiting and diarrhea which are controlled with anti-emetics and/or other supportive care within ≤72hr
- Brief (i.e. lasting ≤ 72 hours) CTCAE Grade 3 fatigue
- Alopecia of any grade
- Isolated, asymptomatic, biochemical laboratory values including electrolyte abnormalities, above or below normal reference ranges, which are judged not clinically significant by the Investigator
- Miscellaneous
- Any patient meeting Hy's law of drug-induced hepatic injury (AST or ALT >3 times ULN with bilirubin 2 times ULN; absence of initial cholestasis with ALP >2 times ULN; no other explanation) is considered a DLT.
- Any toxicity thought to be related to study drug that, at the discretion of the investigator, or his/her designated associate(s), is thought to warrant withholding the drug may be declared as a DLT. Such toxicities might for example be CTCAE Grade 1 or CTCAE Grade 2 toxicities that interfere with the activities of daily life, such as long-lasting fatigue, or anorexia, making a dose reduction necessary in order to ensure the patient's compliance.
- Any toxicity thought to be related to study drug which requires interruption of oral PCLX-001 for longer than 28 consecutive days from the time of scheduled dosing will be declared as a DLT.

In rare instances, an event may fall within the definition of a DLT as defined above but the event may be not be considered dose-limiting (i.e. not clinically meaningful/significant). If this occurs, a meeting with investigators and sponsor will take place to thoroughly review the event, supporting data and reasons for not considering the event a DLT. This will be clearly documented with supporting rationale. Conversely, other events may occur which do not meet the definition of a DLT but are sufficient concern to the investigators and sponsor to be considered a DLT.

Maximum Tolerated Dose (MTD) is defined as the highest dose tested in which fewer than 33% of patients experienced DLT attributable to the study drug(s), when at least six patients were treated at that dose and are evaluable for toxicity. The MTD is one dose level below the lowest dose tested in which 33% or more patients experienced DLT attributable to the study drugs. At least six patients will be treated at the MTD.

Dose escalation and determination of the MTD will be based on the occurrence of DLT's in cycle 1. Patient safety will be monitored on an ongoing basis during this study. If cumulative toxicities are seen in subsequent treatment cycles, a decision regarding modification or discontinuation of the study drug and/or patient enrollment will be made by the investigator in consultation with the sponsor.

3.3 Part A: Dose-Escalation and Determination of MTD

The Dose-Escalation phase will follow a standard 3+3 cohort design. Three patients will be treated at each dose level. If 0/3 patients experience DLT, 3 patients will be treated at the next dose level. If DLT attributable to the treatment is experienced in 1/3 patients, three more patients (for a total of six patients) will be treated at that dose level. If no additional DLT is observed at the expanded dose level (i.e. 1/6 with DLT), the dose will be escalated. Escalation will terminate as soon as two or more patients experience any DLT attributable to study drugs, at a given dose

level. DLT and determination of MTD will be based on cycle 1 toxicities. Intra-patient dose escalation will not be allowed. Six patients will be treated at the MTD. The MTD cohort may be expanded by an additional 10 patients for further toxicity and response assessment. If MTD is not reached, the study team will determine the RP2D for further evaluation in Part B, cohort expansion. If ≥ 2 out of 6 DLTs occur for Dose Levels -1, 1, or 2, the dosing schedule may be amended to determine the appropriate scheduling regimen.

No. of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter patient(s) at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose level.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experiences DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped and this dose is declared the maximally administered dose. Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This will be the MTD. At least 6 patients will be entered at this dose.

3.4 Part A Dose Escalation Schedule and Treatment Schema

Oral PCLX-001 will be provided as continuous daily dosing on a 28-day cycle. The starting dose of PCLX-001 will be 20 mg daily (Section 3.1.1). Dose escalation will follow a modified Fibonacci design such that the magnitude of escalation decreases as the dose level nears the human equivalent dose (HED) of the HNSTD in dogs and then escalate at 1.4 times the previous dose until MTD or RP2D is reached.

The dose level schedule is as below (1 cycle = 28 days):

Dose Level**	Daily Oral Dose (mg)	Number of Capsules	
		10 mg	70 mg
-1	10	1	0
1 (starting dose)*	20	2	0
2	40	4	0
3	70	0	1
4	100	3	1
5	140	0	2
6	210	0	3
7	280***	0	4

* Trial will start at Dose Level 1 and will de-escalate to Dose Level -1 if DLT is observed.
** If ≥ 2 out of 6 DLTs are observed in Dose Level -1, 1 or 2 then consideration will be given to changing dosing schedule (eg. 28-day schedule with each week comprising 4 days on medication and 3 days off medication).
*** If DLT is not observed at the dose of 280 mg, the dose will be considered the MTD. If required, the MTD cohort may be expanded by an additional 10 patients for further toxicity and response assessment.

For each dose-escalation cohort, treatment with the first dose of PCLX-001 will be staggered such that the second participant enrolled in the cohort will receive PCLX-001 at least two weeks after the first participant and all subsequent participants at least one week after the previous participant.

Each participant will be treated with the dose of PCLX-001 they are assigned to, until the occurrence of a DLT or other study stopping point occurs, at which point the dose of PCLX-001 will be modified as per protocol or study drug administration will be discontinued.

If DLT occurs at Dose Level 1, a safety meeting will occur to determine the feasibility of continuing the study at Dose Level -1. Alternative dose schedules may also be considered if DLTs occur during Dose Levels, -1, 1 or 2.

Participants who experience a DLT or have received at least 21 days of PCLX-001 during cycle 1 will be evaluable for toxicity. If a participant does not meet these criteria, the participant may be replaced (Section 4.3).

3.5 Design of Part B Expansion Cohorts

Once the MTD has been defined, preliminary activity will be further evaluated in the expansion part of the study. If clinically indicated, separate cohort(s) may be open for enrollment to evaluate a different schedule of PCLX-001 (for example a break within cycles), based on safety, PK and preliminary activity data and integrated PK/efficacy and PK/safety modelling from the dose escalation. The RP2D will be defined by the sponsor in conjunction with the investigators after reviewing the data from all parts and stages of the study, including available PK data and intensity of adverse events (AEs), and efficacy parameters, including overall response rate (ORR). The RP2D may be the MTD but not necessarily as not only safety data will be taken into account prior to its determination.

Two expansion cohorts will be opened to determine the preliminary clinical activity of PCLX-001. Part B dose expansion Cohort A will occur once the MTD and the RP2D are determined by the sponsor and investigators after data review.

Part B dose expansion cohort B will occur once dose escalation has achieved a dose that has both acceptable safety and achieves drug exposures predicted to have activity in R/R B-cell lymphomas. See Appendix D for the background, rationale, and determinants of the decision to open dose expansion cohort B.

- Expansion Cohort A: 20 participants with advanced solid malignancies showing preclinical sensitivity or molecular markers of sensitivity to PCLX-001: breast, non-small cell lung, small-cell lung, colorectal, and bladder cancers
- Expansion Cohort B: 20 participants with relapsed/refractory (R/R) B-cell lymphoma: diffuse large B-cell lymphoma (including transformed disease), high grade B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and Burkitt lymphoma.

3.6 Treatment Duration and Discontinuation

In the absence of treatment delays due to adverse events, treatment may continue unless the following reasons to discontinue PCLX-001 occur:

- Disease progression
- Intercurrent illness preventing further administration of treatment
- Unacceptable adverse event(s)
- Patient withdrawal from study (patient choice)
- Treating physician choice
- Delay in subsequent cycles of chemotherapy of longer than 28 days due to toxicity
- Failure of patient to adhere to study requirements

3.7 End of Treatment and Follow-Up

All patients (except for patients who died, withdrew consent and objected to further data collection, or were lost to follow-up) will be followed for 30 days (± 4 days) after the last dose of study drug or until all treatment related clinically significant adverse events resolve to Grade ≤ 1. Patients will have their medical records evaluated every 6 months (+/- 1 month) for a period starting three years from enrollment, to determine survival status (alive, deceased, and date of death).

4. STUDY POPULATION

Patients with histologically confirmed solid tumors or B-cell lymphoma resistant or refractory to standard therapy or without standard therapy and in which, in the opinion of the investigator, experimental treatment with PCLX-001 may be of benefit will be recruited.

Patients must have baseline evaluations performed prior to the first dose of study drug and meet all eligibility criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of the patient. The patient must be thoroughly informed about the aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment.

4.1 Inclusion Criteria

Patient must meet all of the following criteria to be eligible for the study.

The following inclusion criteria apply to ALL (dose-escalation and expansion) patients:

1. 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.
2. Male or female patients aged ≥ 18 years
3. **Dose Escalation**
   a. Participants with histologically-confirmed advanced solid tumor (non-breast cancer) who have failed at least one prior therapy and/or are not eligible for therapies expected to provide clinical benefit.
   b. Participants with histologically-confirmed metastatic breast cancer with known hormone receptor status meeting the therapy requirements as listed below (just prior to criterion #4).
   c. 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. These histologic subtypes are based on WHO 2016 criteria.

   Dose Expansion
   Cohort A: Participants with histologically-confirmed advanced 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. Participants with histologically-confirmed metastatic breast cancer with known hormone receptor status meeting the therapy requirements as listed below (just prior to criterion #4).

   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.

Therapy requirements and stratification factors for histologically-confirmed metastatic breast cancer participants in either the dose escalation or dose expansion phases are dependent upon hormone receptor status as follows:

i. **Estrogen Receptor positive and/ or Progesterone Receptor positive, and HER 2 negative disease.**
Prior treatment with:
- Two or more lines of endocrine therapy in the adjuvant or metastatic setting including the following: Selective Estrogen Receptor Modulators (eg. tamoxifen), Aromatase Inhibitors (eg. letrozole, anastrozole, exemestane), Selective Estrogen Receptor Downregulators (fulvestrant), and CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in combination or monotherapy, and
- at least three lines of cytotoxic chemotherapy given in the adjuvant, neoadjuvant, or metastatic setting including an anthracycline, a taxane, and capecitabine.

ii. **Estrogen Receptor and Progesterone Receptor and HER2 negative disease.**
- Prior treatment with at least three lines of cytotoxic chemotherapy in the adjuvant or metastatic setting including the following agents: anthracyclines, taxanes, platinum (carboplatin or cisplatinum), and
- if known BRCA1 or BRCA2 mutated disease, prior PARP inhibitor therapy is required if available to the patient.

iii. **HER2 positive disease with negative Estrogen receptors.**
- Prior treatment with three or more lines of HER2-directed therapy in the adjuvant, neoadjuvant, or metastatic setting including at least three of the following HER2 directed agents: trastuzumab, trastuzumab emtansine, trastuzumab deruxtecan, pertuzumab, lapatinib, neratinib, tucatinib.

iv. **HER2 positive disease with positive Estrogen receptors.**
Prior treatment with:
- three or more lines of HER2-directed therapy in the adjuvant, neoadjuvant, or metastatic setting including at least three of the following HER2 directed agents: trastuzumab, trastuzumab emtansine, trastuzumab deruxtecan, pertuzumab, lapatinib, neratinib, tucatinib, and
- two or more lines of endocrine therapy in the adjuvant or metastatic setting including the following: Selective Estrogen Receptor Modulators (eg. tamoxifen), Aromatase Inhibitors (eg. letrozole, anastrozole, exemestane), Selective Estrogen Receptor Downregulators (fulvestrant), and CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) in combination or monotherapy, and
- at least three lines of cytotoxic chemotherapy given in the adjuvant, neoadjuvant, or metastatic setting including an anthracycline, a taxane, and capecitabine.

4. 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.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Appendix A).
6. Life expectancy of at least 12 weeks

7. 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:
   a. Hemoglobin ≥ 85 g/L
   b. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   c. Platelet count ≥ 100 x 10^9/L for Dose Escalation and ≥ 75 x 10^9/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.

8. Patients must have adequate kidney function, as assessed by both: a) 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), and b) creatinine ≤ 1.5 times the ULN
9. 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:
   a. Prothrombin time/International normalized ratio (PT/INR) ≤ 1.5 for patients not on anticoagulation
   b. 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.

10. Adequate cardiac function per institutional normal measured by echocardiography or multigated acquisition (MUGA) scan (LVEF ≥ 50%)
11. 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 drug.

    Note: 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.

12. 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.

4.2 Exclusion Criteria

The following exclusion criteria apply to ALL (Dose-escalation and expansion) patients:

1. Known hypersensitivity to the study drugs or excipients of the preparations or any agent given in association with this study
2. 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 enrollment date, or uncontrolled cardiac arrhythmias
3. Uncontrolled arterial hypertension despite optimal medical management (per investigator's opinion)
4. Moderate or severe hepatic impairment, i.e. Child-Pugh class B or C
5. Patients with known human immunodeficiency virus (HIV) infection
6. 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.
7. Patients with significantly impaired 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), and/or
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥ 3 times ULN or ≥ 5 times ULN for patients with malignant liver involvement.
8. Infections of CTCAE Grade 2 not responding to therapy or active clinically serious infections of CTCAE Grade > 2
9. 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.
10. Current or past history of central nervous system (CNS) lymphoma

11. Uncontrolled seizure disorder requiring therapy (e.g. strong CYP3A4 inducers such as carbamazepine and phenytoin)
12. 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
13. 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
14. Serious, non-healing wound, ulcer, or bone fracture
15. 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).
16. Any clinical condition that is considered unstable or might jeopardize the safety of the patient and his / her compliance in the study
17. Inability to swallow oral medications
18. Any malabsorption condition
19. Breastfeeding. Female patients must not breastfeed during treatment and until 4 months after last study drug administration.
20. 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.
21. Treatment with systemic steroids (prednisone dose ≥10 mg/day or equivalent dose).
22. 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.)
23. Radiotherapy to target lesions in the 21 days before starting the first dose of study drug. Palliative radiotherapy is allowed to non-target lesions at any time before starting the first dose of study drug.
24. Major surgery or significant trauma within 4 weeks before the first dose of study drug
25. Previous assignment to treatment during this study
26. Concomitant participation in another clinical study with investigational medicinal product(s)
27. Substance abuse, medical, psychological, or social conditions that may interfere with the patient's participation in the study or evaluation of the study results
28. 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)
29. 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.
30. Use of Proton Pump Inhibitors (PPIs) must be discontinued at least 48 hours prior to initiation of study drug.

Note: If a potential participant is on a PPI and requires some form of Acid Reducing Agent(s) (ARAs), the investigator should consider alternatives for the duration of the trial, including Famotidine, or oral antacid drugs such as calcium carbonate.

31. 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.

4.3 Replacement

Patients who discontinue due to a DLT in Cycle 1 will not be replaced.

Patients who discontinue during Cycle 1 due to any reason other than a DLT and patients who were non-compliant in Cycle 1 will be replaced for the purpose of Cycle 1 DLT determinations, but may continue on the study at the discretion of the investigator. Non-compliance is determined by the investigator and can include failure to take medications or failure to have study-related activities performed.

Patients who took less than 21-days of the required dose of study drug during Cycle 1 will be replaced for the purpose of Cycle 1 DLT determinations, but may continue on the study at the discretion of the investigator.

Patients with insufficient PK data may have to be replaced. The decision to replace a patient due to insufficient PK data will be taken on a case-by-case basis after consultation between the investigator and the sponsor.

Patients who discontinue after Cycle 1 will not be replaced.

If the dropout rate in any expansion cohort is ≥ 20%, additional patients may be enrolled to ensure that at least 20 patients per indication will be evaluable for the response assessment.

5. TREATMENTS

5.1 Identity of Study Treatment

All study drugs will be labeled consistent with the requirements of local law and legislation. Label text will be approved consistent with the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

5.2 Dosage and Administration

PCLX-001 will be provided as an oral daily dose on a 28-day cycle. Doses should be taken around the same time each day, within a ±3 hour window. PCLX-001 capsule(s) are to be taken by mouth and swallowed with approximately 250 ml of water, at least ninety minutes after eating solid food. After PCLX-001 is taken, the patient should wait 2 hours before eating solid food. Missed doses for any reason (i.e. outside of the allowable dosing window) will not be administered at a later time. In Part A, dose-escalation levels are provided in Section 3.3. PCLX-001 capsules are available in doses of 10 mg and 70 mg and the number of capsules will be calculated to ensure proper daily dosing is provided.

5.3 Dose Delay and Modifications

Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. Toxicity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 5.0).

5.3.1 Cycle 1 DLT Modifications for Part A Dose-Escalation Cohorts

If a patient experiences a treatment related hematological or non-hematological DLT (as defined in Section 3.2) during Cycle 1, the next dose of PCLX-001 will be delayed for up to 28 days for Part A. If the toxicity fails to resolve to CTCAE Grade ≤2 within 28 days, the patient should be withdrawn from study treatment but followed for safety until resolution.

If the toxicity resolves to CTCAE Grade ≤2, re-treatment with PCLX-001 can be considered. Re-treatment of this patient should be at 1 dose level below the initial dose. Detailed dose modifications are described in Table 5-1. Patients experiencing any drug-related, clinically significant, non-hematological CTCAE Grade 4 toxicity will be withdrawn from study treatment but followed for safety until resolution. There will be no intrapatient dose escalation and no more than two dose reductions will be allowed.

Table 5–1: Dose Modifications of PCLX-001

Existing Dose (mg)	Modified Dose (mg)
280	210
210	140
140	100
100	70
70	40
40	20
20	10
10	Discontinue study drug

5.3.2 Dose Modifications for HEMATOLOGIC Toxicities

For cycle 2 and beyond, Day 1 administration of PCLX-001 requires a platelet count of ≥ $75x10^9$/L and an absolute neutrophil count (ANC) of ≥ $1.5x10^9$/L. CBC's drawn within 72 hours of treatment day may be used provided they meet parameters. However, if treatment parameters are not met, dose interruption will be made on the basis of blood counts taken the day of scheduled treatment. If counts are below this threshold, treatment will be delayed for 1 week and reassessed weekly until these parameters are met.

If a patient experiences a hematologic DLT in the preceding cycle OR if treatment is held for > 7 days due to neutropenia and/or thrombocytopenia, then the subsequent cycle will be administered at one lower dosing level. No more than two dose reductions will be allowed.

Patients should not receive prophylactic G-CSF for cycle 1. Subsequent use will be at the discretion of the treating physician and as per the ASCO guidelines on colony stimulating factors.

5.3.3 Dose Modifications for NON-HEMATOLOGIC Toxicities

For a Grade ≥ 3 non-hematological toxicity considered to be clinically significant and attributed to PCLX-001, treatment will be delayed for up to a maximum of 28 days. If the toxicity resolves to CTCAE Grade ≤ 2, the next dose of PCLX-001 can be considered at 1 lower dose level (Table 5-2). Grade 4 clinically significant toxicities related to PCLX-001 will result in discontinuation of PCLX-001.

There will be no intrapatient dose escalation and no more than two dose reductions will be allowed.

Table 5–2: Non-hematological Criteria for Dose Delay and Dose Modification

CTCAE Grade[a]	Dose delay	Dose modification
0 – 2	Treat on time	No change
3	Delay[b] until CTCAE Grade ≤2	Decrease 1 dose level[c]
4	Discontinue permanently	Discontinue permanently

[a] Excludes alopecia, non-refractory nausea/vomiting, and non-refractory diarrhea. For TLS see Table 5-3
[b] If no recovery after 28-day delay, PCLX-001 treatment will be discontinued.
[c] Dose will not be re-escalated after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

Gastrointestinal Events

Diarrhea: No prophylactic treatment for diarrhea is recommended. Anti-diarrheals can be used when needed. A further dose of study medication should not be given before treatment related diarrhea has recovered to CTCAE Grade ≤ 2.

Nausea/Vomiting: No prophylactic treatments for nausea or vomiting are recommended, but anti-emetic drugs can be used when needed. A further dose of study medication should not be given before treatment related nausea/vomiting has recovered to CTCAE Grade ≤2.

Constipation: Patients can continue laxative as concomitant medication, but start of prophylactic treatments before study drug is administered is not recommended. Laxative can be used when needed.

5.4 Prophylaxis and Monitoring of Tumor Lysis Syndrome

Patients with high tumor burden and who are considered by the Investigator to be at risk for tumor lysis should receive tumor lysis prior prophylaxis prior to the initiation of treatment. Patients should be well-hydrated and maintain a fluid intake of approximately 2 L/day. In addition, patients should be treated with allopurinol 300 mg oral daily (or a suitable alternative as per institutional standard) ideally 24 - 48 hours prior to Cycle 1 Day of PCLX-001 treatment. Patient should continue to receive prophylaxis and adequate hydration as deemed appropriate by the Investigator to mitigate against tumour lysis syndrome (TLS).

The inherent risk of tumor lysis syndrome (TLS) is dependent on the malignancy being treated and individual participant characteristics. The risk of TLS with PCLX-001 in NHL patients is predicted to be highest for those with bulky disease (defined as any lesion > 10 cm on the screening CT scan) and elevated pretreatment lactate dehydrogenase levels, particularly in the presence of dehydration or compromised renal function. Whereas patients with DLBCL, MCL, and Burkitt lymphoma may be at higher risk of TLS compared to FL, any risk assessment based on tumor type must be considered along with the effectiveness of therapy. All patients should be assessed for the need for prophylaxis for TLS.

TLS is an emergency which requires immediate treatment. Balanced or isotonic solutions (without potassium) should be administered to ideally maintain urine output > 100 mL/h. Alkalinization of the urine is not recommended in the treatment of TLS. In the absence of contraindications, patients with established TLS should be considered for rasburicase at a dose of 0.2 mg/kg/day or institutional standard. Intractable fluid overload, hyperkalemia, or reduced urine output in the setting of acute kidney injury should be assessed for the need for renal dialysis.

Dose modifications for TLS are summarized in Table 5-3.

Table 5–3: Tumor Lysis Syndrome Criteria for Dose Delay and Dose Modification

CTCAE Grade	Dose delay	Dose modification
3 or 4	Delay[a] until TLS resolved	Decrease 1 dose level[b] or discuss with Medical Monitor to reinitiate at target dose

[a] If no recovery after 28-day delay, PCLX-001 treatment will be discontinued.
[b] Dose will not be re-escalated after reduction for toxicity. If more than 2 dose reductions are required, treatment will be discontinued.

5.5 Treatment Compliance

PCLX-001 will be dispensed to patients to be taken orally on an ambulatory basis as well as during clinic visits.

During ambulatory treatment, patients will document the intake of PCLX-001 in a compliance diary.

Unused PCLX-001 study drug will be returned by patients. The time and amount of study drug intake will be recorded in the compliance diary. Each patient's compliance will be evaluated by the study center. This information will be transferred into the eCRF taking into account each dose interruption and / or any changes in dosing.

To ensure the required number of patients are evaluable Cycle 1 DLT dose-escalation cohorts, participants will need to have received at least 21-days of the planned total dose (unless a DLT occurs). Patients non-compliant in Cycle 1 will be replaced.

Any discrepancies between actual and expected amount of returned study medication must be discussed with the patient at the time of the visit, and any explanation must be documented in the source records.

6. NON-STUDY THERAPIES

6.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a participant between the 7 days preceding the baseline evaluations and the end of last study visit. All concomitant medications (including start / stop dates, total daily dose, and indication), including vaccinations, should be reported by the Investigator and recorded on the appropriate eCRF.

Permitted Therapies

- Patients may receive palliative and supportive care for any underlying illness.
- Patients may receive vaccinations for COVID-19. Ideally, vaccinations would not be administered during Cycle 1 of study treatment, however, this is not prohibited.
- Corticosteroids use for cytoreduction due to malignancy-related symptom control of B-cell lymphoma may be given prior to initiation of study treatment (up to 100 mg/day of prednisone or equivalent for no more than 5 days).
- Palliative radiotherapy during the study will be allowed for local pain control if:

  - In the opinion of the investigator, the patient does not have progressive disease.
  - Not more than 10% of the patient's bone marrow is irradiated.
  - The radiation field does not encompass a target lesion; the indication for radiation therapy to a target lesion is considered progressive disease.
  - The safety of oral PCLX-001 administered concomitantly to radiation therapy has not been determined. Therefore, oral PCLX-001 treatment should be held on those days where the patient receives palliative radiotherapy, and restarted the day after completion of palliative radiotherapy.
- Patients may continue receiving bisphosphonates prophylactically or for bone metastases while on study treatment.
- Granulocyte colony-stimulating factor and other hematopoietic growth factors may be used for the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion, except their preventive use in Cycle 1.
- CYP3A4 substrates should be used with caution, as exposure may be higher or lower when concomitantly administered with PCLX-001 due to CYP3A4 inhibition or induction, respectively.
- P-gp substrates (e.g. aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, fexofenadine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) should be used with caution.

Prohibited Therapies

- Use of PPIs must be discontinued at least 48 hours prior to initiation of study drug.

  Note: If a potential participant is on a PPI and requires some form of acid reducing agent, the investigator should consider alternatives for the duration of the trial, including Famotidine, or oral antacid drugs such as calcium carbonate.

- Patients may not receive another investigational treatment or other approved antitumor therapy (such as chemotherapy) while on this protocol. In addition, treatment with "non-conventional therapies" (such as herbal supplements) is not permitted.
- The use of strong CYP3A4 inhibitors and inducers is not permitted from 5 days prior to first administration of study drug to the active FU visit.
- Patients should not receive PAXLOVID as components are known to inhibit CYP3A.
- Patients may not receive granulocyte colony-stimulating factor and other hematopoietic growth factors for primary prevention during Cycle 1.

7. STUDY SCHEDULE AND ASSESSMENTS

7.1 Study Calendar

The calendar below lists the assessments and indicates with an "X" the visits when they are performed. Baseline evaluations are to be conducted within 28 days (or 7 days as indicated) prior to start of protocol therapy. Diagnostic imaging and LVEF assessment must be done 28 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 72 hours prior to initiation of the next cycle of therapy.

Table 7A: Schedule of Evaluations (Study Flow Chart) – SCREENING

Measures / actions	Screening	
	Within 28 days	**Within 7 (±3) days**
	before the first dose of PCLX-001	
Informed consent		
Signing of informed consent	X	
Archival tumor tissue [a]	X	
General screening procedures	X	
Check of inclusion / exclusion criteria	X	
Demographics	X	
Complete medical history including documentation of primary diagnosis [b]	X	
Abbreviated medical history		X
Baseline characteristics		
• Prior and concomitant medications (prescribed and OTC)	X	
• Baseline toxicities	X	
Assessment of toxicities (open questioning for AEs)		X
Concomitant medications (prescribed and OTC)		X
Physical examination[j]	X	
Vital signs		
• Blood pressure, heart rate, and body temperature	X	
Body weight and body height	X	
ECOG performance status assessment	X	
Cardiovascular safety assessment		
• 12-lead ECG (standard, triplicate)	X	
• MUGA scan or echocardiogram	X	

Table 7A: Schedule of Evaluations (Study Flow Chart) – SCREENING (continued)

Measures / actions	Screening	
	Within 28 days	**Within 7 (±3) days**
	before the first dose of PCLX-001	
Tumor assessment (CT or MRI)[i]	X	
Blood sample collection for tumor biomarker, if applicable (e.g. CA125, CEA)	X	
PET-CT (optional, NHL patients only) [c]	X	
Fresh tumor biopsy (optional) [d]		X
Blood sample collection for exploratory biomarker analyses		X
Blood / urine sample collection for laboratory safety assessments		
• Hematology [e,]		X
• Blood chemistry [f,]		X
• Calculation of eGFR by Cockcroft-Gault		X
• Coagulation (aPTT, PT/INR)		X
• Thyroid function (TSH and T_4[total or free per local standard])		X
• Virology (HBsAg, anti-HCV) [g]		X
• Pregnancy test (serum) [h]		X
• Urinalysis (dipstick)		X

a. Archival tumor tissue is mandatory for patients enrolled in the dose escalation levels and expansion cohorts. This specimen could have been collected at any time from the initial diagnosis to study entry.
b. Documentation of the primary diagnosis using the complete pathology report. Collection of baseline FLIPI, IPI, or MIPI scores for FL, DLBCL, and MCLC, respectively. Collection of staging information for patients with B-cell lymphoma.
c. This scan should only be performed for NHL patients and is optional (i.e. not required for patients with other histologies). If a PET-CT is performed at screening, it should be repeated once after the sixth cycle if no progressive disease is detected during the course of treatment and / or to confirm complete response or disease progression.
d. Collection of screening fresh tumor biopsy will be optional for patients enrolled in whom an archival biopsy is older than 6 months. The tumor biopsy will be obtained before the first dose of study drug (during the screening period when all other general screening procedures have been completed and patients are eligible for study treatment).
e. Hematology includes CBC + differential (i.e. hemoglobin erythrocytes, leukocytes, platelets, MCV, RDW, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, immature granulocytes, nucleated RBCs).
f. Blood chemistry includes: sodium, potassium, chloride, bicarbonate or total CO^2 (as per site practice), calcium, phosphate, magnesium, total protein, albumin, glucose, serum creatinine, urea, uric acid, total bilirubin, ALT, AST, LDH, alkaline phosphatase, lipase
g. Virology includes: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HB-sAb), and hepatitis C virus antibody (anti-HCV)
h. Only for women of reproductive potential (including women of reproductive potential whose partners are sterilized).
i. CT of the relevant disease region for solid tumors and CT thorax, abdomen, pelvis ± neck for NHL. Patients with neurological symptoms should undergo a CT or MRI brain to rule out brain metastases. The overseeing physician can use their judgement to choose the appropriate scan type to perform.
j. A full physical exam is required at baseline/screening. The exam should review all body systems as follows: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck, lymph nodes, thyroid, musculoskeletal, neurological, and if clinically indicated, any other systems (investigator to specify). Thyroid exams may be included as part of the head and neck review. If the review of head and neck is normal, the thyroid can also be considered normal.

Table 7B: Schedule of Evaluations (Study Flow Chart) – TREATMENT AND FOLLOW-UP

Measures / actions	Treatment[n]									FU	
	Cycle 1					Cycle 2		Cycle ≥ 3	EOT visit	Safety FU visit [b]	Long-Term FU[o]
	D1 [a]	D2	D8	D15	D22	D1	D15	D1			
Before study drug administration											
Check of inclusion / exclusion criteria	X										
Abbreviated medical history	X		X	X	X	X	X	X	X	X	
Concomitant medications [c]	X		X	X	X	X		X	X	X	
Assessment of toxicities (AEs) [d]	X		X	X	X	X	X	X	X	X	
12-lead ECG (standard, triplicate)	X					X			X	X	
Blood pressure, heart rate, & body temperature	X		X	X	X	X	X	X	X	X	
Physical examination[l]	X		X	X	X	X		X	X	X	
Body weight	X		X	X	X	X	X	X	X	X	
ECOG performance status assessment	X		X	X	X	X	X	X	X	X	
Blood sample collection for biomarker analysis [f]	X					X		X	X		
Blood / urine sample collection for laboratory safety assessments											
• Hematology[g]	X		X	X	X	X	X	X	X		
• Blood chemistry [h]	X		X	X	X	X	X	X	X		
• Calculation of eGFR by Cockroft-Gault	X					X					
• Coagulation (aPTT; PT/INR)	X					X					
• Thyroid function (TSH and T_4[total or free per local standard])	X					X			X		
• Virology (HBV DNA, HCV RNA)[m]	X										
• Pregnancy test (serum or urine)[j]	X										
• Urinalysis (dipstick)	X			X		X			X		
Tumor assessment all tumors (CT or MRI)[i]						End of every second cycle					
PET-CT (optional, NHL patients only)[k]						Once after sixth cycle					
Blood sample collection for tumor marker, if applicable (e.g., CA125, CEA, PSA)						End of every second cycle					
Survival status											X[o]

Table 7B: Schedule of Evaluations (Study Flow Chart) – TREATMENT AND FOLLOW-UP (continued)

Measures / actions	Treatment									FU
	Cycle 1					Cycle 2		Cycle ≥ 3	EOT visit	Safety FU visit [b]
	D1 [a]	D2	D8	D15	D22	D1	D15	D1		
Study drug administration										
Review of patient study medication diary and compliance of medication taken at home	X	X	X	X	X	X	X	X		
PCLX-001 administration at study center	X	X	X	X	X	X	X	X		
Before & after study drug administration										
PK sampling (plasma) for PCLX-001[e] escalation	X	X	X	X	X	X	X	X	X	
PK sampling (plasma) for PCLX-001 [e] expansion	X			X		X		X		

a. Any of the assessments scheduled before drug administration on C1D1 may be missed without protocol deviation if the same assessment has been obtained and reviewed within 3 days before the start of treatment (except PK and exploratory biomarker analysis).
b. If a patient discontinues study treatment at any time during the study for any reason (except for patients who died, withdrew consent and objected to further data collection, or were lost to FU), an active FU assessment should be performed 30 days (±4 days) after the last dose of the last study drug.
c. Prescribed and OTC.
d. Questioning for AEs will be conducted at clinic visits; in addition, spontaneous reports of AEs will be collected throughout the study.
e. PK sampling: For patients in dose escalation, see Table 7C for schedule. For patients in dose expansion, see Table 7D for schedule.
f. To be taken pre-dose of each cycle Day 1 within 60 min before the morning dose and EOT
g. Hematology includes CBC + differential (i.e. hemoglobin erythrocytes, leukocytes, platelets, MCV, RDW, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, immature granulocytes, nucleated RBCs). Detection of CTCAE Grade 4 neutropenia (only Cycle 1) will trigger twice-weekly white blood cell counts to be performed, so that DLT determination can be made.
h. Blood chemistry includes: sodium, potassium, chloride, bicarbonate or total CO^2 (as per site practice), calcium, phosphate, magnesium, total protein, albumin, glucose, serum creatinine, urea, uric acid, total bilirubin, ALT, AST, LDH, alkaline phosphatase, lipase.
i. Window for tumour assessment is ± 5 days from Day 28 of the even-numbered cycles. CT of the relevant disease region for solid tumors and CT thorax, abdomen, pelvis ± neck for NHL.
j. Women of childbearing potential (including women of childbearing potential whose partners are sterilized) must have a negative pregnancy test.
k. This scan should only be performed for NHL patients and is optional (i.e. not required for patients with other histologies). If a PET-CT is performed at screening, it should be repeated once after the sixth cycle if no progressive disease is detected during the course of treatment and / or to confirm complete response or disease progression.
l. Exam to be symptom-directed.
m. To be performed if clinically indicated (e.g. positive HBsAg and/or anti-HCV tests as performed during screening).
n. Unless otherwise indicated, the window for visits is ± 2 days.
o. Electronic records will be used to assess patient survival monthly (± 1 week) from the date of the follow-up visit.

7.2 Visit Description

If not stated otherwise, the examinations listed in the following sections will be performed by, or under the supervision of, an investigator or a qualified delegate.

Unscheduled visits may occur as necessary, when clinically indicated at the investigator's discretion. Relevant and clinically significant laboratory data and AEs obtained at the unscheduled visits should be entered into the eCRF and recorded in the source documentation as necessary.

7.2.1 Screening

Pre-study examinations will be performed within 28 days before first administration of PCLX-001.

Because some patients may not satisfy all inclusion and exclusion criteria, more patients than the pre-specified number of evaluable patients will be screened. As soon as fulfillment of all criteria is confirmed by the investigator, the patient will be allowed to enter the treatment phase of the study.

A signed written informed consent form (ICF) will be obtained before any general screening procedure for the study may begin.

7.2.2 Treatment Visits

At each visit, laboratory investigations and/or measures and action will be as per the Schedule of Evaluations (Tables 7A and 7B).

7.2.3 Follow-Up Visits

If a patient discontinues study drug at any time during the study for any reason (except for patients who died, withdrew consent and objected to further data collection, or were lost to FU), an active FU assessment should be performed 30 days (± 4 days) after the last dose of the last study drug (Table 7B).

Long-term follow up will occur monthly to assess patient survival only. Patients will not be contacted for these visits; electronic records will be reviewed to complete the assessments.

7.2.4 End of Treatment Visit

If a patient discontinues the study for any reason except death, withdrawal of consent and objection to further data collection, loss to FU, or extended treatment interruption, an EOT evaluation should be performed as soon as possible after the last dose of the study drug, but always within 30 days (± 4 days) after the last dose of study drug.

The EOT visit should be performed as a clinic visit (except for patients who died, withdrew consent and objected to further data collection, or were lost to FU).

The assessments to be performed at the EOT visit are described in the Schedule of Evaluations (Table 7B).

7.3 Determination of Efficacy Outcomes

Tumor response and progression of solid tumors and NHL will be evaluated by the investigator at each study center consistent with RECIST 1.1 criteria (see Appendix B), or Lugano Classification of Lymphoma response (see Appendix C).

Tumor markers can play a role in detecting disease and assessing response to therapy in selected groups of patients. In monitoring patients for disease progression, tumor marker levels should be determined according to clinical practice (e.g., CA125 for ovarian cancer, CEA for colorectal cancer, PSA for prostate cancer).

Solid Tumors

In *measurable* lesions (i.e. at the primary site, visceral [≥1.0 cm long axis], or nodal [in lymph nodes ≥1.5 cm short axis] lesions), the objective response will be assessed by contrast-enhanced CT or MRI and documented consistent with RECIST 1.1 criteria (see Appendix B). Tumor measurements for efficacy evaluation will be made every 2 cycles, beginning with a baseline scan and unless progression is noted, all lesions will be assessed and reported at the end of every second cycle, starting at the end of Cycle 2.

Non-Hodgkin's Lymphoma

Efficacy will be assessed based on radiological tumor evaluations, which will include neck, chest, abdomen, and pelvis by contrast-enhanced CT / MRI scans. PET-CT can be utilized throughout the study if it is considered standard of care at the institution. Scans will be performed as shown in Table 7A and Table 7B and will be evaluated locally at the study site.

PET-CT is optional in this study and should be done based on institutional standards whereas the CT portion of the PET-CT should be of diagnostic quality, i.e. appropriate radiation dose and contrast enhancement. In case the CT portion of the PET-CT is performed for attenuation correction only an additional whole body CT in diagnostic quality is needed. If a PET-CT with a PET positive finding was performed at screening an interim PET-CT should be done after the sixth cycle. For any imaging follow-up after interim PET-CT it is recommended to confirm any changes in previous metabolic overall response that were assessed with CT alone with PET-CT.

Response assessment will be based on the Lugano Classification (see Appendix C).

7.4 Pharmacokinetics

7.4.1 Drug Measurements

In patients enrolled in Part A dose escalation, serial blood (plasma) samples will be collected at the time points shown in Table 7C to assess PK of PCLX-001. For patients enrolled in Part B dose expansion, serial blood (plasma) samples will be collected at the pre-dose time points shown in Table 7D.

Whenever possible, all efforts should be made to adhere to the blood-sampling schedules given in Tables 7C and 7D. However, based on practical considerations, the following time ranges are provided as guidance:

Pre-dose samples should be collected within 15 min before the administration of PCLX-001. For 0.5 hours post dose, the PK sample should be collected within ± 6 minutes. Subsequent PK samples should be collected ± 15 minutes of planned time point. Sampling times outside these suggested intervals will not be considered as protocol deviations. The date and time of actual blood sampling and dose administration will have to be documented in the eCRF because PK calculations will be based on the actual sampling times relative to dosing times.

Cumulated substantial deviations of sampling times and / or consecutive, missing PK samples may lead to an insufficient (inadequate) description of the plasma concentration *vs.* time profiles of PCLX-001, and thus affect the quality of the PK evaluation of the respective patient(s). In this case, these deviations should be classified as "important" and may lead as declared "validity findings" to the exclusion of the respective patient(s) from the PK analysis set.

Details on sampling procedures, sample storage, and shipment are documented in separate sample handling documentation.

Table 7C: Schedule of pharmacokinetic blood sampling time points in Part A Dose Escalation

Procedures	Study Treatment Period 1 Cycle = 28 days								
	Cycle 1					Cycle 2		Cycle 3/ Beyond	EOT Visit
Visit Identifier (Visit Window)	**Day 1**	**Day 2**	**Day 8 (±2)**	**Day 15 (±2)**	**Day 22 (±2)**	**Day 1 (± 2)**	**Day 15 (±2)**	**Day 1 (±2)**	
	X	X	X	X	X	X	X	X	X
Pharmacokinetics									
Pre-dose* (-15 min)	X	X	X	X	X	X	X	X	X
0.5 hour (± 6 min)	X			X					
1 hours (± 15 min)	X			X					
2 hours (± 15 min)	X			X					
4 hours (± 15 min)	X			X					
8 hours (± 15 min)	X			X					

*If patient is receiving a dose on that day

Table 7D: Schedule of pharmacokinetic blood sampling time points in Part B Dose Expansion

Procedures	Study Treatment Period 1 Cycle = 28 days								
	Cycle 1					Cycle 2		Cycle 3/ Beyond	EOT Visit
Visit Identifier (Visit Window)	**Day 1**	**Day 2**	**Day 8 (±2)**	**Day 15 (±2)**	**Day 22 (±2)**	**Day 1 (± 2)**	**Day 15 (±2)**	**Day 1 (±2)**	
	X			X		X		X	
Pharmacokinetics									
Pre-dose* (-15 min)	X			X		X		X	

*If patient is receiving a dose on that day

7.5 Pharmacodynamics

Tissue and blood samples will be collected to understand the pharmacodynamic effect of PCLX-001.

7.5.1 Tissue Samples

Archived tissue samples will be requested from all patients and pre-treatment biopsies will be optional for patients enrolled in whom an archival biopsy is older than 6 months. These will be collected for response prediction analyses and exploratory research. Archived tumour blocks will be returned to the clinical investigator at the end of the study or, if requested, once sections have been obtained for biomarker analysis.

7.5.2 Blood Samples

Collection of blood samples for exploratory biomarker research is also a part of this trial. Blood samples will be collected from all patients in this study as specified in the Schedule of Evaluations (Table 7A and 7B). Specimens will be stored and may be used for research purposes to identify biomarkers useful for predicting and monitoring PCLX-001.

8. STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The exact sample size for Part A dose-escalation cannot be pre-determined and depends on the number of cohorts needed to reach MTD. Part A will enroll at least 9 patients and up to 52 patients. In Part B, there are two expansion cohorts of 20 patients each for a total of 40 patients.

8.2 Populations for Analyses

Table 8-1: Analysis Populations

Population	Description
Efficacy	All participants who received at least one dose of PCLX-001 and had at least one on-treatment tumour assessment will be included in the efficacy analysis.
Safety	All participants who received at least one dose of study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
MTD-determining population (Part A only)	All participants from the safety analysis population who follow the protocol-specified dose regimen within the DLT observation period and have undergone the scheduled safety evaluations, or who discontinued earlier due to a DLT, will be included in the MTD-determining analysis.
Pharmacokinetic	All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria or deviate significantly from the protocol or if their data are unavailable or incomplete, which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

8.4 Statistical Analyses

Descriptive statistics will be utilized to present study patient population and toxicity data.

8.5 Pharmacokinetic Analyses

PK parameters of PCLX-001 will be determined via non-compartmental analysis. Individual and mean serum PCLX-001 concentration versus time data will be listed by patient and tabulated by dose level. Graphical displays of PK data may also be provided.

Other PK variables will be summarized using descriptive statistics only. These will include:

- C_{max}
- Minimum observed serum concentration (C_{min}) at the beginning of Cycle 2 and at the beginning of every subsequent cycle where PK data are available
- Time to reach maximum serum concentration (t_{max})
- AUC
- CL
- Volume of distribution (Vd)

9. ADVERSE EVENT REPORTING

9.1 Definition of an Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

9.2 Reporting, Recording and Follow-up of Adverse Events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for adverse event reporting.

For all AEs, relationship to study drug will be reported on the appropriate AE eCRF page. The PI must judge whether the study drug caused or contributed to the AE in which case it is considered to be an adverse drug reaction, and report it as either:

Related (definitely, probably or possibly): there is a reasonable possibility that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for the determination of relatedness:

- There is a plausible time sequence between onset of the AE and study drug administration;
- There is a plausible biological mechanism through which study drug may have caused or contributed to the AE;

Not related: It is highly unlikely or impossible that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for a determination of not related:

- another cause of the AE is evident and most plausible;
- the temporal sequence is inconsistent between the onset of the AE and study drug administration; a causal relationship is considered biologically implausible.

All AEs and SAEs occurring after initiation of study drug, regardless of relationship to intervention, will be reported from time of first dose until 30 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events that the investigator believes have at least a reasonable possibility of being related to the investigational product.

The investigator should follow each adverse event until the event has resolved to baseline grade or better or is assessed as stable by the investigator or until the patient is lost to follow-up or withdraws consent. Every effort should be made to follow all serious adverse events considered related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event electronic Case Report Form (eCRF) and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

9.3 Serious Adverse Events

Serious adverse events (SAE) as defined by the Good Clinical Practice Guideline is any untoward medical occurrence that at any dose:

- results in death

- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

SAEs due to progressive disease (including death) should not be reported as SAEs unless the investigator also deems there is a possible contribution of the study drug or intervention. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.

9.3.1 SAE Reporting

All SAEs defined as per ICH guidelines and other adverse events must be recorded on case report forms. In addition, all serious adverse events must be reported by using the SAE form and must be submitted to Ozmosis Research Inc.

Serious Adverse Event Reporting Instructions

All serious adverse events must be reported as follows:

Within 24 hours: Report initial information (on trial specific SAE report form) by fax to:

Ozmosis Research Inc.

Phone: 416-634-8300

Fax: 416-634-8333

The initial information should always contain:

- Name of Reporter/Investigator,
- Subject Identification,
- Adverse Event Term,
- Study Drug Dose and Start/Stop Dates

On the next working day: Fax completed trial-specific Serious Adverse Event form

All follow-up SAE reports should be submitted to Ozmosis as soon as possible.

The PI/Sponsor will be made aware of all Serious Adverse Events within 24 hours. All SAEs will be reported to the local research ethics board (REB) and regulatory authorities, as applicable, in accordance with local guidelines. Health Canada, any collaborating centres and any pharmacovigilance teams (as applicable) will be notified by the Sponsor in an expedited manner of all SAEs which are unexpected and related to the investigational product.

10. MONITORING, AUDITING, AND INSPECTING

The investigator(s)/institution(s) will permit trial-related monitoring, audits, REB, Safety Monitoring, and regulatory inspection(s), providing direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital

patient charts and investigator study files). Monitoring of this study will be conducted as per the study monitoring plan.

Audits may be conducted by the study sponsor, the sponsor's designate, and/or the jurisdiction appropriate regulatory agencies (e.g Health Canada, the FDA). All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, outpatient department). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any monitoring or auditing activity.

10.1 Source Data

The Investigator will maintain accurate source records from which the case report forms are based. The investigator agrees to allow the monitor direct access to all relevant documents

10.2 Quality Control and Assurance

The sponsor / designee will monitor the site activity to verify that:

- The rights and well-being of human participants are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements(s).

10.3 Safety Monitoring Plan

A safety monitoring plan will be established for this study in conjunction with Pacylex Pharmaceuticals, Inc and Ozmosis Research.

Regular meetings will occur prior to dose escalation to monitor the safety aspects of the trial and review safety data. Additional meetings may be scheduled as necessary and if any of the safety stopping rules are met.

10.4 Deviations

The investigator is responsible to identify, document, assess and report all protocol deviations in accordance with Sponsor's, REB's and Health Canada's / the FDA's (as applicable) requirements.

10.5 Safety Stopping Rules

Accrual will be on hold and a meeting held with the principal investigator, investigators and safety monitoring team if the following occurs:

- If there is a death or unacceptable toxicity (SAE or AE grade ≥3,) attributed as: possibly, probably or definitely related to the experimental product.
- If there is a protocol treatment-related Serious Adverse Event (any SAEs deemed by PI to be definitely, probably or possibly related to study drug), or any significant safety concerns
- If the first 2 patients enrolled experience DLT

A decision will be made by the PI and safety monitoring team regarding whether the study will be re-opened for the next patient in the study or not. If there is disagreement in the SAE causality assessment or whether or not to re-open accrual between the different parties, the final decision will rest on the safety monitoring team. Ozmosis Research will notify all sites and applicable parties on the decision and whether accrual has re-opened. Only when it is deemed safe can the next patient start the treatment phase of the study.

11. DATA COLLECTION AND DATA MANAGEMENT

11.1 Data Collection and Case Report Forms

An electronic data capture system will be used in this trial. A case report form will be completed for each consented patient. The site maintains a separate source of data. This data will be entered by the site into the electronic data capture system.

The investigator is ultimately responsible for the collection and timely reporting of all applicable data entered in CRFs and any other data collection forms (source documents) and ensuring they are accurate, original, attributable, complete, legible, contemporaneous, and available when required. Changes to entries made in CRF and source documents must be dated, initialed and explained (if necessary). Changes should not obscure original entry.

Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The CRF must be signed by the investigator or by authorized delegate to attest the data in the CRF is true.

11.2 Dose Escalation Safety Cohort Review

Within 7 working days of each patient completing cycle 1 of Part A dose escalation, the following sections of the eCRF and source documentation for laboratory results must be completed and submitted to the Clinical Trials Specialist/Manager at Ozmosis Research Inc.:

- Study Treatment Administration
- Adverse Effects
- Hematology and Biochemistry Results
- Bone Marrow Results, if performed (optional)
- Lab normal ranges page, if applicable

Additional information may also be requested by Ozmosis Research Inc. from the study site. It is imperative that the eCRF pages listed above are received at Ozmosis Research Inc. within 7 working days after the patient completes cycle 1 and starting cycle 2 day 1 study drug administration, as the information will be used to assess safety at the opened dose level and to determine the feasibility of proceeding to a new dose level.

12. ADMINSTRATIVE, ETHICAL, AND REGULATORY STANDARDS

12.1 Compliance Statement

This trial will be conducted in compliance with the protocol, ICH-GCP's and the applicable regulatory requirement(s).

12.2 Ethics

This trial will be submitted and approved by the local Research Ethics Board prior to patient accrual.

12.3 Regulatory Requirements

The following documents are required:

<u>For participating Canadian centres:</u>

- All Investigators must complete and sign the Health Canada Qualified Investigator Undertaking form. The completed forms must be returned to the sponsor prior to any drug shipment.
- All applicable regulatory documents as listed in the Protocol Activation Checklist provided by Ozmosis Research Inc. to the sites.

- Ozmosis Research Inc. will submit via fax or e-mail to Health Canada a completed Health Canada Clinical Trial Site Information Form after local activation of each participating Canadian centre.

For participating U.S.A. centres:

- All Investigators must complete and sign FDA Form 1572. The completed forms must be returned to the sponsor prior to site activation.
- All Investigators must complete and submit a Financial Disclosure Statement.
- All Investigators must also submit to Ozmosis Research Inc. an up-to-date (current to within 2 years of the study start) curriculum vitae.
- Laboratory certification / accreditation and normal ranges for local lab(s).
- Consent forms, reviewed by Ozmosis Research Inc. before submission to the local Institutional Review Board (IRB).
- A completed site delegation list.
- A copy of the initial full board approval letter from the local IRB. Continuing approval (full board) will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purpose.

12.4 Confidentiality and Data Protection

12.4.1 Participant Protection

The responsible investigator will ensure that this study is conducted in compliance with the protocol and in agreement with the Declaration of Helsinki.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice.

The local research ethics board must approve the protocol, Informed Consent Form and any trial materials given to participants.

All potential serious breaches of GCP must be reported to Sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the participants of the study or the scientific value of the study.

12.4.2 Participant Identification

A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all CRFs.

12.4.3 Confidentiality of Trial Documents and Patient Records

The investigators must assure that participants' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs patients should not be identified by their names, but by an identification code. Investigators should keep patients' written consent forms and a patient enrolment log at the site showing codes, names and addresses.

12.4.4 Retention of Patient Records and Study Files

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, whichever is longer.

12.5 Protocol Registration

The sponsor has committed to the global industry position on disclosure of information about clinical trials. The International Committee of Medical Journal Editors (ICMJE) also requires trial registration as a condition of the publication of research results generated by a clinical trial. The

information regarding this trial will be made publicly available on the internet at www.clinicaltrials.gov.

12.6 Protocol Amendments

Before study initiation, the Sponsor (or designee) must have written and dated approval/favorable opinion from the REB/IRB/Independent Ethics Committee (IEC) and Health Canada (HC) (if applicable) for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other written information to be provided to participants. The Sponsor should also provide the REB/IRB/IEC and HC (if applicable) with a copy of the Investigator Brochure, Product Monograph, etc. (as applicable).

The Sponsor or designee should provide the REB/IRB/IEC and HC (if applicable) with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

13. CRITERIA FOR TERMINATION OF TRIAL

The Sponsor (or designee) has the right to close this study (or, if applicable individual segments thereof at any time, which may be due but not limited to the following reasons:

13.1 Futility

If the study conduct (e.g. recruitment rate, drop-out rate, data quality, protocol compliance) does not suggest a proper completion of the study within a reasonable time frame the Sponsor may consider terminating the trial. This will be done in consultation with the DSMB.

13.2 Safety

If risk-benefit ratio becomes unacceptable owing to, for example,

- Safety findings from this study (e.g. SAEs);
- Results of any interim analysis
- Results of parallel clinical studies
- Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

13.3 Efficacy

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. REB; competent authorities; study centre(s)) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.
- In case of a partial study closure, ongoing participants, including those in post study follow-up, must be taken care of in an ethical manner

14. PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Principal Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. Authors of the manuscript and abstracts will include at least the Principal

Investigator (as first author) and co-investigators who have i) included eligible patients in the trial (by order of inclusion) or ii) contributed significantly to the design, conduct and data interpretation regarding companion basic science studies.

The data collected during this study are confidential.

15. REFERENCES

Beauchamp E, et al. Targeting N-myristoylation for therapy of B-cell lymphoma. *Nature Communications*. 11:5248 (2020).

Weickert Mt et. al. Nonclinical efficacy and toxicity and selection of a safe clinical starting dose for an NMT inhibitor in development for hematological malignancies. ASH 2020 Meeting, *Blood*, abstr 141910.

Steven H., et. al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 127:2375-2390 (2016).

16. LIST OF APPENDICES

Appendix A. Eastern Cooperative Oncology Group Scale for Performance Status Grade Description

0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, officework).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix B. Response Evaluation Criteria In Solid Tumors (RECIST Version 1.1)

The following information is extracted/summarized from Eisenhauer, 2009, New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version 1.1). Please refer to the primary reference for further information.

Definitions

At screening, tumor lesions/lymph nodes will be categorized as measurable or non-measurable.

Measurable Disease

Tumor Lesions. Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Choosing Target Lesions

- Select up to 5 lesions (up to 2 per organ).
- Select largest reproducibly measurable lesions.
- If the largest lesion cannot be measured reproducibly, select the next largest lesion which can be.
- Add up longest diameters (LD) of non-nodal lesions (axial plane).
- Add short axis diameters of nodes.
- This is the sum of the longest diameters (SLD).

Nontarget Lesions

- All other sites of disease present at baseline and not classified as target lesions will be classified as nontarget lesions, including any measurable lesions that were not chosen as target lesions.
- It is possible to record multiple nontarget lesions involving the same organ as a single item on the eCRF (eg, “multiple enlarged pelvic lymph nodes”).
- Measurements are not required but these lesions should be noted at baseline and should be followed as “present,” “absent,” or “unequivocal progression.”

Determining Response

- Assess at baseline and on study with consistent modalities (CT, MRI, PET/CT).
  – Measure target lesions and calculate SLD.
  – Visually assess nontarget lesions.
  – Search for new lesions.
  – Combine these assessments into the overall response.

Target Lesion Response

Complete response (CR)	• Disappearance of all extranodal target lesions. • All pathological lymph nodes must have decreased to <10 mm in short axis.
Partial response (PR)	• At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	• SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest). • SLD must also demonstrate an absolute increase of at least 5 mm. (2 lesions increasing from, for example, 2 mm to 3 mm, does not qualify).
Stable disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Nonevaluable (NE)	• One or more lesions cannot be evaluated because of missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (eg, PD based on other findings).

Abbreviations: SLD, sum of the longest diameters.

Nontarget Lesion Response

Complete response (CR)	• Disappearance of all extranodal nontarget lesions. • All lymph nodes must be nonpathological in size (<10 mm short axis). • Normalization of tumor marker level.
Non-CR/non-PD	• Persistence of 1 or more nontarget lesions(s) and/or maintenance of tumor marker level above the normal limits.
Progressive disease (PD)	• Unequivocal progression of existing nontarget lesions (subjective judgment by experienced reader).
Unable to evaluate (UE)	• One or more lesions cannot be evaluated because of missing data or poor image quality unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response (eg, PD based on other findings).

New Lesions

- Should be unequivocal and not attributable to differences in scanning technique or findings which may not be a tumor (does not have to meet criteria to be “measurable”).
- If a new lesion is equivocal, continue to next time point. If confirmed then, PD is assessed at the date when the lesion was first seen.
- Lesions identified in anatomic locations not scanned at baseline are considered new.
- New lesions on ultrasound should be confirmed on CT or MRI.

Evaluation of Overall Time Point Response for Patients With Measurable Disease at Baseline

Abbreviations: CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; NE, nonevaluable.

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Appendix C. The Lugano Classification Criteria for the Evaluation of Non-Hodgkin Lymphoma

The following information is extracted/summarized from Cheson, 2014, Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.

Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increase FDG uptake
		Nonavid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, liliary lesions, nodules
		Nonavid disease	CT	> 13cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Nonavid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT*, biopsy	Lymphoma involvement

CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; MRI = magnetic resonance imaging; PET = positron emission tomography.
* PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake	Not applicable

	compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

* A score of 3 in many Subjects indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

† PET 5PS:

1, no uptake above background;

2, uptake < mediastinum;

3, uptake > mediastinum but < liver;

4, uptake moderately > liver;

5, uptake markedly higher than liver and/or new lesions;

X, new areas of uptake unlikely to be related to lymphoma.