TITLE PAGE

Protocol title: A Phase 1/2a, Open-label, Dose-escalation, Dose-expansion, Parallel Assignment Study to Evaluate the Safety and Clinical Activity of PBCAR20A in Study Subjects with Relapsed/Refractory (r/r) Non-Hodgkin Lymphoma (NHL) or r/r Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

Protocol number: PBCAR20A-01 (version 5.0)

Product: PBCAR20A allogeneic anti-CD20 chimeric antigen receptor (CAR) T cells

Sponsor: Precision BioSciences, Inc.

Legal registered address:

302 East Pettigrew Street

Dibrell Building, Suite A-100

Durham, North Carolina 27701

Regulatory agency identifying number(s): IND 19190

Protocol date: 10FEB2021

Confidentiality statement

SIGNATURE PAGE

Sponsor's approval

The protocol has been approved by Precision BioSciences, Inc.

Sponsor's authorized officer:

[redacted]

Digitally signed by [redacted]
Date: 2021.02.10 09:19:56 -05'00'

Date

Precision BioSciences, Inc.
302 East Pettigrew Street
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INVESTIGATOR'S AGREEMENT

I have read the PBCAR20A-01 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed name of investigator

_____

Signature of investigator

_____

Date

STUDY CONTACT LIST

Table 1: Key study contact information

Role in study/purpose	**Name/title/affiliation**	**Telephone number and e-mail address**
Serious Adverse Event Reporting	Precision BioSciences Pharmacovigilance	Email [redacted]
Medical monitor	[redacted] IQVIA Biotech	Phone: [redacted] E-mail
Study manager	[redacted] IQVIA Biotech	Phone: [redacted] E-mail:
Precision BioSciences medical representative	[redacted] Precision BioSciences, Inc.	Mobile [redacted] E-mail:

SYNOPSIS

Name of sponsor/company:
Precision BioSciences, Inc.

Name of investigational product:
PBCAR20A allogeneic anti-CD20 chimeric antigen receptor (CAR) T cells

Name of active ingredient:
PBCAR20A allogeneic anti-CD20 CAR T cells

Title of study:
A Phase 1/2a, Open-label, Dose-escalation, Dose-expansion, Parallel Assignment Study to Evaluate the Safety and Clinical Activity of PBCAR20A in Subjects with Relapsed/Refractory (r/r) Non-Hodgkin Lymphoma (NHL) or r/r Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

Study centers: Approximately 10-15 study sites in the United States.

Objectives:

Primary:

Phase 1

To evaluate the safety and tolerability of PBCAR20A in subjects with r/r cluster of differentiation (CD) 20-positive ($CD20^+$) NHL including r/r $CD20^+$ CLL/SLL and find an appropriate dose to optimize safety and efficacy.

Phase 2a

Evaluate initial efficacy and safety of PBCAR20A in subjects with $CD20^+$ NHL, specific to the population described by the inclusion/exclusion criteria

Secondary:

Phase 1

To evaluate the clinical activity of PBCAR20A in subjects with r/r $CD20^+$ NHL including r/r $CD20^+$ CLL/SLL.

Phase 2a

To characterize the pharmacologic properties and evaluate the safety, tolerability, and clinical benefit of PBCAR20A treatment regimens in subjects with $CD20^+$ r/r NHL and to generate hypotheses for studies to definitively demonstrate efficacy.

Criteria for evaluation:

Safety:

- Identification of the maximum tolerated dose (MTD) based on the incidence of dose-limiting toxicities (DLTs)

Clinical activity:

- Objective response rate (ORR=CR+PR):
  - NHL: Lugano 2016 criteria

- CLL/SLL: International Workshop on Chronic Lymphocytic Leukemia 2018 guidelines

- Duration of Response (DOR) – defined as the duration (days) from first response to disease progression
- Progression-free survival (PFS)
  - Defined as the duration (days) from Day 0 to disease progression or death
- Incidence of AESI, SAEs, and DLTs related to the investigational product

Methodology:

This is a Phase 1/2a, nonrandomized, open-label, dose escalation, and dose-expansion study to evaluate the safety and clinical activity of PBCAR20A in adult study subjects with r/r $CD20^+$ NHL, including r/r $CD20^+$ CLL/SLL, and to identify a treatment regimen to optimize clinical efficacy while maintaining a favorable safety profile.

The Phase 1 portion of the study will enroll and treat all subjects as one cohort.

Three treatment arms are incorporated into Phase 2a to evaluate the effects of alternative dosing regimens in specific NHL subpopulations. Evaluation criteria will include PBCAR20A cell expansion and persistence as well as clinical activity and safety profile.

All subjects will receive assigned lymphodepletion and PBCAR20A dose. Please refer to the Pharmacy Manual for the specific lymphodepletion regimen as it may be modified if satisfactory CAR T-cell expansion is not observed; lymphodepletion status will be discussed between the Sponsor Medical Monitor, Principal Investigators, and contract research organization Medical Monitor.

On Day 0 of the Treatment Period, all subjects will receive an intravenous (IV) infusion of PBCAR20A. After the DLT evaluation has been completed, subjects may be considered for retreatment if there is evidence of clinically meaningful tumor response to initial dose of PBCAR20A followed by documented either a disease progression or residual disease at subsequent visit; the criteria and procedures for retreatment are described in the protocol.

Phase 1 (dose escalation):

In Phase 1, up to 3 escalating dose levels will be enrolled and treated sequentially, with the possibility of a single de-escalation dose. Within each dose level, up to 6 subjects will be treated with PBCAR20A using a standard 3 + 3 design. The starting dose of PBCAR20A will be 1×10^6 CAR T cells/kg body weight. Subjects in subsequent dose levels will be treated with escalating doses up to a flat dose of 480×10^6 CAR T cells. If no MTD is reached additional dose levels may be explored.

The first treated subject in each dose level (including the dose de-escalation level, i.e., Dose -1) will be observed for 14 days for safety before any subsequent subject receives any study treatment to provide an adequate safety monitoring window. Once the first subject in each dose level has completed Day 14 of dosing with no DLTs, any subsequent subjects can be enrolled without delays into that dose level.

A DLT is defined as any treatment-emergent adverse event (TEAE) that meets the criteria specified. If a DLT is observed in ≤1 of 3 subjects at a given dose level, up to 3 additional subjects (for a total of up to 6 subjects) may be enrolled and treated at that dose level. When 3 additional subjects are added to the dose group, the dose will be increased to the next dose level if ≤1 of 6 subjects experience a DLT. If ≥2 of the 3 to 6 subjects in a dose group experience DLTs, the MTD has been exceeded, and up to 3 additional subjects (for a total of 6) will be treated at the previous (lower) dose level.

Dose escalation may proceed once safety of the current dose level has been established, which is dependent upon the last subject enrolled in the current dose level completing the 28-day DLT evaluation period.

The MTD in this study is defined as the highest dose at which ≤1 of 6 study subjects experiences a DLT. If the MTD is not exceeded, the sponsor will choose the recommended Phase 2a dose based on observations of clinical efficacy, safety, and/or cell kinetics.

The investigators, medical monitor, and sponsor, designated as the Safety Review Committee (SRC), will monitor and convene to review safety data, including any delayed toxicities caused by PBCAR20A, at regular intervals to discuss any unexpected significant toxicities and to determine whether dose escalation is appropriate.

After the conclusion of Phase 1, the SRC will convene to determine whether Phase 2a of the study can proceed.

If DLTs are found to occur predominantly in one subtype of NHL subjects (i.e., those with indolent lymphoma, including follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and marginal zone lymphoma or aggressive lymphoma, such as diffuse large B cell lymphoma, PMBCL, Burkitt lymphoma, and other high grade T cell lymphomas), the possibility of separating the cohorts for dose escalation may be explored.

For characterization of the pharmacology, safety profile, and clinical benefit profile, up to 18 subjects total may be enrolled in any given dose level for which safety has been established (i.e., ≤1 of 6 subjects experiences a DLT). These additional subjects (any subjects after subject 6) will not be considered for determination of the MTD and can be enrolled without delays into that dose level. Additionally, these subjects may receive modified lymphodepletion regimens as described in the Pharmacy Manual to evaluate regimens which may increase anti-tumor effect and improve PBCAR20A cellular kinetics.

All subjects are monitored for DLTs and AEs during the Treatment Period through Day 28.and will continue to be monitored for safety after Day 28 until death, disease progression, stem cell transplant, withdrawal of consent, or Day 360, whichever occurs first.

Phase 2a (dose expansion):

Upon selection of the recommended Phase 2a dose (RP2D) and preferred lymphodepletion regimen, specific populations (defined by inclusion/ exclusion criteria for Arms A, B and C in the full protocol) will be enrolled to characterize clinical efficacy, safety, and pharmacology in that population.

Long-term follow-up study:

Study subjects who receive a dose of PBCAR20A will be followed in a separate long term follow up (LTFU) study after exiting this study (due to either discontinuation or completion). The LTFU study procedures will be described in a separate protocol.

Number of subjects (planned):

Phase 1 (dose escalation): Approximately 9 to 30 evaluable study subjects are planned to be enrolled.

Evaluable study subjects for the primary variable assessment of safety and tolerability, related to the incidence of DLTs, are defined as those who either complete their treatment period through Day 28 or experience a DLT. Non-evaluable study subjects will be replaced.

Phase 2a (dose expansion): Approximately up to 20 subjects are planned to be enrolled in any active Phase 2a arm. Any arm may be discontinued if evidence of futility (e.g., unexpectedly low ORR) is observed. A realistic expectation for enrollment is approximately 40 subjects.

Diagnosis and main criteria for inclusion:

Study subjects are eligible to be included in the study only if all of the following criteria apply:

Disease characteristics

Criteria for NHL (Phase 1):

1. Subject has r/r $CD20^+$ B-cell NHL that is histologically confirmed by archived tumor biopsy tissue from the last relapse and corresponding pathology report. Alternatively, if at least 1 site is accessible at Screening, the subject's diagnosis will be confirmed by pretreatment biopsy (excisional when possible). If a subject never had a complete response (CR) during prior lines of therapy, a sample from the most recent biopsy is acceptable.
2. Measurable or detectable disease (positron emission tomography [PET]-positive) with evidence of disease progression after most-recent therapy according to the Lugano classification.
3. Primary refractory disease or r/r disease after treatment with 2 prior regimens, unless per standard of care treatment guidance (e.g., National Comprehensive Cancer Network [NCCN]) no second line therapy of known benefit exists. Subjects including but not limited to those with the following types of lymphoma and have received the associated standard therapies are eligible:
    a. Primary mediastinal B-cell lymphoma (PMBCL)/follicular lymphoma (FL) including Grade 3B or transformed FL/high-grade B-cell lymphoma/diffuse large B-cell lymphoma (DLBCL) including Richter's transformation. Subjects must have received rituximab or other anti-CD20 antibody and anthracycline-based chemotherapy. All subjects should be evaluated for approved anti-CD19 CAR T-cell therapy when applicable.
    b. Indolent B-cell lymphoma (Grades 1, 2, and 3A)/transformed CLL (Richter's)/marginal zone lymphoma. Subjects must have received 2 prior lines of systemic therapy including an alkylator (e.g., bendamustine, cyclophosphamide/vincristine/ prednisone) plus an anti-CD20 antibody and have had documented disease progression.
    c. Subjects with r/r Burkitt's lymphoma must have failed 1 prior therapy.
    d. MCL. Subjects must have received 2 prior lines of systemic therapy including chemotherapy (bendamustine/rituximab; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); or Nordic-type regimen) with or without autologous stem cell transplant (ASCT) and a Bruton's tyrosine kinase (BTK) inhibitor (e.g., ibrutinib, acalabrutinib) and have had documented disease progression.

Criteria for CLL/SLL (Phase 1):

4. Diagnosis of $CD20^+$ CLL with indication for treatment based on the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines and clinically measurable disease or $CD20^+$ SLL (lymphadenopathy and/or splenomegaly and $<5 \times 10^9$ $CD19^+$ and $CD5^+$ clonal B cells/L in peripheral blood at diagnosis) with measurable disease that is biopsy-proven SLL.
5. Subjects with CLL/SLL must have previously progressed following at least 2 prior lines of systemic targeted therapy including a BTK inhibitor and venetoclax ± rituximab.

Criteria for Phase 2a Arm A:

6. Diagnosis of $CD20^+$ CLL/SLL for which subject is currently receiving, and has been receiving for the past 12 months, ibritunib therapy as standard of care, regardless of line of therapy, with best response of partial response or stable disease (no CR or CRi). Subjects must have high risk disease, as defined by deletion 17p or TP53 mutation.

Criteria for Phase 2a Arm B:

7. Diagnosis of $CD20^+$ DLBCL with PET/CT indicating a partial response, but not a complete response, per Lugano 2016 criteria (Cheson JCO 2016), after completion of upfront chemoimmunotherapy (R-CHOP, per NCCN 2020 NHL Guidelines). Subjects who had refractory disease to (progressive disease through) upfront treatment are not eligible.

Criteria for Phase 2a Arm C:

8. Diagnosis of $CD20^+$ high-grade B cell lymphoma after previous treatment with autologous CD19-targeted CAR T therapy, regardless of response.

Criteria for all subjects (Phase 1 and 2a):

9. Subject has $CD20^+$ tumor. Note: If the tumor is CD20-negative by flow cytometry, it should be evaluated by immunohistochemistry as flow assays may result in false negatives due to competition with CD20-targeting treatment antibodies (e.g., rituximab).
10. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.
11. Subject has adequate bone marrow, renal, hepatic, pulmonary, and cardiac function defined as:
    a. Estimated glomerular filtration rate >30 mL/min/1.73 m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation). A 24-hour urine collection for creatinine clearance may be used at the investigator's discretion.
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels both ≤3 times the upper limit of normal (ULN), unless there is suspected disease (tumor) in the liver.
    c. Total bilirubin <2.0 mg/dL, except in subjects with Gilbert's syndrome, who must have total bilirubin ≤3 × ULN, or except those with disease (tumor) in the liver.
    d. Platelet count ≥50,000/μL and ANC of ≥1000/ μL. Transfusions within 14 days of screening are not allowed, except for patients in B-ALL or NHL cohorts with high marrow disease burden (>70%) in which case it must be discussed with medical monitor. In the case of extensive bone marrow disease burden, adequate bone marrow recovery after prior treatment is required to be documented.
    e. Left ventricular ejection fraction (LVEF) >45% as assessed by an echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan performed within 1 month before starting lymphodepleting chemotherapy. The ECHO results performed within 6 months before Screening and at least 28 days after the last cancer treatment may be acceptable if the subject has not received any treatment with cardiotoxicity risks.
    f. No evidence of pericardial effusion or pleural effusion causing clinical symptoms and needing immediate intervention. Any known effusion must be stable without need for drainage within 2 weeks of enrollment.
    g. Baseline oxygen saturation >92% on room air.

Subject characteristics

12. Subject must be 18 years of age or older at the time of signing the informed consent form.
13. Any sex.

14. All subjects must be willing to practice birth control and refrain from donating sperms or oocytes from the time of enrollment in this study through 3 months after receiving the study treatment.
15. Women of childbearing potential (WOCBP) must be tested negative for pregnancy at Screening because of the potentially harmful effects of the preparative chemotherapy to the fetus. The WOCBP are defined as any women who are not postmenopausal or who have not had a hysterectomy. Postmenopausal is defined as women over the age of 55 years who have not had a menstrual period for at least 1 year.
16. Capable of giving signed informed consent.

Exclusion criteria:

Subjects are excluded from the study if any of the following criteria apply:

17. Requirement for urgent therapy due to mass effects such as bowel obstruction, spinal cord, or blood vessel compression.
18. Any history of central nervous system (CNS) disease. If active CNS involvement is suspected, negative imaging(CT or MRI) and negative lumbar puncture are required at Screening.
19. Subject has had a malignancy, besides the malignancies of inclusion (B-cell NHL or CLL/SLL), that in the investigator's opinion, has a high risk of relapse in the next 2 years.
20. Recent, clinically significant fungal, bacterial, viral, protozoal, or other infection requiring therapeutic anti-microbial medications within 7 days of lymphodepletion. Note: subjects with elevated or rising C-reactive protein (CRP) must undergo infectious disease (ID) workup and recommendations must be discussed with the medical monitor. CRP must be trending toward the normal range for the laboratory. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if the subject is responding to active treatment and with medical monitor approval.
21. Any form of primary immunodeficiency (e.g., severe combined immunodeficiency disease).
22. History of human immunodeficiency virus (HIV) infection.
23. Active hepatitis B or hepatitis C confirmed by polymerase chain reaction (PCR). Subjects testing positive for inactive hepatitis B will be allowed to enroll if on prophylactic treatment.
24. Any known uncontrolled cardiovascular disease at the time of Screening that, in the investigator's opinion, is clinically significant and renders the subject ineligible.
25. History of hypertension crisis or hypertensive encephalopathy within 3 months prior to Screening.
26. History of severe immediate hypersensitivity reaction to any of the agents used in this study.
27. Presence of a CNS disorder that, in the opinion of the investigator, renders the subject ineligible for treatment.
28. Abnormal findings during the Screening Period or any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardize the subject's safety.
29. History of a genetic syndrome such as Fanconi anemia, Kostmann syndrome, Shwachman -Diamond syndrome, or any other known bone marrow failure syndrome.

Prior/concomitant therapy (Phase 1 and 2a)

30. Subjects who have received ASCT within 45 days of Screening are excluded.
31. Subjects who have received systemic corticosteroid (greater than physiologic replacement) therapy for at least 7 days prior to initiating lymphodepletion chemotherapy are excluded.
32. Subjects who have received a live vaccine within 4 weeks before Screening are excluded. Non-live virus vaccines are not excluded.
33. Subjects undergoing Radiotherapy to target lesions within 4 weeks before Screening are excluded.

34. Subjects who have an indwelling catheter (i.e., pleural, peritoneal, pericardial as well as biliary and ureteral stents) are excluded. This does not apply to intravenous lines.

Other exclusions (Phase 1 only)

35. Subjects are excluded unless there has been documented progression of the disease after prior most recent systemic anti-cancer therapeutic agents and resolution of adverse events caused by their administration.

Other exclusions (Phase 2a Arm A)

36. Subjects are excluded specifically from Arm A if they have:
    a. CR has been achieved with Previous ibrutinib therapy. Note: progression is not required for enrollment if stable disease or partial response has been achieved and maintained.
    b. Ongoing grade ≥ 2 non-hematologic toxicity related to ibrutinib.
    c. High-grade transformed disease (e.g., Richter's transformation)

Other exclusions (Phase 2a Arm B)

37. Subjects are excluded specifically from Arm B if they have a diagnosis of transformed high grade lymphoma (e.g., Richter's transformation or transformed follicular lymphoma).

Other exclusions (Phase 1 and 2a)

38. Pregnant or breastfeeding women.
39. In the investigator's judgment, the subject is unlikely to complete all protocol required study visits or procedures, including follow-up visits, or is unlikely to comply with the study requirements for participation.
40. Any mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study, and/or evidence of an uncooperative attitude.

Investigational product, dosage, and mode of administration:

PBCAR20A for IV infusion.

Phase 1:

Single escalating dose at 1×10^6 or 3×10^6 CAR T cells/kg body weight and flat doses of 240×10^6 or 480×10^6 CAR T cells. A de-escalation dose (Dose -1) at 3×10^5 cells/kg body weight may be tested if necessary.

Phase 2a:

Arms in Phase 2a will use a dose at or below the MTD as determined in Phase 1. The dose will be determined based on PK/PD analysis, safety evaluation, and preliminary evidence of clinical activity. Refer to the Pharmacy Manual for the specific dosing regimen to be used in each Arm in Phase 2.

Study duration:

Maximum: 389 days

- Screening: Days -28 to -1

- Treatment period: Days 0 to 28
- Follow-up: up to Day 360

Reference therapy, dosage and mode of administration:

None.

Statistical methods:

For Phase 1, dose escalation of PBCAR20A will follow a standard 3 + 3 design with sequential groups of 3 study subjects treated with incrementally higher doses of PBCAR20A until a DLT is observed and the MTD is established.

For Phase 2a, up to 20 subjects will be enrolled into any Arm for dose expansion and preliminary evaluation of efficacy at the RP2D for a total of up to 60 subjects. The data collected from subjects enrolled in the dose expansion will be used to confirm safety, explore potential biomarkers, and evaluate preliminary efficacy of PBCAR20A. Descriptive statistics will be used to describe the efficacy, safety, and biomarker endpoints.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

ACT	adoptive cell therapy
AE	adverse event
AESI	adverse events of special interest
ALL	acute lymphocytic leukemia
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
B-ALL	B-cell acute lymphoblastic leukemia
BID	Twice daily
BMA	bone marrow aspiration
BSA	body surface area
BTK	Bruton's tyrosine kinase
CAR	chimeric antigen receptor
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CGT	Cell and Gene therapy
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DoR	duration of response
DRE	disease-related event

ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
FL	follicular lymphoma
GCP	Good Clinical Practice
GvHD	graft-versus-host disease
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
LD	lymphodepletion
LDH	lactate dehydrogenase
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

MUGA	multiple gated acquisition
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PC	pentostatin + cyclophosphamide
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PMBCL	primary mediastinal B-cell lymphoma
PR	partial response
PT	preferred term
qPCR	quantitative polymerase chain reaction
QTcF	QT interval corrected by Fredericia
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
r/r	relapsed/refractory
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
scFv	single-chain variable fragment
SD	stable disease
SLL	small lymphocytic lymphoma
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell count

WOCBP	women of childbearing potential

1. INTRODUCTION

PBCAR20A is an allogeneic antihuman-cluster of differentiation (CD) 20 chimeric antigen receptor (CAR) T-cell product derived from qualified donor T cells that have been genetically edited to remove the expression of the endogenous T-cell receptor (TCR). Insertion and expression of the anti-CD20 CAR provides the ability to specifically target and bind CD20-positive ($CD20^+$) cells, and the removal of the TCR significantly reduces the possibility of developing graft-versus-host disease (GvHD) when it is administered to human leukocyte antigen (HLA)-mismatched subjects. PBCAR20A is being developed as an off-the-shelf treatment for certain B-cell malignancies.

1.1. Study rationale

PBCAR20A is a Phase 1/2a, first-in-human study of PBCAR20A designed to evaluate the safety and clinical activity and optimize the treatment regimen of PBCAR20A in adult study subjects with relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), or small lymphocytic lymphoma (SLL). As described in the following sections, PBCAR20A offers potential therapeutic benefits compared with autologous CAR T-cell treatment for certain blood cancers.

1.2. Background

1.2.1. Drug development

During the past 10 years, advances in molecular and cellular biology have led to the creation of genetically modified T cells in which a CAR is inserted and stably expressed in a T lymphocyte. CAR T cells designed to target CD19, an antigen present on B lymphocytes in all stages of development except for terminally differentiated plasma cells, have been used to treat subjects with $CD19^+$ tumors. Autologous CAR T-cell therapies have progressed into clinical trials, with recent Food and Drug Administration (FDA) approvals for tisagenlecleucel (Kymriah™) to treat subjects with r/r B-cell acute lymphoblastic leukemia (B-ALL) up to 25 years of age (August 2017) and adult subjects with r/r large B-cell lymphoma (May 2018). Axicabtagene ciloleucel (Yescarta™) has also been approved to treat r/r large B-cell lymphoma (October 2017). A Phase 1/2a study evaluating the safety and clinical activity of PBCAR0191, an allogeneic antiCD19 CAR T-cell therapy, in adults with r/r B-ALL and r/r NHL is currently ongoing (Investigational New Drug [IND] 18396).

There are drawbacks to autologous CAR T-cell therapy. First, it can be difficult to obtain enough quality T cells from some subjects with cancer to produce a therapeutic product, particularly from subjects who have failed several previous lines of treatment. Second, subjects need to undergo apheresis and then wait several weeks while their autologous drug product is being manufactured. Bridging chemotherapy is often required during this waiting period, which can result in chemotherapy-related toxicities that can render the patient too sick to receive their CAR T-cell therapy. In addition, autologous CAR T-cell therapies are inherently heterogeneous. Using qualified donor lymphocytes as the starting material to generate CAR T cells can mitigate these problems.

Approximately half of subjects with relapsed leukemia after anti-CD19 therapy lose CD19 expression and require alternative treatments (Maloney, 2012; Sotillo et al, 2015; Gardner et al,

2016). CD20 is an attractive target because it is expressed in over 90% of B-cell lymphomas, does not internalize upon binding, and is stable on the cell surface (Press et al, 1989; Reff et al, 1994). The CD20 antigen is another well-established target for B-cell malignancy treatments, as demonstrated by extensive clinical trials with rituximab, an anti-CD20 antibody. Thus, CAR T-cell therapy directed against CD20 provides an alternative option for subjects who relapse from anti-CD19 therapy.

PBCAR20A is produced in bulk from T cells derived from qualified donors to generate hundreds of vials of drug product that is stored frozen and available off-the-shelf. Therefore, subjects will not need to undergo apheresis and bridging chemotherapy while they wait for an autologous CAR T-cell product to be manufactured and shipped to the treatment center for administration. In addition, the source of the starting material for PBCAR20A production, i.e., T cells from qualified donors that meet prespecified criteria, allows for better control of the CAR T-cell manufacturing process and production of a more homogenous and better-defined drug product. However, allogeneic T cells can lead to the development of GvHD when they are infused into HLA-mismatched recipients. In PBCAR20A, gene-editing technology is used in donor T cells to prevent the expression of the native TCR; thus, reducing or eliminating the likelihood of GvHD resulting from administration of the allogeneic CAR T-cell product. Transduction leads to insertion and expression of the CD20-targeting CAR transgene, thereby redirecting the specificity of the T cells with the goal of creating off-the-shelf CAR T-cell products that can be consistently manufactured and safely administered to any patient when needed.

In this study, the allogeneic CAR T-cell product, PBCAR20A, will be administered to adult study subjects with r/r $CD20^+$ NHL including r/r $CD20^+$ CLL/SLL.

1.2.2. Place in treatment – Phase 1

Hematologic B-cell malignancies comprise a large, heterogeneous group of lymphoproliferative disorders that range from the slow-growing, indolent NHLs (e.g., follicular lymphoma [FL], SLL, and CLL) to more aggressive forms (e.g., diffuse large B-cell lymphoma [DLBCL] and B-ALL) (Boffetta, 2011; Hallek, 2015). B-cell disorders represent more than 85% of all NHL cases (Howlader et al, 2016) and 75% to 80% of all types of acute lymphocytic leukemia (ALL) (Chiaretti et al, 2014). The NHL incidence rates are higher among the elderly population than in the younger population, with diagnoses of NHL most common among subjects 65 to 74 years of age (Howlader et al, 2016). The most common subtype of NHL is DLBCL, which accounts for 30% to 40% of all NHL cases (Al-Hamadani et al, 2015). FL is the second most common form of NHL, accounting for about 20% to 35% of all NHL cases; approximately 15% of FL cases are Grade 3B (Shustik et al, 2011). CLL/SLL is the third most commonly diagnosed and accounts for approximately 25% to 30% of leukemias in the United States; CLL is the most common type of leukemia in adults >19 years of age and accounts for about 35% to 40% of cases (Seigel et al, 2019).

Typically, front-line anthracycline-based immunochemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or similar regimens are used to treat DLBCL, FL Grade 3B, and Stage III to V mantle cell lymphoma (MCL). While R-CHOP is expected to provide benefits to more than 50% of newly diagnosed subjects, at least one-third will be refractory to first-line chemotherapy, achieve only partial remission, or relapse

after achieving complete remission (Habermann et al, 2006; Sud and Friedberg, 2008; Fakhri and Kahl, 2017; Casulo et al, 2015).

Management of B-cell lymphomas after failure of immunochemotherapy is challenging. While salvage chemotherapy followed by autologous hematopoietic cell transplant is an option, it is associated with significant toxicities that would preclude many subjects with comorbidities or advanced age. Thus, the prognosis of r/r B-cell lymphoma as a group remains poor (Casulo et al, 2015; Rovira et al, 2015; Van Den Neste et al, 2016; Vose, 2017). In adult subjects with r/r large B-cell lymphoma, axicabtagene ciloleucel (Yescarta™) showed an objective response rate (ORR) of 72% and a median duration of response (DoR) of 9.2 months and tisagenlecleucel (Kymriah™) had an ORR of 50% and the DoR was not reached, indicating that CAR T-cell therapy may significantly improve the prognosis for these subjects.

CLL is the most common type of leukemia in adults; the median age of diagnosis is 70 years and the 5-year survival rate is 84% (Surveillance, Epidemiology, and End Results [SEER]-Medicare Linked Database, 2019). CLL is a biologically heterogeneous disease, and morphologic, immunologic, cytogenetic, biochemical, and molecular genetic characterization of leukemia lymphoblasts are needed to establish the diagnosis and classify the subtypes. Subjects with CLL have had limited success with autologous CAR T-cell therapies, likely due to the T-cell exhaustion associated with this malignancy (Riches et al, 2013). Thus, the administration of healthy donor T cells in allogeneic CAR T-cell therapy has the potential to overcome current challenges in CLL treatment.

As noted above, allogeneic CAR T-cell therapy offers potential advantages compared with autologous CAR T-cell therapies. The activity of PBCAR20A has been investigated in immunodeficient mice. In a subcutaneous B-cell lymphoma model, all mice in the control group showed evidence of increasing tumor burden and only 1 of 5 mice survived past Day 22; at Day 56, 3 of the 5 mice treated with PBCAR20A survived and were tumor free. These results show potent in vivo clearance of $CD20^+$ tumor cells by PBCAR20A and support its development as an allogeneic CAR T-cell therapy.

Based on this context, PBCAR20A will be initially evaluated (Phase 1) for safety in subjects with no standard treatment options. After a recommended Phase 2 dose (RP2D) and lymphodepletion regimen are established, other lines of therapy in specific populations may be considered in Phase 2a, based on evidence of efficacy and safety observations that would inform risk/benefit rationale for Phase 2a Arms.

1.2.3. Lymphodepletion

Due to the allogeneic nature of PBCAR20A, it is expected that allogeneic rejection will occur at some point after infusion. At the time of study initiation, it is unknown what the timeframe of rejection will be.

Based on observations with other PBCAR products that have been in the clinic longer than PBCAR20A, such as PBCAR0191, Precision Biosciences has reason to believe that alternative lymphodepletion regimens may be required to maximize expansion and persistence of PBCAR20A. As a result, alternative lymphodepletion regimens are under consideration. Potential regimens are based on historical clinical trial data and/or in vitro evaluations suggesting the selected regimens are likely to reduce rejection of allogeneic cells without reducing the

ability of PBCAR20A to kill target tumor cells. The standard (initial) lymphodepletion strategy is described in Section 1.2.3.1. Alternative lymphodepletion strategies available to subjects in both Phase 1 and Phase 2a are included as options in the pharmacy manual and are described in Section 1.2.3.2, 1.2.3.3, and 1.2.3.4.

1.2.3.1. Standard Lymphodepletion

The initial lymphodepletion regimen is intended for two purposes. First, to provide the known required cytokine support for CAR T cell expansion as previously demonstrated in autologous CAR T clinical trials, and second, to reduce the subject's population of immune cells that might cause allogeneic rejection. It is assumed that T cells will be the main mediators of allogeneic rejection, and that has been confirmed in mixed lymphocyte reactions in vitro using unmatched donor peripheral blood mononuclear cells (PBMC) and PBCAR cells. The regimen employed initially in PBCAR studies, defined below, has resulted in expected results in terms of serum cytokine production and CAR T expansion support. [redacted] The regimen is as follows:

- Fludarabine 30 mg/m^2/day x 3 days (days -5 to -3)
- Cyclophosphamide 500 mg/m^2/day x 3 days (day -5 to -3)
- PBCAR20A full dose on day 0

1.2.3.2. Lymphodepletion Alternative: Enhanced Lymphodepletion

Clinical trials using autologous T cell therapies have previously evaluated higher doses of fludarabine and cyclophosphamide than those outlined above, demonstrating increased cytokine production and prolonged T cell depletion with an acceptable safety profile. One of these regimens, described below, has been evaluated in our PBCAR0191-01 clinical trial:

- Fludarabine 30 mg/m^2/day x 4 days on days -6, -5, -4, and -3
- Cyclophosphamide 1000mg/m^2/day x 3 days on days -5, -4, and -3
- PBCAR20A treatment dose on day 0

To date, in the PBCAR0191-01 trial we have observed close to 100x increase in peak CAR T expansion using this regimen as compared to that observed with the standard lymphodepletion regimen, which is likely due to deeper host (subject) T cell suppression. When plotted over time, this has also resulted in an increased area under the curve of CAR T cells in the peripheral blood of 50x. This results in an approximate 3-7-day delay in T cell recovery as well as recovery of other cell lines in comparison with the standard lymphodepletion fludarabine and cyclophosphamide doses used in this (and the PBCAR0191) trial. This regimen does come with the resulting increased risk of infectious adverse events. As a result, stricter standards have been implemented to assess bone marrow reserve prior to enrollment (in all PBCAR studies), requiring demonstration that no ongoing infections or indwelling catheters that could serve as an infectious source are present as well as adequate platelet counts that cannot be supplemented by

transfusion and adequate neutrophil counts. Prophylactic antibiotics, antivirals, and antifungals are encouraged per institutional standards.

1.2.3.3. Lymphodepletion Alternative: Tolerance induction

Based on the observations of clinical efforts to reduce graft versus host disease (GvHD) in haploidentical allogeneic stem cell transplant, a post-transplant cyclophosphamide (PTCy) regimen may have the potential to selectively target T cells activated against mismatched allogeneic antigens. Indeed, haploidentical allogeneic stem cell transplant after preparative chemotherapy results in clonal expansion of donor T cells against patient normal tissue antigens (allogeneic priming). When this is followed by high dose cyclophosphamide at a specified interval, those expanding T cells are selectively destroyed, which significantly reduces the GvHD complications in this setting (Storb et al, 1970). Following this immunologic rationale, it is possible that a "priming" dose of PBCAR20A may cause allogeneic activation of T cell populations against the allo-antigens in PBCAR20A, providing a window of opportunity to use high dose cyclophosphamide after a low dose of PBCAR20A to reduce allogeneic rejection. Following that, a full dose of PBCAR20A would be administered for full treatment effect. However, it is known that cyclophosphamide alone does not provide adequate cytokine support for CAR T expansion in autologous CAR T studies and that the addition of fludarabine can significantly increase CAR T expansion (Hay et al, 2017). This is also consistent with our observations in our PBCAR0191-01 clinical trial. Therefore, in addition to the high dose cyclophosphamide used in PTCy, this regimen will also include fludarabine 30mg/m^2/day x 3 days. The resulting regimen is:

- PBCAR20A 30 x 10^6 cells (flat dose) on day -7
- Cyclophosphamide 50m/kg/day x 2 days on days -5 and -4
- Fludarabine 30mg/m2/day x 3 days on days -5, -4 and -3
- PBCAR20A treatment dose on day 0

1.2.3.4. Lymphodepletion Alternative: Sirolimus

Because the fludarabine and cyclophosphamide regimens (both standard and enhanced) have effectively resulted in CAR T expansion, those regimens may be best suited to combine with an additional agent that could delay T cell mediated allogeneic rejection. Based on our observations, it is likely that an agent that could prevent T cell rejection could increase peak CAR T expansion and delay rejection, both of which would increase the AUC of PBCAR20A.

Multiple agents are used in clinical practice to prevent T cell mediated allogeneic antigen targeting, specifically to prevent or reduce the severity of GvHD after allogeneic stem cell transplant. Of those agents, sirolimus is known to inhibit GvHD by interfering with the production of Th1 cytotoxic cytokines (Blazar et al, 1998; Arman et al, 2008) This mechanism prevents native T cell receptor (TCR) signaling from inducing T cell activation. However, CAR T cells, including PBCAR20A (and other PBCAR products), do not require native TCR signaling for target engagement, activation, and killing because the signaling motifs are built into the CAR construct. Prior reported preclinical data suggest CAR T cells can function as well or better in the presence of sirolimus compared with the absence of sirolimus (Oldham et al, 2018). Because the balance of positive effects (reducing host T cell allogeneic rejection of PBCAR20A)

would be difficult to assess relative to the potential negative effect (impact on PBCAR20A tumor-killing and expansion capability) and because the risk to the subjects is expected to be lower than severe lymphodepletion using chemotherapy, we seek to explore the impact of sirolimus in the only known relevant model for this combination, in human subjects with active cancer.

Taken together, the net benefit of sirolimus may allow better CAR T efficacy as a result of minor impact on CAR T expansion and killing while significantly delaying CAR T rejection. The resulting regimen is:

- Either standard or enhanced lymphodepletion regimens as described
- PBCAR20A treatment dose on day 0
- Sirolimus 16 mg oral loading dose day 1
- Sirolimus 4 mg/day until day 60*

* Note: 4mg/day maintenance dose may be adjusted up or down based on sirolimus serum levels, with a target serum concentration of 20-30 ng/dL; site staff will be reminded to stop sirolimus dosing immediately if evidence of infection is observed.

1.2.4. Rationale for Phase 2a populations

1.2.4.1. Arm A – PBCAR20A in subjects with CLL/SLL being treated with ibrutinib therapy for at least 12 months

Preclinical and clinical data indicate ibrutinib may be synergistic with CAR T therapy in CLL. Indeed, longer prior treatment with ibrutinib seems to portend greater CAR T cell efficacy in this population (Fraietta et al, 2016). It has been suggested that CAR T cell "consolidation" therapy may be ideally timed after initial response to ibrutinib in advanced CLL (Gauthier et al, 2020; Kater et al, 2020). Based on published literature, the use of PBCAR20A in subjects who have been treated for at least 12 months with ibrutinib may provide substantial benefit by further reducing tumor burden. Due to the decreased tumor burden expected from ibrutinib therapy, it is also possible that the CAR T expansion will not need to reach a high peak, decreasing the risk of CRS and ICANS. Subjects will also be likely to have received less total CD20-targeting therapy over time, increasing the likelihood of target antigen presence at time of treatment. Together, this population may be an ideal opportunity to evaluate the clinical benefit of PBCAR20A.

1.2.4.2. Arm B – PBCAR20A in subjects with high grade DLBCL who did not achieve complete response after 2 cycles of front-line therapy

The clinical benefit of autologous CAR T cells has been linked, retrospectively, to lower tumor burden at baseline. Multiple publications have suggested that peak CAR T expansion relative to baseline tumor burden is closely correlated with likelihood of complete response (CR) and durability of response (Cappell et al, 2020; Locke et al, 2020). Recent clinical data from the Zuma-12 clinical trial (Neelapu, ASH 2020) suggests greater efficacy may be attainable in earlier lines of therapy when tumor burden is lower and there may be less tumor heterogeneity and potential antigen loss. Because CD20 expression can be lost or reduced over time with repeated

treatment with CD20 targeting agents, a deeper and more durable anti-tumor effect may be achieved by using a CD20 targeting CAR T in the earliest therapeutic setting in which an opportunity exists and no conflict with standard of care is present. In this group of patients, who are being treated with front line therapy (R-CHOP) and do not achieve complete response, overall prognosis is poor (Van Den Neste et al, 2015; Klink et al, 2020; Crump et al, 2017; Ekberg et al, 2017; Koh et al, 2018). Additionally, no standard of care is established in this setting, providing an opportunity to evaluate a novel agent that may improve outcomes for these subjects. By selecting subjects in whom initial chemotherapy (R-CHOP) has debulked the initial tumor (PR required for eligibility), and because only limited use of CD20 targeting therapy has been employed, PBCAR20A therapy may result in deep and meaningful clinical response with overall lower risk of adverse events (compared to later stage disease with bulky tumor masses) due to lower initial tumor burden.

1.2.4.3. Arm C – PBCAR20A in subjects with high grade B cell Non-Hodgkin's Lymphoma (NHL) who have previously been treated with autologous CAR T products and have subsequently experienced disease progression

After treatment with commercially available autologous CAR T products, most patients with high grade B cell Non-Hodgkin's lymphoma are left with no treatment options of known benefit, and, in most cases, repeat treatment with autologous CAR T cells is not a viable option due to cost or loss of CD19 expression. As of January 2021, we have enrolled 6 subjects with high grade lymphomas who have previously received autologous CAR T cells. Of those, most (4 of 6, 66.6%) had been documented as being refractory to CD19 CAR T therapy as best response prior to enrollment in the present PBCAR20A study; the remaining subjects were 1 PR and 1 CR. Five of the 6 have now been evaluated for PBCAR20A response to date, with 3 of 5 (60%) achieving partial (2 of 5, 40%) or complete (1 of 5, 20%) response. The patient who reached complete response is in an ongoing complete response after 7 months on study. Arm C will more prospectively explore PBCAR20A treatment effect in this population otherwise lacking treatment options once the RP2D and LD regimen have been defined.

1.3. Benefit/risk assessment

As this will be the first clinical trial of PBCAR20A, the benefit to subjects with NHL and CLL/SLL is not known.

In a Phase 2a study (NCT01735604), an autologous anti-CD20 CAR T immunotherapy demonstrated a significant clinical benefit versus current standard of care in subjects with advanced B-cell lymphomas as measured by ORR, the proportion of subjects with complete response (CR), partial response (PR), and progression free survival, with no significant toxicities (Zhang et al, 2016). Axicabtagene ciloleucel (Yescarta™), an autologous anti-CD19 CAR Tcell immunotherapy, was shown in clinical trials to provide a significant clinical benefit versus current standard of care as measured by complete remission rate and DoR and has been approved for the treatment of adult subjects with r/r large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal Bcell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL arising from FL. Tisagenlecleucel (Kymriah™), an autologous anti-CD19 CAR T immunotherapy, was shown in clinical trials to

provide a significant clinical benefit versus current standard of care as measured by complete remission rate, the duration of CR, and the proportion of subjects with a CR and minimal residual disease (MRD) <0.01% by flow cytometry, and has been approved for treatment of B-ALL that is refractory or in a second or later relapse in subjects up to 25 years of age and in adult subjects with r/r large B-cell lymphoma after ≥2 lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from FL. Toxicities, including serious and life-threatening toxicities associated with development of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), were observed in clinical trials for both of these anti-CD19 CAR T-cell therapies. Such toxicities are associated with the mechanism of action of these drugs and, for most subjects, resolve over a period of days to weeks with appropriate supportive care or, in severe cases, with medical intervention.

The potential of PBCAR0191 to cause GvHD was examined in a xenogeneic immunodeficient NSG mouse model. The NSG mice were sublethally irradiated on Day 1 to stimulate cell damage and tissue repair, which results in the activation of antigen-presenting cells and upregulation of major histocompatibility complex molecules on mouse tissues. On Day 2, the mice were injected with a control vehicle, T-cell control (mock gene-edited, TCR^+ human $CD4^+/CD8^+$ T cells or peripheral blood mononuclear cells [PBMC]), or gene-edited (TCR^-) CAR T cells from the same donor. Animals that received the mock gene-edited or unmanipulated PBMC (TCR^+) donor T cells lost weight and developed clinical symptoms consistent with GvHD. In contrast, all animals that received the gene-edited (TCR^-) CAR T cells behaved similarly to animals that were treated with the control vehicle and continued to gain weight and groom normally showing no behavioral signs of toxicity after recovery from radiation. The findings are supported by a confirmatory study using PBCAR20A and together demonstrate a lack of GvHD upon administration of gene edited CAR T cells.

PBCAR20A is a second generation anti-CD20 CAR T-cell product manufactured using healthy donor T cells as the starting material through a process that preserves naïve and central memory phenotypes and comprises an approximately equal proportion of $CD4^+$ and $CD8^+$ T cells. Although one might expect the nature and severity of toxicities to be similar to those observed for the approved anti-CD19 CAR T-cell products, Yescarta™ and Kymriah™, the uniform composition and phenotype of the CAR T cells within PBCAR20A may result in improved clinical responses. As there are no currently approved anti-CD20 CAR T-cell therapies, PBCAR20A may provide benefit in subjects who have failed autologous anti-CD19 therapies and subjects with CLL who exhibit features of T-cell exhaustion.

PBCAR20A has been reproducibly manufactured to the desired specifications from multiple healthy donors at a commercial manufacturing scale. Multiple batches of PBCAR20A have been evaluated for various parameters to characterize the genetic stability of the product. Importantly, the gene edited- CAR T-cell batches have similar profiles including consistent targeted insertion of the CAR transgene at the intended location within the T-cell receptor alpha constant locus with similar low frequency of translocations and off-target gene-editing between batches. The potential risks of CRS, ICANS, and GvHD will be managed and mitigated during the study (Section 7.3).

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PBCAR20A can be found in the Investigator's Brochure (IB).

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary objective and endpoint

2.1.1. Phase 1

The primary objective of Phase 1 is to evaluate the safety and tolerability of PBCAR20A in subjects with r/r $CD20^+$ NHL including r/r $CD20^+$ CLL/SLL and find an appropriate dose to optimize safety and efficacy.

The primary endpoint is the identification of the maximum tolerated dose (MTD) based on the incidence of dose-limiting toxicities (DLTs).

2.1.2. Phase 2a

The primary objective for Phase 2a is to evaluate initial efficacy and safety of PBCAR20A in subjects with $CD20^+$ NHL, specific to the population described by the inclusion/exclusion criteria

The primary endpoint for each Phase 2a Arm is:

- Phase 2a Arm A – complete response rate as measured by International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 guidelines
- Phase 2a Arm B – complete response rate as measured by Lugano 2016 criteria
- Phase 2a Arm C – objective response rate (ORR) as measured by Lugano 2016 criteria, including partial and complete response rates (PR and CR rates)

2.2. Secondary objective and endpoints

2.2.1. Phase 1

The secondary objective of Phase 1 is to evaluate the clinical activity and safety profile of PBCAR20A in study subjects with r/r $CD20^+$ NHL including r/r $CD20^+$ CLL/SLL.

The secondary endpoints for Phase 1 are:

- ORR:
  - NHL: Lugano 2016 criteria
  - CLL/SLL: International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 guidelines
- Progression-free survival (PFS)
  - Defined as the duration (days) from Day 0 to disease progression or death
- Incidence of AESI, SAEs, and DLTs related to the investigational product

Additional secondary endpoints for Phase 2a only are:

- CAR T-cell persistence:

a. Defined as detectable CAR T cells in the peripheral blood by qPCR and/or flow cytometry at a given study visit time point

2.2.2. Phase 2a

The secondary objectives of Phase 2a are to characterize the pharmacologic properties and evaluate the safety, tolerability, and clinical benefit of PBCAR20A treatment regimens in subjects with r/r $CD20^+$ NHL, including CLL/SLL and to generate hypotheses for studies to definitively demonstrate efficacy.

The secondary endpoints for Phase 2a (all arms) are:

- Duration of Response (DoR) – defined as duration (days) from first date of response until disease progression or death
- Progression-free survival (PFS)
  - Defined as the duration (days) from Day 0 to disease progression or death
- Incidence of AESI, SAEs, and DLTs related to the investigational product

The response criteria are detailed in Section 8.1 and Table 12, respectively.

2.3. Exploratory objectives and endpoints

The exploratory objectives of this study are to evaluate the following:

- CAR T-cell expansion and persistence:
  - Defined as detectable CAR T cells in the peripheral blood by qPCR and/or flow cytometry at a given study visit time point
- Proportion of study subjects who subsequently receive stem cell transplant
- Expansion, trafficking, phenotype, and persistence of PBCAR20A
- Potential development of anti-PBCAR20A immune response
- Immune cell depletion and reconstitution after lymphodepletion and PBCAR20A treatment
- Potential loss of CD20 expression on leukemia/lymphoma cells
- Effect of anti-CD20 antibody levels on efficacy
- Collection of blood and other biological specimens for future research analyses

The exploratory endpoints will be described in the Statistical Analysis Plan (SAP).

3. STUDY DESIGN

3.1. Overall study design

This is a Phase 1/2a, nonrandomized, open-label, dose escalation, and dose-optimization study to evaluate the safety and clinical activity of PBCAR20A in adults with r/r $CD20^+$ B-cell NHL,

including r/r $CD20^+$ CLL/SLL, and identify a treatment regimen to optimize clinical efficacy while maintaining a favorable safety profile. The Phase 1 study schematic and Schedule of Activities (SoA) are shown in Table 2 and Section 3.1.1, respectively.

In this protocol amendment (Version 5.0), specific populations have been defined for potential enrollment in Phase 2a to evaluate the preliminary efficacy of PBCAR20A using the identified RP2D and selected lymphodepletion regimen as well as to further characterize safety profile and correlative biology.

All subjects will receive an intravenous (IV) PBCAR20A on Day 0 of the study. Lymphodepletion chemotherapy will also be administered. The initial lymphodepletion chemotherapy regimen will be composed of fludarabine (30 mg/m^2/day) and cyclophosphamide (500 mg/m^2/day) during the Screening Period from Days -5 to -3. However, the lymphodepletion regimen may be modified if satisfactory CAR T-cell expansion and/or persistence is not observed. The lymphodepletion regimen will be assigned at the time of registration to treatment. Alternative lymphodepletion strategies will only be employed after safety has been established in each dose level. Please refer to the Pharmacy Manual for the specific regimen assigned at the time of registration; the lymphodepletion regimen may be discussed between the Sponsor Medical Monitor, Principal Investigators, and contract research organization Medical Monitor prior to assignment.

For Phase 2a, the treatment regimen is expected to be uniform for all subjects enrolled into each arm.

Specific criteria must be met for repeat lymphodepletion prior to repeat PBCAR20A infusion. In all Phase 1 Dose levels and the Phase 2a Arms, subjects may be considered for retreatment if there is documented clinically meaningful response to the initial treatment with PBCAR20A as determined by the Investigator; the criteria and procedures for retreatment are described in Section 3.7.

3.1.1. Phase 1 (dose escalation):

In Phase 1, 3 escalating dose groups will be enrolled and treated sequentially, with the possibility of a single de-escalation (see Section 3.5). Within each dose group, at least 3 and at most 6 study subjects will be treated with a single dose of PBCAR20A using a standard 3 + 3 design. The starting dose of PBCAR20A will be 1×10^6 CAR T cells/kg body weight. In the absence of DLTs (as described in Section 3.8), subsequent dose groups will be treated with escalating doses to a maximum flat dose of 480×10^6 CAR T cells. If no MTD is reached additional dose levels may be explored.

The first treated subject in each dose level (including the dose de-escalation group, i.e., Dose -1) will be observed for 14 days for safety before any subsequent subject receives any study treatment to provide an adequate safety monitoring window. once the first study subject in each dose level has completed Day 14 after dosing with no DLTs, then subsequent subjects can be enrolled without delays into that dose level.

Dose escalation may proceed once safety of the current dose level has been established, which is dependent upon the last study participant enrolled in the current dose level completing the 28-day DLT evaluation period.

A DLT is defined as any treatment-emergent adverse event (TEAE) that meets the criteria specified in Section 3.8. If a DLT is observed in ≤1 of 3 study subjects at a given dose level, up to 3 additional study subjects (for a total of up to 6 study subjects) may be enrolled and treated at that dose level. When 3 additional study subjects are added to the dose group, the dose will be increased to the next dose level if ≤1 of 6 study subjects experiences a DLT. If ≤2 of the 3 to 6 study subjects in a dose group experience DLTs, the MTD has been exceeded, and up to 3 additional study subjects (for a total of 6) will be treated at the previous (lower) dose level.

The MTD in this study is defined as the highest dose at which ≤1 of 6 study subjects experiences a DLT. If the MTD is not exceeded, the sponsor will choose the recommended Phase 2a dose based on observations of clinical efficacy, safety, and/or cell kinetics.

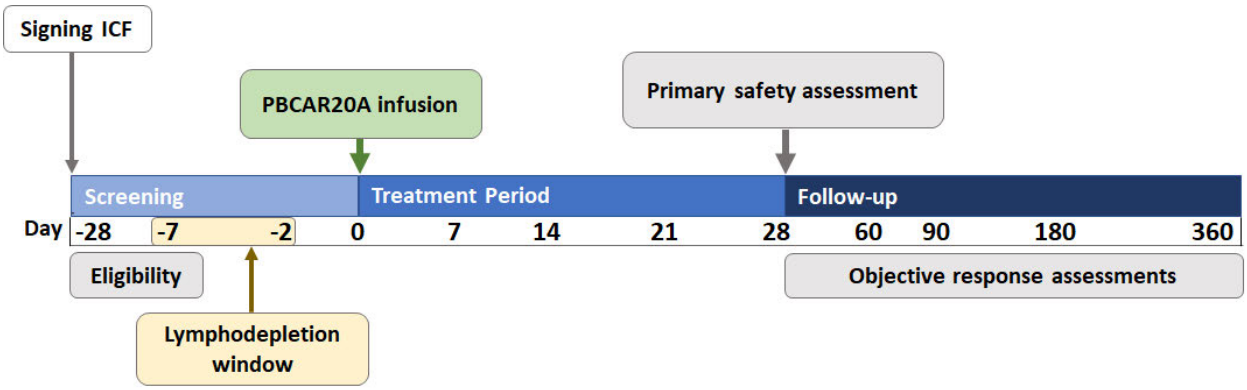
The investigators, medical monitor, and sponsor, designated as the Safety Review Committee (SRC) will monitor and convene to review safety data, including any delayed toxicities caused by PBCAR20A, at regular intervals to discuss any unexpected significant toxicities and to determine whether dose escalation is appropriate.

After the conclusion of Phase 1, the SRC will convene to determine whether Phase 2 can proceed. If DLTs are found to occur predominantly in one subtype of NHL subjects (i.e., those with indolent lymphoma, including follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and marginal zone lymphoma or aggressive lymphoma, such as diffuse large B cell lymphoma, PMBCL, Burkitt lymphoma, and other high grade T cell lymphomas), the possibility of separating the cohorts for dose escalation may be explored.

Up to 18 subjects total may be enrolled in any given dose level for which safety has been established (i.e.,0 of 3 or ≤1 of 6 subjects experiences a DLT) for characterization of the pharmacology, safety profile, and clinical benefit profile. These additional 12 subjects (any subjects after [redacted] or [redacted], respectively) will not be considered for determination of the MTD and can be enrolled without delays into that dose level. In these additional subjects, modified lymphodepletion regimens may be employed, as assigned at the time of study registration and defined in the Pharmacy Manual, to evaluate regimens which may increase anti-tumor effect and improve PBCAR20A cellular kinetics.

All study subjects are monitored for DLTs and AEs during the Treatment Period through Day 28. Study subjects will continue to be monitored for safety after Day 28 and will be followed until death, disease progression, stem cell transplant, withdrawal due to intolerable toxicity, withdrawal of consent, or Day 360, whichever occurs first.

Figure 1: Study schema



Abbreviations: ICF=informed consent form.

3.1.2. Phase 2a (dose expansion)

Phase 2a Arms are intended to evaluate preliminary efficacy and further characterize safety in specific subject populations. As a result, the inclusion and exclusion criteria for these Arms are more specific than Phase 1.

Phase 2a Arms will use a dose level at or below the MTD established in Phase 1. The dose will be determined based on PK/PD analysis, safety evaluation, and preliminary evidence of clinical activity. Refer to the Pharmacy Manual for the specific treatment regimen, including lymphodepletion, to be used in each Arm.

All Phase 2a Arms will initiate simultaneously and will enroll in parallel.

Upon selection of the recommended Phase 2a dose (RP2D) and associated lymphodepletion regimen, subjects will be enrolled to characterize clinical efficacy, safety, and pharmacology in that population. The populations are defined by the inclusion / exclusion criteria for Phase 2a. All subjects in any Phase 2a group are expected to meet all eligibility criteria and be treated in a consistent fashion within the group.

3.1.2.1. Phase 2a Arm A Population: CLL/SLL being treated with ibrutinib therapy for at least 12 months

Phase 2a Arm A will enroll subjects with a confirmed diagnosis of $CD20^+$ CLL/SLL who are being treated with ibrutinib. Subjects must have started ibrutinib at least 12 months prior to treatment with PBCAR20A and must have achieved SD or a PR and be receiving maintenance ibrutinib. No prior CR is allowed. Subjects must also have high risk cytogenetics, defined as del17p or TP53 mutation. Other inclusion exclusion, in common with Phase 1, are found in Section 4.1 and Section 4.2.

3.1.2.2. Phase 2a Arm B Population: DLBCL who did not achieve complete response after 2 cycles of front-line therapy

Phase 2a Arm B will enroll subjects with diagnosis of DLBCL who have completed treatment with first line chemotherapy (R-CHOP) and have reached PR but not CR. Subjects must have evidence of measurable or evaluable disease demonstrating a lack of CR to first line therapy. Subjects who have progressed on (are refractory to) first line therapy are not eligible. Other medical criteria in common with Phase 1 must be met, as identified in Section 4.1 and Section 4.2.

3.1.2.3. Phase 2a Arm C Population: High grade B cell Non-Hodgkin's Lymphoma (NHL) who have previously been treated with autologous CAR T products and have subsequently experienced disease progression

Phase 2a Arm C will enroll subjects who have relapsed or refractory (r/r) high grade B cell lymphomas as defined in Section 4.1 who have been previously treated with CD19-targeted autologous CAR T therapy. Response to prior CAR T therapy is not required, but subjects must have evidence of progressive disease to be eligible. Disease must be measurable or evaluable by Lugano Criteria.

3.1.3. Long-term follow-up study:

Study subjects who receive a dose of PBCAR20A will be followed in a separate LTFU, PBCAR-LTF, study after exiting this study (due to either discontinuation or completion). The LTFU study procedures will be described in a separate protocol.

3.2. Study schedule

Table 2: Study schedule: Phase 1 and 2a

	Treatment Period									Follow-up							
Month	**-**	**1**								**2**		**3**	**4**	**5**	**6**	**9**	**12**
Day	**-28**[a]	**0**	**1**	**3**	**7**	**10**	**14**	**21**	**28**	**42**	**60**	**90**	**120**	**150**	**180**	**270**	**360/ ET**
Visit window (days)			**+1**	**+1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**
Informed consent	X																
Inclusion and exclusion criteria	X																
Demography	X																
Weight	X	X							X			X			X	X	X
Full physical examination	X	X							X			X			X	X	X
Medical history	X	X								X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Viral serology[c]	X																
HLA haplotype	X																
Anti-HLA antibodies	X								X			X					
Brain MRI	X[d]																
Lumbar puncture (History of CNS involvement)	X[e]																
LVEF (ECHO or MUGA)	X																

	Treatment Period									Follow-up							
Month	**-**	**1**								**2**		**3**	**4**	**5**	**6**	**9**	**12**
Day	**-28**[a]	**0**	**1**	**3**	**7**	**10**	**14**	**21**	**28**	**42**	**60**	**90**	**120**	**150**	**180**	**270**	**360/ ET**
Visit window (days)			**+1**	**+1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**
Serum pregnancy test (WOCBP only)	X																
Clinical laboratory assessments[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation panel[g]	X	X															
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)[i]	X																
ECOG Performance Status	X	X							X			X			X	X	X
Fludarabine + cyclophosphamide[j]																	
Study treatment administration[k]		X															
Study participant diary[l]		----------X----------															
PET-CT scan (NHL only)	X[m]						X[n]		X		X	X			X	X	X
Tumor/liquid biopsy	X[o]						X[p]										
Serum and whole blood samples for analyses[q]	X	X[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Treatment Period									Follow-up							
Month	**-**	**1**								**2**		**3**	**4**	**5**	**6**	**9**	**12**
Day	**-28**[a]	**0**	**1**	**3**	**7**	**10**	**14**	**21**	**28**	**42**	**60**	**90**	**120**	**150**	**180**	**270**	**360/ ET**
Visit window (days)			**+1**	**+1**	**±1**	**±1**	**±2**	**±2**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**
BMA/bone marrow biopsy (Diagnosed w BM involvement)[s]	X								X		X	X			X	X	X
CT scan (if preferred to PET/CT for CLL/SLL only)	X								X		X	X			X	X	X
Objective response assessment									X		X	X			X	X	X
MRD assessment[t]	X								X		X	X			X	X	X
Concomitant medications	X																
AE review	X																
AESI[u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; AESI=adverse event of special interest; BMA=bone marrow aspiration; CAR=chimeric antigen receptor; CLL=chronic lymphocytic leukemia; CNS=central nervous system; CT=computed tomography; DLBCL=diffuse large B-cell lymphoma; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ECHO=echocardiogram; ET=early termination; eCRF=electronic case report form; HLA=human leukocyte antigen; HIV=human immunodeficiency virus; IV=intravenous; LD=lymphodepletion; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multigated acquisition scan; NHL=non-Hodgkin lymphoma; PBMC=peripheral blood mononuclear cell; PET=positron emission tomography; SLL=small lymphocytic lymphoma; WOCBP=women of childbearing potential.

[a] Lymphodepletion regimens will be administered as described in the Pharmacy Manual.

[b] Study subjects are asked about the current status of their disease and treatment, including stem cell transplant.

[c] Viral screening to include HIV antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, HLA haplotype, and anti-HLA antibodies.

[d] Brain MRI is recommended for all study subjects at Baseline to assess the presence of brain disease or abnormalities. A negative MRI is required at Screening for NHL study subjects with a history of CNS disease. An MRI conducted as a part of the routine care within 6 weeks of initiating lymphodepletion chemotherapy may be used for Screening.

[e] A negative lumbar puncture is required at Screening only if the study participant has a history of CNS disease. A lumbar puncture conducted as a part of the routine care within 6 weeks of initiating lymphodepletion chemotherapy may be used for Screening.

[f] Clinical laboratory tests for safety assessments are outlined in Section 7.1.4. Clinical laboratory tests can be performed up to 24 hours before dosing on Day 0.

[g] Coagulation panel may be performed after Baseline if the investigator considers it necessary.

[h] Vital signs should be measured on the day of dosing at 5 minutes (±2 minutes) before dosing, then at the end of infusion (±5 minutes), 60 minutes after the end of infusion (±10 minutes), and 4 hours (±15 minutes) after the end of infusion. Vital signs should also be collected as clinically indicated.

[i] Additional ECGs will be collected as clinically indicated.

[j] The initial lymphodepletion chemotherapy regimen will be composed of fludarabine (30 mg/m^2/day IV) and cyclophosphamide (500 mg/m^2/day IV) during the Screening Period from Days -5 to -3. However, modified lymphodepletion regimens may be used after safety is established in dose level. The lymphodepletion regimen will be specified at the time of registration. Please refer to the Pharmacy Manual for the lymphodepletion dosing regimen; lymphodepletion status may be discussed between the Sponsor Medical Monitor, Principal Investigators, and contract research organization Medical Monitor prior to registration.

[k] Study subjects are evaluated for the following restrictions 2 hours (±60 minutes) prior to receiving the PBCAR20A infusion: new uncontrolled infection after receipt of lymphodepletion, fever, taking any corticosteroid beyond the replacement details, rapid acceleration of malignant disease, and any organ dysfunction since Screening. Additional details are provided in Section 5.1.1. At the investigator's discretion, study subjects may receive premedication 1 hour (±15 minutes) prior to receiving the PBCAR20A infusion with oral acetaminophen and oral or IV diphenhydramine according to the institutional standards.

[l] Study participant diaries will be provided to study subjects on Day 0 to monitor temperature, at least daily, during the first 28 days.

[m] . The PET-CT scan conducted as part of the routine care within 4 weeks of PBCAR20A administration may be used for Screening purposes. If the scan is performed as a part of routine care, the result will be obtained from the study participant's physician or medical record.

[n] A PET-CT scan on Day 14 is optional and will be determined by the investigator. Additional details are provided in Section 8.4.

[o] Screening tumor biopsy may be omitted if a study participant has had a biopsy showing CD20$^+$ disease within 6 months before Screening and has not received any anti-CD20$^+$ therapy since then. Note: If the tumor is CD20-negative by flow cytometry, it should be evaluated by immunohistochemistry as flow assays may result in false negatives due to competition with CD20 targeting treatment antibodies (e.g. rituximab).

[p] Tumor biopsy may be performed to confirm imaging changes as clinically indicated. Additional biopsies may be performed pending Sponsor approval.

[q] Exploratory analyses will be performed by the central laboratory. Additional analyses performed at the site that are not required by the protocol should be captured in the eCRF.

[r] Blood samples will be collected before PBCAR20A administration on Day 0.

[s] If available, the central laboratory will also test fresh BMA or bone marrow core samples for CAR T cells.

[t] MRD assessment will be performed at Screening for all study subjects. Please consult the Laboratory Manual for specific sample requirements at Screening. At subsequent visits, MRD assessment will only be performed for study subjects who meet other standard response criteria (see Section 8.1). Please consult the Laboratory Manual for specific sample requirements at all subsequent visits. Note that these samples are disease-specific and may be different between Screening and all subsequent visits.

[u] AESIs are listed in Section 7.2.1.3.

3.3. Number of subjects

Phase 1 (dose escalation): Approximately 9 to 30 evaluable subjects are planned to be enrolled in the dose escalation phase of the study.

Phase 2a (dose expansion): Each arm may enroll up to 20 subjects for a total of up to 60 subjects. Futility may be determined in a rolling fashion at the sponsor's discretion.

3.4. Number of Study Centers

Approximately 10-15 study centers in the United States.

3.5. Discussion of study design and dose justification

This is a first-in-human, Phase 1/2a study intended primarily to evaluate the safety and tolerability of PBCAR20A in study subjects with NHL including CLL/SLL. A single-arm, open label design has been chosen because of the early stage of development and the need for close monitoring for safety. This study is not controlled because of the serious nature of the conditions being studied and the lack of alternative therapies.

Unlike small molecules and biologic drugs, optimum dosing in adoptive cell therapy (ACT) cannot be determined using classical pharmacokinetic (PK)/pharmacodynamic parameters based on body weight or body surface area (BSA). This is because cellular immunotherapies are "living" drugs that may expand within a patient following administration. Cellular immunotherapies, such as CAR T-cell products, are not metabolized in the liver or excreted by the kidney, and the sites and volume of distribution are not clearly understood. Therefore, dosing of CAR T-cell therapies based on weight or BSA is not driven by a clear understanding of PK parameters. Furthermore, the relationship between toxicity and therapeutic activity is not monotonic for ACTs. According to the FDA's guidance, "…conventional allometric scaling methods for cell and gene therapy (CGT) products may be less precise than for small molecule drugs, and traditional PK and pharmacodynamic correlations might not be possible. Therefore, it may be difficult to establish an initial starting dose based on the considerations used for small-molecule drugs. If available, previous clinical experience with the CGT product or related products, even if by a different route of administration or for a different condition, might help to justify the clinical starting dose" (FDA, 2015).

Dose-finding trials in oncology are designed to find the MTD, the highest dose at which the observed toxicity rate is less than a prespecified target probability. A starting dose that is thought to be safe in humans is normally selected based on a combination of PK, pharmacodynamics, toxicity, and efficacy observations in animal models of human disease. However, in the case of CAR T-cell therapies, there is no relevant species other than humans that can be used to model drug safety and efficacy. Observations of toxicity or efficacy based on doses of human CAR T cells administered to immunodeficient mice bearing human tumors are useful as qualitative indicators of the likelihood of toxicity or efficacy in humans, but those data cannot be quantitatively translated (i.e., allometrically scaled) in selecting a safe starting dose in humans.

In this study, we selected a starting dose, dose-escalation intervals, and 4 dose levels (including possible de-escalation) to be evaluated in Phase 1 based upon toxicity observed in

immunodeficient mice (tumor bearing and nontumor bearing) that were administered various doses of PBCAR20A, as well as on the observations of toxicity and antitumor activity in human clinical studies of autologous anti-CD20 CAR T-cell treatments. For example, doses as high as 1.0×10^7 PBCAR20A CAR T cells (equivalent to 5.0×10^8 cells/kg in humans based solely on mg/kg conversion) were administered to immunodeficient mice bearing disseminated human lymphoma tumors without signs of toxicity, while doses in an order of lower magnitude still provided for significant antitumor efficacy. The potential for PBCAR20A to cause GvHD was evaluated in a xenogeneic mouse model in which doses as high as 3.0×10^7 PBCAR20A cells, the equivalent of 1.2×10^9 cells/kg in a human (based solely on cells/kg conversion), were administered without any signs of development of GvHD. Several studies involving HLA nonidentical stem cell transplant procedures have concluded that a threshold of approximately 5.0×10^4 residual $CD3^+$ donor T cells/kg can be contained within the donor graft without significant risk of resulting GvHD (Muller et al, 1999; Aversa et al, 1998). The proposed starting dose of PBCAR20A for this study is 1×10^6 CAR T cells/kg of body weight. This dose would contain 1.5 to 6.0×10^3 residual $CD3^+$ T cells/kg, which is within the range considered to be a low risk for GvHD based on literature from unrelated donor bone marrow and stem cell transplants (Muller et al, 1999), and thus, should not represent a significant risk for causing GvHD in an HLA-mismatched host.

The proposed starting dose and the dose-escalation intervals are also supported by observations of safety and efficacy in clinical trials of autologous anti-CD19 CAR T cells in adult and pediatric study subjects with r/r ALL and r/r NHL. Greater emphasis was given to trials of autologous CAR T-cell products in which the CD19-targeting moiety (FMC63 murine antihuman-CD19 single-chain variable fragment [scFv]) and signaling domains (4-1BB + CD3ζ) are more similar to the CAR construct of PBCAR0191, namely Novartis' CTL019 (tisagenlecleucel) and Juno Therapeutics' JCAR017; however, dosing information for Kite Pharmaceuticals KTE-19 (axicabtagene ciloleucel), an autologous anti-CD19 CAR T-cell product in which the CAR construct consists of FMC63 scFv and CD28 and CD3ζ signaling domains, was also considered. For each of these CAR T-cell therapies, total doses of between 1×10^7 and 6×10^8, with target doses of between 1×10^6 and 1×10^7 CAR T cells/kg, have been used in the clinic in adult subjects and resulted in acceptable levels of toxicity and a high rate of efficacy in terms of complete remissions. Our proposed starting dose at 1×10^6 CAR T cells/kg falls below this range and is expected to provide an opportunity for meaningful efficacy while preserving a significant margin for safety.

The initial lymphodepletion regimen (fludarabine [30 mg/m^2/day] and cyclophosphamide [500 mg/m^2/day]) in this study is a common conditioning treatment before CAR T-cell therapy (Locke et al, 2017). The need to explore additional dosing and lymphodepletion regimens is based on findings from the currently ongoing PBCAR0191-01 study, in which PBCAR0191 has been well tolerated across doses ranging from 3 x 10^5 cells/kg to 6 x 10^6 cells/kg : as of 06 November 2020, 27 subjects enrolled in the PBCAR0191-01 study across Dose Levels 1-4 have completed Day 28, all with no observations of GvHD and no Grade ≥3 CRS or ICANS. Similarly, PBCAR20A has been well tolerated in the subjects enrolled to date across doses ranging from 1 x 10^6 to 3 x 10^6 cells/kg, with 1 Grade 3 ICANS event was observed in a patient enrolled in Dose level 1 that was downgraded to Grade 2 within 24 hours. The classical development model for a novel therapy would be to increase the dose until either toxicity or maximum clinical benefit is reached; thus, the protocol was modified (Version 4.0) based on

safety data from Phase 1 dose levels 1 and 2. [redacted] This finding indicates allogeneic rejection, and the same observation has been made in the subjects enrolled into the present PBCAR20A study to date. As a result of these observation, the alternative lymphodepletion strategies described in Section 1.2.3 will be considered in dose levels for which safety has been established.

3.6. Cohorts and dose escalation

Study subjects with NHL and CLL/SLL will be enrolled into a single cohort in both Phase 1 and Phase 2 of the study.

Phase 1 (dose escalation):

In Phase 1, 3 dose groups will be sequentially enrolled planned with the possibility of a single de-escalation (Table 3). Note that dose levels -1, 1, 2, and 3 are not to exceed a total dose of 3×10^7, 1×10^8, 2.4×10^8, and 4.8×10^8 cells, respectively.

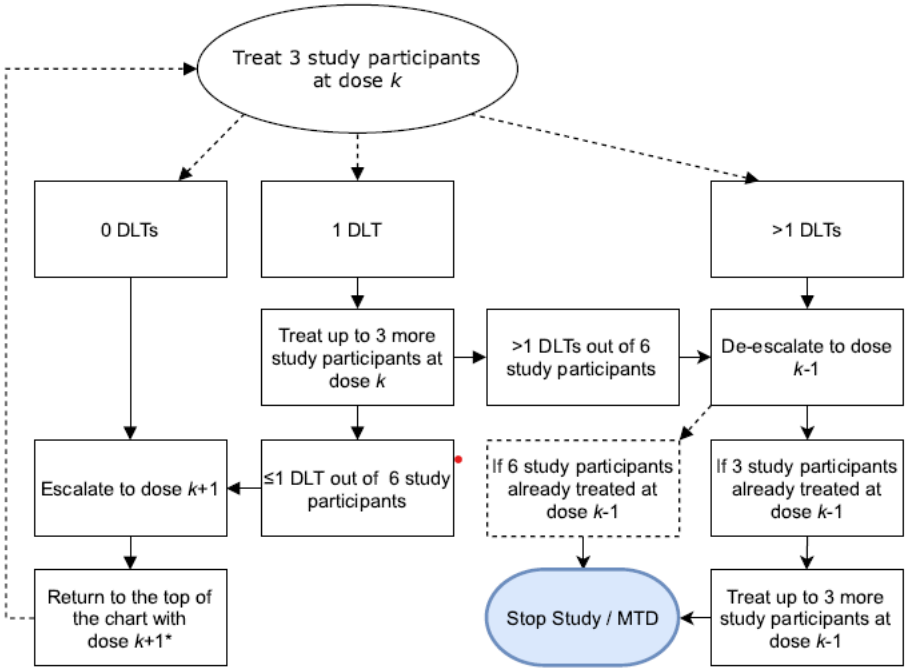
Table 3: Single escalating doses of PBCAR20A

Dose level	Number of CAR T	Max cells/dose[a]
Dose -1	3×10^5 cells/kg	3×10^7
Dose 1 (starting)	1×10^6 cells/kg	1×10^8
Dose 2	240×10^6 cells	2.4×10^8
Dose 3	480×10^6 cells	4.8×10^8

CAR=chimeric antigen receptor.
[a] Based on number of cells for 100 kg subject.

The number of study subjects in each dose group, dose escalation, and determination of the MTD will depend on the incidence of DLTs following the 3 + 3 design (Figure 2).

Figure 2: Dose escalation algorithm



Abbreviations: DLT=dose-limiting toxicity; MTD=maximum tolerated dose.
*If at 480 × 10^6 cells (Dose 3), this would be the MTD.

Phase 2a (dose optimization):

Arms in Phase 2a will use a dose at or below the MTD as determined in Phase 1. The dose will be determined based on PK/PD analysis, safety evaluation, and preliminary evidence of clinical activity. Refer to the Pharmacy Manual for the specific dose and treatment regimens to be used in each Arm. Phase 2a Arms are described in Section 3.1.2.

3.7. Retreatment criteria

Retreatment refers to the specific scenario in which a subject receives all planned treatment and has some evidence of benefit followed by evidence of disease progression.

All subjects will receive PBCAR20A as per Table 2. A subject may receive an additional dose of PBCAR20A if he/she meets retreatment criteria as determined by the investigator and agrees to be retreated.
Subjects are eligible for retreatment only if the following criteria are met:

- Subject has documented evidence of clinically meaningful tumor response to initial dose of PBCAR20A followed by documented either a disease progression at subsequent visit or has residual disease.

Subject has biopsy-proven $CD20^+$ tumor prior to re-treatment, unless it is deemed not safe by multi-disciplinary team, Subject has no evidence of GvHD and no new unresolved disease-

related central nervous system (CNS) involvement that in the opinion of the investigator would impair the assessment of neurotoxicity events.

- Subject has adequate bone marrow, renal, hepatic, pulmonary, and cardiac function as defined in Section 4.1.
- Subject has not received another systemic treatment for NHL.

Subjects who meet the retreatment criteria and have had a study visit within 30 days will undergo lymphodepletion chemotherapy and follow the SoA from the beginning. Subjects who meet the retreatment criteria and have discontinued the study will need to be re-enrolled into an open slot (Phase 1 or Phase 2a). Retreatment visits, starting from lymphodepletion visits, will be distinguished from initial visits in the electronic case report form (eCRF).

Subjects eligible for retreatment may receive PBCAR20A at the highest dose level with established safety (see Section 3.1).

3.8. Criteria for DLTs

During the DLT period (28 days after dosing the last subject in a dose level), severity grades will be determined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 unless otherwise specified.

Regardless of the investigator attribution or unless there is a clear alternative explanation, a DLT is defined as any of the following TEAEs:

- CRS (per American Society for Transplantation and Cellular Therapy [ASTCT] consensus grading; see Section 7.3.1):
  - Any Grade 4
  - Any Grade 3 that does not resolve or reduce to Grade ≤2 within 72 hours of onset
- GvHD: Acute GvHD Grade ≥2 regardless of the organ involved that does not resolve with appropriate treatment within 14 days.
- Any Grade ≥3 neurotoxicity (per American Society for Transplantation and Cellular Therapy [ASTCT] ICANS criteria provided in Table 15) that does not resolve or reduce to Grade ≤2 within 72 hours of onset.
- Any seizure
- Grade 3 or 4 infusion reactions related to the study treatment that does not resolve or decrease to Grade ≤2 within 48 hours
- Any Grade 4 hematologic toxicity, except lymphopenia, that does not resolve or decrease to Grade ≤2 within 42 days
- Any Grade 4 non-hematologic toxicity
- Any Grade 3 toxicity involving heart and lungs

- Any Grade 3 toxicity involving kidney and liver that does not resolve or reduce Grade ≤2 within 7 days of onset
- Any Grade 3 toxicity to other organs that does not resolve or reduce Grade ≤2 within 72 hours of onset
- Any Grade 5 toxicity that was not due to underlying malignancy

If an AE is clearly due to progressive or underlying disease and unrelated to the study treatment, the event would not be considered a DLT.

3.9. Criteria for treatment interruption

The infusion of PBCAR20A should be interrupted immediately if the following situation occurs:

- Severe hypersensitivity reaction, including anaphylaxis

The investigator will evaluate the study participant and determine whether the infusion can be resumed or should be permanently discontinued. If infusion is resumed, study subjects should receive the remainder of the dose not yet administered at one-half the rate of the initial infusion. If the infusion will not be completed within 2 hours from thawing, a new dose should be prepared for the remainder. If not already administered within 2 hours of restarting infusion, a minimum dose of 25 mg diphenhydramine (oral) should be administered prior to restarting infusion.

3.10. Criteria for temporarily suspending treatment

In addition to the staggered dosing schedule (14 days between the first 2 study subjects in each dose group, including the dose de-escalation group if applicable), dosing in all study subjects, regardless of cohort and dose group, will temporarily stop if any of the following events occur:

- Any Grade 4 toxicity that is possibly or probably related to PBCAR20A
- Grade ≥3 GvHD
- Any death that is possibly or probably related to the study treatment

Investigators and the medical monitor will conduct a comprehensive assessment of the event, the causal relationship to study treatment, and cumulative evidence of toxicity to determine whether the study can continue.

3.11. Criteria for study termination

The study can be terminated by the sponsor, Safety Review Committee, Institutional Review Board (IRB), or FDA at any time.

4. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1. Inclusion criteria

Study subjects are eligible to be included in the study only if all of the following criteria apply:

<u>Criteria for NHL (Phase 1):</u>

1. Subject has r/r $CD20^+$ B-cell NHL that is histologically confirmed by archived tumor biopsy tissue from the last relapse and corresponding pathology report. Alternatively, if at least 1 tumor involved site is accessible at Screening, the subject's diagnosis will be confirmed by pretreatment biopsy (excisional when possible). If a subject never had a complete response (CR) during prior lines of therapy, a sample from the most recent biopsy is acceptable.
2. Measurable or detectable disease (positron emission tomography [PET]-positive) with evidence of disease progression after most-recent therapy according to the Lugano classification.
3. Primary refractory disease or r/r disease after treatment with 2 prior regimens, unless per standard of care treatment guidance (e.g., National Comprehensive Cancer Network [NCCN]) no second line therapy of known benefit exists. Subjects including but not limited to those with the following types of lymphoma and have received the associated standard therapies are eligible:
    - Primary mediastinal B-cell lymphoma (PMBCL)/follicular lymphoma (FL) including Grade 3B or transformed FL/high-grade B-cell lymphoma/diffuse large B-cell lymphoma (DLBCL) including Richter's transformation. Subjects must have received rituximab or other anti-CD20 antibody and anthracycline-based chemotherapy. All subjects should be evaluated for approved anti-CD19 CAR T-cell therapy when applicable.
    - Indolent B-cell lymphoma (Grades 1, 2, and 3A)/transformed CLL (Richter's)/marginal zone lymphoma. Subjects must have received 2 prior lines of systemic therapy including an alkylator (e.g., bendamustine, cyclophosphamide/vincristine/ prednisone) plus an anti-CD20 antibody and have had documented disease progression.
    - Subjects with r/r Burkitt's lymphoma must have failed 1 prior therapy.
    - MCL. Subjects must have received 2 prior lines of systemic therapy including chemotherapy (bendamustine/rituximab; rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); or Nordic-type regimen) with or without autologous stem cell transplant (ASCT) and a Bruton's tyrosine kinase (BTK) inhibitor (e.g., ibrutinib, acalabrutinib) and have had documented disease progression.

<u>Criteria for CLL/SLL (Phase 1):</u>

4. Diagnosis of $CD20^+$ CLL with indication for treatment based on the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines and clinically measurable disease or $CD20^+$ SLL (lymphadenopathy and/or splenomegaly and $<5 \times 10^9$ CD19+ and CD5+ clonal B cells/L in peripheral blood at diagnosis) with measurable disease that is biopsy-proven SLL.
5. Subjects with CLL/SLL must have previously progressed following at least 2 prior lines of systemic targeted therapy including a BTK inhibitor and venetoclax ± rituximab.

<u>Criteria for Phase 2a Arm A:</u>

6. Diagnosis of $CD20^+$ CLL/SLL for which subject is currently receiving, and has been receiving for at least 12 months, ibrutinib therapy as standard of care, regardless of line

of therapy, with best response of partial response or stable disease (no CR or CRi). Subjects must have high risk disease, as defined by deletion 17p or TP53 mutation.

Criteria for Phase 2a Arm B:

7. Diagnosis of CD20+ DLBCL with PET/CT indicating a partial response, but not a complete response, per Lugano 2016 criteria (Cheson JCO 2016), after completion of upfront chemoimmunotherapy (R-CHOP, per NCCN 2020 NHL Guidelines). Subjects who had refractory disease to (progressive disease through) upfront treatment are not eligible.

Criteria for Phase 2a Arm C:

8. Diagnosis of $CD20^+$ high-grade B cell lymphoma after previous treatment with autologous CD19-targeted CAR T therapy, regardless of response.

Criteria for all subjects (Phase 1 and 2a):

9. Subject has $CD20^+$ tumor. Note: If the tumor is CD20-negative by flow cytometry, it should be evaluated by immunohistochemistry as flow assays may result in false negatives due to competition with CD20 targeting treatment antibodies (e.g., rituximab).
10. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.
11. Subject has adequate bone marrow, renal, hepatic, pulmonary, and cardiac function defined as:
    - Estimated glomerular filtration rate >30 mL/min/1.73 m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation). A 24-hour urine collection for creatinine clearance may be used at the investigator's discretion.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels both ≤3 times the upper limit of normal (ULN), unless there is suspected disease (tumor) in the liver.
    - Total bilirubin <2.0 mg/dL, except in subjects with Gilbert's syndrome, who must have total bilirubin ≤3 × ULN, or except those with disease (tumor) in the liver.
    - Platelet count ≥50,000/µL and ANC of ≥1000/ µL. Transfusions within 14 days of screening are not allowed, except for patients in B-ALL or NHL cohorts with high marrow disease burden (>70%) in which case it must be discussed with medical monitor. In the case of extensive bone marrow disease burden, adequate bone marrow recovery after prior treatment is required to be documented.
    - Left ventricular ejection fraction (LVEF) >45% as assessed by an echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan performed within 1 month before starting lymphodepleting chemotherapy. The ECHO results performed within 6 months before Screening and at least 28 days after the last cancer treatment may be acceptable if the subject has not received any treatment with cardiotoxicity risks.
    - No evidence of pericardial effusion or pleural effusion causing clinical symptoms and needing immediate intervention. Any known effusion must be stable without need for drainage within 2 weeks of enrollment.

- Baseline oxygen saturation >92% on room air.

Subject characteristics

12. Subject must be 18 years of age or older at the time of signing the informed consent form.
13. Any sex.
14. All subjects must be willing to practice birth control and refrain from donating sperms or oocytes from the time of enrollment in this study through 3 months after receiving the study treatment.
15. Women of childbearing potential (WOCBP) must be tested negative for pregnancy at Screening because of the potentially harmful effects of the preparative chemotherapy to the fetus. The WOCBP are defined as any women who are not postmenopausal or who have not had a hysterectomy. Postmenopausal is defined as women over the age of 55 years who have not had a menstrual period for at least 1 year.
16. Capable of giving signed informed consent.

4.2. Exclusion criteria:

Subjects are excluded from the study if any of the following criteria apply:

Criteria for NHL (Phase 1 and 2a):

17. Requirement for urgent therapy due to mass effects such as bowel obstruction, spinal cord, or blood vessel compression.

Criteria for NHL and CLL/SLL (Phase 1 and 2a):

18. Any history of central nervous system (CNS) disease. If active CNS involvement is suspected, a negative lumbar puncture is required at Screening.
19. Subject has had a malignancy, besides the malignancies of inclusion (B-cell NHL or CLL/SLL), that in the investigator's opinion, has a high risk of relapse in the next 2 years.
20. Recent, clinically significant fungal, bacterial, viral, protozoal, or other infection requiring therapeutic anti-microbial medications within 7 days of lymphodepletion. Note: subjects with elevated or rising C-reactive protein (CRP) must undergo infectious disease (ID) workup and recommendations must be discussed with the medical monitor. CRP must be trending toward the normal range for the laboratory. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if the subject is responding to active treatment and with medical monitor approval.
21. Any form of primary immunodeficiency (e.g., severe combined immunodeficiency disease).
22. History of human immunodeficiency virus (HIV) infection.
23. Active hepatitis B or hepatitis C confirmed by polymerase chain reaction (PCR). Subjects testing positive for inactive hepatitis B will be allowed to enroll if on prophylactic treatment.

24. Any known uncontrolled cardiovascular disease at the time of Screening that, in the investigator's opinion, is clinically significant and renders the subject ineligible.
25. History of hypertension crisis or hypertensive encephalopathy within 3 months prior to Screening.
26. History of severe immediate hypersensitivity reaction to any of the agents used in this study.
27. Presence of a CNS disorder that, in the opinion of the investigator, renders the subject ineligible for treatment.
28. Abnormal findings during the Screening Period or any other medical condition(s) or laboratory findings that, in the opinion of the investigator, might jeopardize the subject's safety.
29. History of a genetic syndrome such as Fanconi anemia, Kostmann syndrome, Shwachman-Diamond syndrome, or any other known bone marrow failure syndrome.

Prior/concomitant therapy (Phase 1 and 2a)

30. Subjects who have received ASCT within 45 days of Screening are excluded.
31. Subjects who have received systemic corticosteroid (greater than physiologic replacement) therapy for at least 7 days prior to initiating lymphodepletion chemotherapy are excluded.
32. Subjects who have received a live vaccine within 4 weeks before Screening are excluded. Non-live virus vaccines are not excluded.
33. Subjects undergoing Radiotherapy to target lesions within 4 weeks before Screening are excluded.
34. Subjects who have an indwelling catheter (i.e., pleural, peritoneal, pericardial as well as biliary and ureteral stents) are excluded. This does not apply to intravenous lines.

Other exclusions (Phase 1 only)

35. Subjects are excluded unless there has been documented progression of the disease after prior most recent systemic anti-cancer therapeutic agents and resolution of adverse events caused by their administration.

Other exclusions (Phase 2a Arm A)

36. Subjects are excluded specifically form Arm A if they have:
    a. Previous CR has been achieved with ibrutinib therapy. Note: progression is not required for enrollment if stable disease or partial response has been achieved and maintained.
    b. Ongoing grade ≥ 2 non-hematologic toxicity related to ibrutinib.
    c. High-grade transformed disease (e.g., Richter's transformation)

Other exclusions (Phase 2a Arm B)

37. Subjects are excluded specifically from Arm B if:

d. Diagnosis is transformed high grade lymphoma (e.g., Richter's transformation or transformed follicular lymphoma)

Other exclusions (Phase 1 and 2a)

38. Pregnant or breastfeeding women.
39. In the investigator's judgment, the subject is unlikely to complete all protocol required study visits or procedures, including follow-up visits, or is unlikely to comply with the study requirements for participation.
40. Any mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study, and/or evidence of an uncooperative attitude.

4.3. Screening

4.3.1. Screening procedures

After signing the ICF, potential study subjects will be screened (starting at Day -28) for eligibility to participate in the prior to receiving lymphodepletion chemotherapy (Day -5). The Screening procedures are listed in the SoA (Table 2).

Brain MRI is required at Screening for all NHL study subjects with a history of CNS disease who have not had an MRI within 6 weeks of initiating lymphodepletion chemotherapy.

Screening PET-CT scan for NHL subjects should be performed prior to initiating lymphodepletion treatment. The PET-CT scan conducted as a part of the routine care within 4 weeks of PBCAR20A administration may be used for Screening purposes. If the scan is performed as a part of routine care, the result will be obtained from the study participant's physician or medical record.

Recent tumor biopsy results, obtained within 6 months before study entry, are acceptable to confirm histological diagnosis, provided the study participant has not received any anti-CD20 therapy between the time of the biopsy and study entry.

4.3.2. Screen failures

Screen failures are defined as study subjects who consent to participate in the clinical study but are not subsequently enrolled or treated. A minimal set of screen failure information is required to be recorded at the site to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened study subjects should be assigned the same study participant number as for the initial screening.

4.4. Study discontinuation or withdrawal

Study interventions, including lymphodepletion and PBCAR20A administration, should be discontinued by the investigator if the investigator believes that it is in the best interest of the study participant or if any of the following situations occur:

- Disease progression; subjects should complete the 28-day safety evaluation period if possible
- Death
- Initiation of another systemic treatment for NHL, SLL, or CLL
- Investigator's decision
- Study participant noncompliance/protocol violations
- Study terminated by sponsor (see Section 3.11)
- Study participant withdrawal (see Section 4.4.1)
- Lost to follow-up (see Section 4.4.2)

Upon completion, study subjects will be followed in a separate LTFU study.

4.4.1. Study participant withdrawal

A study participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the study participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a study participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

4.4.2. Lost to follow-up

A study participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

The following actions must be taken if a study participant fails to return to the study center for a required study visit:

- The site must attempt to contact the study participant to reschedule the missed visit as soon as possible, counsel the study participant on the importance of maintaining the assigned visit schedule, and ascertain whether the study participant wishes to and/or should continue in the study.
- Before a study participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the study participant (where possible, 3 telephone calls and, if necessary, a certified letter to the study participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the study participant's medical record.

- Should the study participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

4.5. Study completion

A subject is considered to have completed the study's primary evaluation if he/she has completed Day 28. Subjects experiencing disease progression prior to day 28 should continue on the study through Day 28 to allow for completion of study's primary evaluation as long as another systemic therapy is not started. A subject is considered to have completed the entire study if the subject is followed according to the protocol to the Day 360 visit, disease progression, death, or receiving a new treatment for the diagnosed malignancy (including stem cell transplant), whichever occurs first.

5. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

5.1. Description of study treatment

In this study, treatments include the investigational product, PBCAR20A, and lymphodepletion chemotherapy agents, fludarabine and cyclophosphamide.

5.1.1. Pre-infusion restrictions

Before receiving the PBCAR20A infusion, each study participant will be evaluated for the following restrictions. If any of the restrictions are met, the infusion will not be given, and the investigator should discuss with the medical monitor to reschedule or suspend the study treatment in the study participant.

- New uncontrolled infection after receipt of lymphodepletion chemotherapy
- Fever (body temperature ≥38.0°C)
- Taking any corticosteroid beyond the replacement dose (masking of fever in neutropenic study subjects)
- Rapid acceleration of malignant disease
- Any organ dysfunction since Screening

5.1.2. Study treatments

Study treatments to be administered are outlined in Table 4. In Phase 1, the lymphodepletion regimen will be administered as described in the pharmacy manual. In Phase 2a, doses will be provided in the pharmacy manual and confirmed prior to subject starting treatment.

Table 4: List of study treatments

Study treatment	**PBCAR20A**	**Fludarabine**	**Cyclophosphamide**	**Sirolimus**
Dosage formulation	A vial of cryopreserved solution for IV infusion	Commercial product	Commercial product	Commercial product
Route of administration	IV	IV	IV	tablets
Dosing instruction	Per Pharmacy Manual	Per institutional guidelines	Per institutional guidelines	Per institutional guidelines
Packaging and labeling	PBCAR20A will be provided in cryopreserved vials as described in Section 6.1	Commercial product	Commercial product	Commercial product
Manufacturer	Precision BioSciences, Inc.	N/A	N/A	N/A

Abbreviations: CAR=chimeric antigen receptor; IV=intravenous; N/A=not applicable.

5.1.3. Hospitalization

Study subjects with Burkitt lymphoma or high tumor burden DLBCL/Richter's transformation CLL should receive prophylaxis for tumor lysis syndrome (including rasburicase, if indicated) and be hospitalized to undergo frequent monitoring (chemistries, lactate dehydrogenase [LDH], and uric acid every 6 hours for up to 96 hours post-treatment). If tumor lysis does occur, there should be aggressive correction of electrolytes.

For the remaining study subjects, inpatient hospitalization is generally not required for any component during the study. However, the investigator may choose to hospitalize study subjects based on his or her clinical judgment regarding the risks of tumor lysis syndrome or other conditions.

5.2. Concomitant medications

Medications used for the management of AEs may be provided by the investigator according to institution guidelines and will be recorded as concomitant medications in the electronic Case Report Form (eCRF), but these treatments are not considered study treatments.

5.2.1. Premedication

Before the administration of PBCAR20A, premedication according to institutional standards may be given at the investigator's discretion.

5.2.2. Prohibited medications and substances

Study subjects must not receive corticosteroids at doses higher than 5 mg/day of prednisone or equivalent at any time after the CAR T-cell infusion, except when medically necessary.

Study subjects must not receive filgrastim during the immediate pre-infusion period from Days -7 to 0 and post-infusion for 10 days, except when medically necessary.

Study subjects must not receive any additional anticancer therapy, except those expressly intended by the protocol (e.g. ibrutinib in Arm A), without prior discussion with the medical monitor.

Study subjects are prohibited from excessive use of alcohol (defined as 4 or more alcoholic drinks per day) and from any use of illegal drugs.

5.3. Treatment compliance

Study personnel are required to record the date, time, study intervention (including fludarabine and cyclophosphamide), and dose administered to each study participant in the eCRF.

5.4. Randomization and blinding

Not applicable. This is a nonrandomized, open-label study.

6. MATERIALS AND MANAGEMENTOF INVESTIGATIONAL PRODUCT

6.1. Investigational Product

Cryopreserved PBCAR20A allogeneic T cells will be supplied in 6 mL vials and stored in the vapor phase of liquid nitrogen.

6.2. Investigational product storage

PBCAR20A vials will be stored in the vapor phase of liquid nitrogen (temperature not to exceed 130°C). The manufactured drug product will be stored centrally (Fisher BioServices) and delivered to study centers. Individually overwrapped vials will be stored in a box in racks in the manufacturer-supplied dry shipper package, which can be held for up to 21 days prior to dosing; sites that are able to store the drug product in liquid nitrogen will not be limited by this duration.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved prior to study treatment administration.

6.3. Investigational product handling, preparation, and administration

Personal protective gear should be worn when opening the shipper and boxes to remove the vials. Thawing instructions are specified in the Pharmacy Manual.

Only study subjects enrolled in the study may receive study intervention and only authorized study staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study staff.

Detailed instructions for the preparation and handling of PBCAR20A and information for the final disposition of unused study interventions are provided in the Pharmacy Manual for PBCAR20A. The study is not randomized or controlled.

6.4. Investigational product accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for the study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

7. ASSESSMENT OF SAFETY

7.1. Safety parameters

Planned time points for all safety assessments are provided in the Table 2. Institutions should follow institutional guidelines for monitoring CAR T-cell infusion-related side effects. Study participant diaries will be provided to subjects to monitor temperature, at least daily, during the first 28 days.

7.1.1. Vital signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed at the time points listed in Table 2.

7.1.2. Physical examination

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.1.3. Electrocardiogram

Single 12-lead electrocardiograms (ECGs) will be obtained at time points listed in Table 2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, QTc, and QT corrected by Fredericia (QTcF) intervals.

The ECGs are required to be done in triplicate; 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

7.1.4. Laboratory assessments

Clinical laboratory tests can be performed up to 24 hours before dosing on Day 0. The tests listed below will be performed by local laboratories.

Hematology:

- Hemoglobin
- Hematocrit
- Red blood cell count and indices:
  - Mean corpuscular volume
  - Mean corpuscular hemoglobin
- White blood cell count (WBC) with differential:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Platelets

Biochemistry:

- Serum cytokines (when part of standard study site practice; additional biomarkers will be tested for exploratory purposes)
- Sodium
- Potassium
- Calcium
- Chloride
- Glucose
- Total protein
- Creatinine

- Blood urea nitrogen
- Total and direct bilirubin
- AST/serum glutamic-oxaloacetic transaminase
- ALT/serum glutamic-pyruvic transaminase
- Alkaline phosphatase
- LDH
- C-reactive protein (CRP)
- Ferritin

Urinalysis:

- Specific gravity
- pH, glucose, protein, blood, ketones by dipstick
- Microscopic examination (if blood or protein is abnormal)

Recommended coagulation panel (coagulation panel may be performed after Baseline if investigator considers it necessary):

- Prothrombin time
- Activated partial thromboplastin time
- D dimer
- Fibrinogen

Other Screening tests:

- Serum or urine pregnancy test
- Serology:
  - HIV (antibody)
  - Hepatitis B surface antigen
  - Hepatitis B core (antibody)
  - Hepatitis C virus ([HCV]; antibody, then HCV ribonucleic acid by PCR if antibody is positive)
  - HLA haplotype
  - Anti-HLA antibodies

The investigator must review the laboratory report, document this review, and record any clinically relevant changes that meet the definition of AEs in the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the study participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated weekly until the values return to normal/Baseline or are no longer considered clinically significant by the investigator or medical monitor.

If clinically significant abnormal values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology should be determined, and the sponsor should be notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

7.1.5. Immunogenicity

Blood samples will be collected from all study subjects according to Table 2 and analyzed at the local laboratory. These samples may be tested for immune reactivity against PBCAR20A when PBCAR20A is not detectable at early time points after administration. Blood samples may also be tested by local laboratories for donor-specific HLA antibodies.

Blood samples should also be collected at the final visit and shipped to the central laboratory for study subjects who have discontinued study treatment or withdrawn from the study.

7.2. AEs and SAEs

7.2.1. Definition of AEs

7.2.1.1. AE

An AE is defined as any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs will be collected from the initiation of lymphodepletion chemotherapy until death, disease progression, subsequent systemic therapy, withdrawal due to intolerable toxicity, withdrawal of consent, or Day 360, whichever occurs first and be recorded in the eCRF, regardless of whether or not they are related to the study treatment. All AEs collected through Day 28 will be used for assessment of DLTs; any AEs occurring after Day 28 will be considered in dose-escalation decisions and monitoring procedures as appropriate.

All AEs, including SAEs, that occur after signing the ICF and before administration of any protocol-specified treatment will be recorded as Medical History in the appropriate eCRF.

7.2.1.2. SAE

An SAE is an AE occurring during the study and at any dose of the investigational product, comparator, or placebo that fulfills at least 1 of the following:

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the study participant or may require medical intervention to prevent one of the outcomes listed above

All SAEs that occur during the AE review period as noted above must be recorded in the eCRF, whether or not they are related to the study treatment.

7.2.1.3. Adverse events of special interest

The following adverse events of special interest (AESIs) are AEs that are of particular concern in CAR T-cell therapy:

- CRS
- ICANS (note: in the event of encephalitis, notify sponsor within 24 hours)
- GvHD

Because AESIs may theoretically occur after Day 28, AESIs will be assessed separately from AEs. Study subjects will be assessed for AESI from the administration of PBCAR20A through Day 360. Any occurrence of an AESI will be monitored closely until stabilization or resolution.

See Section 7.2.5 for additional details regarding reporting AESIs.

7.2.2. Assessment of intensity

The investigator will assess the intensity of each AE reported during the study based on the NCI CTCAE version 5.0 (NCI CTCAE, 2018). If an AE is not addressed in NCI CTCAE, intensity will be assessed according to the standards presented in Table 5. It is important to note that an AE of severe intensity may not necessarily be considered serious (refer to SAE criteria in Section 7.2.1.2).

The intensity of AEs and SAEs related to CRS and ICANS will be assessed based on the ASTCT grading and management recommendations (see Table 7 and Table 8, respectively).

Table 5: Assessment of AE intensity

Intensity grade	Intensity assessment standard
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[b]
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviations: ADL=activities of daily living; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events.

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: NCI CTCAE, version 5.0 (NCI CTCAE, 2018).

7.2.3. Relationship to study treatment

An investigator must make the determination of relationship to the investigational product for each AE ("related" or "not related") according to the definitions and guidance provided in Table 6. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study treatment. If no valid reason exists for suggesting a relationship, then the AE should be classified as "not related." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

Table 6: Relationship assessment definitions

Relationship assessment	Definition/guidance
Not related	Event or laboratory test abnormality, with a time to drug intake that makes a relationship unlikely; is more likely explained by disease or other drugs.
Related	Event or laboratory test abnormality with reasonable time relationship to treatment administration that makes a relationship likely. Unlikely to be attributed to disease or other medications.

7.2.4. Recording AEs

AEs spontaneously reported by the subject and/or in response to an open question from the study staff or revealed by observation will be recorded during the study at the study center. Abnormal values that constitute an AE or lead to discontinuation of the administration of the study treatment must be reported and recorded as an AE. The AE term should be reported in standard

medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome, and whether it caused the study participant to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria presented in Section 7.2.2. An AE of severe intensity may or may not be considered serious.

7.2.5. Reporting AEs

The sponsor is responsible for notifying both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.

The IND safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives a safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and file it along with the IB and notify the IRB, if appropriate, according to local requirements.

Expedited reporting to the FDA will be conducted for the following types of AEs:

- SUSAR
- Serious adverse reaction
- Death regardless of attribution if it occurs within 30 days of the infusion of the study treatment
- Grade ≥4 PBCAR20A-related infusion reactions
- Any ICANS or CRS event that reaches the definition of DLT (see Section 3.8)

7.2.6. Disease-related events and/or disease-related outcomes that do not qualify as AEs or SAEs

Disease-related events (DREs) that are common in the study population, i.e., study subjects with r/r NHL or r/r CLL/SLL, can be serious and life-threatening (shown below). However, because these events are typically associated with the disease under study and with prior treatment, they may not be reported as individual case safety reports even though the event may be listed in the study reference safety information. These events will be recorded in the corresponding eCRF page in the study participant's eCRF during the study.

DREs and prior treatment-related events:

- Progression of the underlying disease.
- Cytopenias related to bone marrow involvement due to the underlying disease, including thrombocytopenia, anemia, neutropenia, lymphopenia.

- Infections associated with disease-related immunodeficiencies and due to extensive prior chemotherapy of the underlying disease. These include fever and bacterial, fungal, and viral infections. These infections may develop at various sites, but most typically develop in blood (bacteremia, fungemia), lungs (pneumonia), urinary tract (urinary tract infection, pyelonephritis), and skin and soft tissues. These infections may be caused by opportunistic pathogens, e.g., aspergillosis, pneumocystis, herpes simplex, and herpes zoster infections.
- Bleeding related to thrombocytopenia or a bleeding diathesis including bleeding in the CNS, lungs, or other sites.

NOTE: However, the event must be recorded as an SAE and not a DRE if investigator considers that there is a reasonable possibility that the event was related to the study treatment based on greater intensity, frequency, or duration than expected for the individual study participant.

Such an event will then be assessed for expedited reporting and reported within regulatory timelines if it meets the IND Safety Reporting criteria per 21 Code of Federal Regulations (CFR) 312.32.

DREs will be assessed at least monthly to determine if there is a greater incidence of any DRE than would be expected from historical rates in study subjects with r/r NHL, r/r CLL, and r/r SLL. If such an imbalance is identified, the case series will be reported as an IND Safety Report per 312 CFR 312.32.

7.2.7. Pregnancy

Details of all pregnancies in female study subjects and, if indicated, female partners of male study subjects will be collected throughout the study (through Day 360).

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 1.

Pregnancy in itself is not regarded as an AE; however, complications of pregnancy or certain pregnancy outcomes may constitute an AE. Contraceptive failure attributed to the investigational product may be an AE.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the study participant was discontinued from the study.

All reports of congenital abnormalities/birth defects will be considered SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

7.3. Management of CRS, ICANS, and GvHD

Once discharged from the study center or hospital, study subjects will be advised to maintain ready access to a caregiver and health care facilities (recommend access to treating hospital within 30 minutes of driving) through Day 28 in the event of a medical emergency.

Educational material will be provided to each study participant/caregiver to monitor for possible signs of CRS, ICANS, and GvHD at home, along with instructions to contact the study center or local hospital as needed.

7.3.1. CRS

CRS is identified based on clinical presentation. Investigators will evaluate and treat other causes of fever, hypoxia, and hypotension. Key manifestations include high fever, lower than normal blood pressure, difficulty breathing, and may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy. Risk factors for severe CRS are high pre-infusion tumor burden (>50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes. Infusion of PBCAR20A should be delayed if the study participant has unresolved serious adverse reactions from preceding chemotherapy or worsening tumor burden. CRS is associated with significantly elevated cytokines including interleukin (IL)-10, IL-6, and interferon (IFN)-ɣ. In subjects with CRS, IL-6 levels are elevated during maximal T-cell proliferation. Targeting IL-6 by using IL-6 inhibitor tocilizumab showed rapid reversal of CRS in subjects treated with CAR T cells and blinatumomab (Teachey et al, 2013). Tocilizumab (Actemra®) IV injection has been approved for the treatment of CAR T cell-induced severe or life-threatening CRS in subjects 2 years of age or older.

In this study, study subjects will be closely monitored for CRS and managed according to severity defined by the ASTCT consensus grading (Lee et al, 2019). The CRS grading and management recommendations are outlined in Table 7; complete ASTCT CRS consensus grading is provided in Table 14. Treatment with tocilizumab, or a combination of tocilizumab and corticosteroids if indicated, will be provided if CRS is suspected. Study subjects who experience Grade 2 or higher CRS (e.g., hypotension that is not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For study subjects experiencing severe CRS, consider performing an ECHO to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 7: CRS grading and management recommendations

ASTCT CRS Grade	Management
Grade 1 Fever with temperature ≥38°C but no hypotension or hypoxia	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Consider growth factors and antibiotics if neutropenic to address neutropenic fever
Grade 2 Fever (≥38°C) with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula	• Supportive care as in Grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab[a] ± dexamethasone or its equivalent of methylprednisolone
Grade 3 Fever (≥38°C) with hypotension requiring a vasopressor with or without vasopressin, and/or hypoxia requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	• Supportive care as in Grade 1 • Consider monitoring in intensive care unit • Vasopressor support and/or supplemental oxygen • Tocilizumab[a] + dexamethasone 1 to 20 mg IV every 6 hours or its equivalent of methylprednisolone
Grade 4 Fever (≥38°C) with hypotension requiring multiple vasopressors (excluding vasopressin) and hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, mechanical ventilation)	• Supportive care as in Grade 1 • Monitoring in intensive care unit • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab[a] + methylprednisolone 1000 mg/day

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; IV=intravenous.

[a] Tocilizumab 8 mg/kg IV over 60 min or per institutional standards. If no clinical improvement in signs/symptoms of CRS after first dose, up to 3 additional doses may be administered with at least 8 hours between consecutive doses.

7.3.2. ICANS

ICANS, which can be fatal or life-threatening, has been observed following administration of anti-CD20 CAR T therapies. In the majority of cases, ICANS occurs within the first 8 weeks following CAR T-cell infusion and can be concurrent with CRS. The most common symptoms include headache, encephalopathy, tremor, dizziness, delirium, aphasia, insomnia, and anxiety. Study subjects should be monitored for signs and symptoms of ICANS for 4 weeks after administration of PBCAR20A infusion and treated promptly if indicated; ASTCT ICANS grading and management guidelines are outlined in Table 8 (Lee et al, 2019). Complete ASTCT ICANS consensus grading is provided in Table 15. Other causes of neurologic symptoms should be ruled out. Study subjects with Grade ≥2 ICANS should be monitored with continuous cardiac telemetry and pulse oximetry. Intensive care support should be provided for study subjects with severe or life-threatening ICANS, and best care should be provided according to the investigator's experience. Investigators should consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for Grade ≥2 ICANS.

Table 8: ASTCT ICANS grading and management guidelines

ASTCT ICANS grade	Defining features of grade	Management
Grade 1	• ICE score 7 to 9 and/or depressed level of consciousness but awakens spontaneously • No seizures, motor weakness, or raised ICP/cerebral edema	• Aspiration precautions and IV hydration • Seizure prophylaxis with levetiracetam • EEG • Imaging of brain • Consider tocilizumab if there is concurrent CRS
Grade 2	• ICE score 3 to 6 and/or depressed level of consciousness but awakens to voice • No seizures, motor weakness, or raised ICP/cerebral edema	• Supportive care as in Grade 1 • Consider dexamethasone or its equivalent of methylprednisolone
Grade 3	• ICE score 0 to 2 and/or depressed level of consciousness but awakens to tactile stimulus • Any clinical seizure focal or generalized that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention • No motor weakness • Focal/local edema on neuroimaging	• Supportive care as in Grade 1 • Dexamethasone 10 to 20 mg IV every 6 hours or its equivalent of methylprednisolone • Control seizures with benzodiazepines (for short-term control) and levetiracetam ± phenobarbital and/or lacosamide • Dexamethasone 10 to 20 mg IV every 6 hours or its equivalent of methylprednisolone • High-dose methylprednisolone 1000 mg/day

ASTCT ICANS grade	Defining features of grade	Management
Grade 4	• ICE score 0 and study participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma • Life-threatening prolonged seizure (>5 minutes); or repetitive clinical or electrical seizures without return to Baseline in between • Deep focal motor weakness such as hemiparesis or paraparesis • Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad	• Supportive care as in Grade 1 • High-dose methylprednisolone 1000 mg/day • Control seizures with benzodiazepines (for short-term control) and levetiracetam ± phenobarbital and/or lacosamide • Imaging of spine • Lower ICP by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt
Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; EEG=electroencephalogram; ICANS=immune effector cell-mediated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; IV=intravenous.		

7.3.3. GvHD

Study subjects who develop GvHD will be assigned a single grade based on organ involvement and severity according to Jacobsohn and Vogelsang (2007) (Table 9). Whenever possible, the clinical diagnosis of a GvHD should be confirmed by biopsy of an affected end organ, and other complications affecting the skin, liver, and gastrointestinal tract should be ruled out by appropriate testing.

Table 9: GvHD grading system based on organ involvement

Grade			
I	Stages 1 to 2 skin, none in liver and gut		
II	Stage 3 skin **or** Stage 1 liver **or** Stage 1 gut		
III	Stages 2 to 3 liver **or** Stages 2 to 4 gut		
IV	Stage 4 skin **or** Stage 4 liver		
Stage	**Skin**	**Liver (bilirubin)**	**Gut (stool output/day)**
0	No GvHD rash	<2 mg/dL	<500 mL/day or persistent nausea
1	Maculopapular rash <25% BSA	2 to 3 mg/dL	500 to 999 mL/day
2	Maculopapular rash 25% to 50% BSA	3.1 to 6 mg/dL	1000 to 1500 mL/day
3	Maculopapular rash >50% BSA	6.1 to 15 mg/dL	Adult: >1500 mL/day
4	Generalized erythroderma plus bullous formation	>15 mg/dL	Severe abdominal pain with or without ileus

Abbreviations: BSA=body surface area GvHD=graft-versus-host disease.

Treatment for GvHD should follow the established institutional guidelines or the consensus by National Institutes of Health (Carpenter et al, 2015) (Table 10). Decisions to begin treatment depend not only on the severity of GvHD manifestations but also on the rate of progression. Rapidly progressing GvHD manifestations require prompt treatment (Martin et al, 2012).

Table 10: GvHD management recommendations

Organ system	**Prevention**	**Treatment**
Skin and appendages	Photoprotection – sun avoidance and physical sunblockers (e.g., protective clothing, UVA, and UVB sunscreens). Avoidance of photosensitizing agents (e.g., voriconazole). Surveillance for malignancy.	For intact skin – topical emollients including urea-containing products, corticosteroids, antipruritic agents, and others (e.g., PUVA or narrow band UVB, calcineurin inhibitors). For erosions/ulcerations – microbiologic cultures, topical antimicrobials, protective films or other dressings, debridement, hyperbaric oxygen, wound care specialist consultation.
Mouth and oral cavity	Maintain good oral/dental hygiene. Routine dental cleaning and radiographs. Surveillance for infection and malignancy.	Topical high and ultra-high potency corticosteroids and topical calcineurin inhibitors. Topical analgesics. Therapy for oral dryness (e.g., salivary

Organ system	Prevention	Treatment
	Nutritional counseling, if needed.	stimulants, sialogogues) and for prevention of related complications (i.e., dental decay).
Eyes	Photoprotection. Surveillance for infection, cataract formation, and increased intraocular pressure.	Artificial tears, ocular ointments, topical corticosteroids or cyclosporine, punctal occlusion, humidified environment, occlusive eye wear, moisture chamber eyeglasses, cevimeline, pilocarpine, gas-permeable scleral contact lens, autologous serum, microbiologic cultures, topical antimicrobials, doxycycline.
Vulva and vagina	Surveillance for estrogen deficiency, infection (herpes simplex virus, human papilloma virus, yeast, bacteria), and malignancy.	Water-based or silicone lubricants, topical estrogens, topical corticosteroids or calcineurin inhibitors, dilators or vibrators, surgery for extensive synechiae or obliteration, early gynecology consultation. Avoid glycerin, paraben, fragrance, and other additive products.
Gastrointestinal tract and liver	Surveillance for infection (viral, bacterial, fungal, parasites).	Rule out other potential etiologies. Dietary modification, enzyme supplementation for pancreatic insufficiency, bile salt resins, gastroesophageal reflux management, esophageal dilatation, ursodeoxycholic acid, topical glucocorticoids, limitation of ethanol/intake, avoidance of hepatotoxins.
Lungs	Surveillance for infection (*Pneumocystis jirovecii*, viral, fungal, bacterial).	Rule out other potential etiologies (e.g., infection, gastroesophageal reflux). Inhaled corticosteroids, bronchodilators, supplementary oxygen, pulmonary rehabilitation. Consideration of lung transplantation in appropriate candidates.
Hematopoietic	Surveillance for infection (cytomegalovirus, parvovirus).	Rule out other potential etiologies (e.g., drug toxicity, infection). Hematopoietic growth factors, immunoglobulin for immune cytopenias.
Neurologic	Calcineurin drug level monitoring. Seizure prophylaxis as indicated, including blood pressure control, electrolyte replacement, anticonvulsants. Electromyography monitoring and staging in symptomatic	Occupational and physical therapy to prevent falls and improve function, treatment of neuropathic syndromes with tricyclic antidepressants, SSRI, or anticonvulsants.

Organ system	Prevention	Treatment
	study subjects taking medications known to cause neuropathy. Close monitoring of distal extremities for wounds in insensate study subjects.	Orthotics and assistive devices (canes and walkers). Bracing, splinting or surgical release for entrapment neuropathies.
Immunologic and infectious diseases	Immunizations and prophylaxis against *Pneumocystis jirovecii*, varicella zoster virus, and encapsulated bacteria based on CDC guidelines. Consider immunoglobulin replacement based on levels and recurrent infections. Surveillance for infection (viral, bacterial, fungal, atypical).	Organism-specific antimicrobial agents. Empiric parenteral broad-spectrum antibacterial coverage for fever.
Musculoskeletal	Surveillance for decreased range of motion, bone densitometry, calcium levels and 25-OH vitamin D. Physical therapy, calcium, vitamin D, and bisphosphonates. Flexion-extension X-rays to look for instability.	Physical therapy, bisphosphonates for osteopenia, and osteoporosis. Spinal orthosis for instability and/or intractable pain. Walking program, resistance training, core strengthening.

Abbreviations: CDC=Centers for Disease Control; GvHD=graft-versus-host disease; PUVA=psoralen and ultraviolet A; SSRI=selective serotonin reuptake inhibitor; UVA=ultraviolet A; UVB=ultraviolet B.

8. ASSESSMENTS OF CLINICAL ACTIVITY

8.1. Assessment of response

Blood samples will be drawn from study subjects at time points indicated in Table 2 to measure complete blood count (CBC), WBC with differentials, and CAR T cells. The criteria for response are outlined below.

MRD assessment will be performed at Screening for all study subjects. The MRD assessment method and status for study subjects with a CR will be determined as clinically indicated using flow cytometry, qPCR, Next Generation Sequencing, or by local institutional standard. Acceptable samples for MRD assessment include BMA or PBMCs for study subjects with CLL, plasma for study subjects with DLBCL, and PBMCs for study subjects with NHL (including SLL). Further details for sample preparation and shipping are specified in the Laboratory Manual.

NHL

The response criteria for local and central assessments of study subjects with NHL are based on the revised Lugano classification (Cheson et al, 2016), which incorporates PET-CT (Table 11).

The PET-CT scan or CT scan for study subjects without PET-avid tumors will be performed for NHL study subjects at time points specified in the study schedules, Section 3.2.

The ORR is the rate of CR + PR.

Table 11: Revised Lugano classification of response

Response and site	**PET-CT-based response**
Complete	Complete metabolic response.
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 (e.g., 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.
New lesions	None.
Bone marrow	No evidence of FDG-avid disease in marrow.
Partial	Partial metabolic response.
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.
New lesions	None.
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with Baseline (diffuse uptake 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.
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.
New lesions	None.
Bone marrow	No change from Baseline.
Progressive disease	Progressive metabolic disease.
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from Baseline and/or new foci compatible with lymphoma.
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.

Response and site	PET-CT-based response
Nonmeasured lesions	None.
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
Bone marrow	New or recurrent FDG-avid foci.

Abbreviations: 5PS=5-point scale; CT=computed tomography; FDG=fluorodeoxyglucose; MRI=magnetic resonance imaging; PET=positron emission tomography.

Note: PET 5-point scale: 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.

CLL/SLL

The response criteria for local and central assessments of subjects with CLL/SLL are based on the iwCLL 2018 guidelines as outlined in Table 12.

Table 12: iwCLL definition of response

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% from Baseline[a]	Increase ≥50% from Baseline or from response	Change of -49% to +49%
	Liver and/or spleen size[b]	Spleen size <13 cm; liver size normal	Decrease ≥50% from Baseline	Increase ≥50% from Baseline or from response	Change of -49% to +49
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from Baseline	Increase ≥50% from Baseline	Change of -49% to +49
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over Baseline	Decrease of ≥50% from Baseline secondary to CLL	Change of -49% to +49
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11.0 g/dL or increase ≥50% over Baseline	Decrease of ≥2 g/dL from Baseline secondary to CLL	Increase <11.0 g/dL or <50% over Baseline, or decrease <2 g/dL

	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

Abbreviations: CLL=chronic lymphocytic leukemia; CR=complete response; CT=computed tomography; iwCLL=International Workshop on Chronic Lymphocytic Leukemia; PD=progressive disease; PR=partial response; SD=stable disease; SLL=small lymphocytic lymphoma

[a] Sum of the products of 6 or fewer lymph nodes as evaluated by CT scans and physical examination.
[b] Spleen size is considered normal if <13 cm as evaluated by imaging and manual palpation.

8.2. Expansion, persistence, and phenotype of PBCAR20A

For exploratory purposes and to understand basic PK and pharmacodynamic properties, including persistence, PBCAR20A cells will be measured in whole blood, tumor tissue and bone marrow specimens using quantitative polymerase chain reaction (qPCR) and flow cytometry by the central laboratory, if available.

The phenotype of PBCAR20A cells in blood, tumor tissue and bone marrow samples will be evaluated by flow cytometry evaluating the expression of markers of T-cell maturation such as CD45RO and CD45RA, CCR7 or CD62L, CD25, and HLA-DR.

Instructions for blood sample collection and tumor tissue or bone marrow samples (when available) and shipping to the central laboratory will be provided in the Laboratory Manual.

8.3. CRS biomarkers

Thirty cytokines and other potential markers for CAR toxicities, including IFN-γ, IL-6, and CRP (through Day 28) in blood samples will be quantified using a multiplex electrochemiluminescence assay (Cytokine Panel 1, Chemokine Panel 1, and Proinflammatory Panel 1 from Meso Scale Discovery) enzyme-linked immunosorbent assay at the time points noted in the study schedules, Section 3.2.

Most exploratory analyses are performed by the central laboratory and a select few will be performed at local laboratories; instructions for collecting and shipping whole blood samples for exploratory testing are described in the Laboratory Manual.

8.4. PET-CT scan

PET-CT scan should be performed at least 7 days prior to study treatments. If the scan is performed as a part of routine care, the result will be obtained from the subject's physician or medical record.

A PET-CT scan on Day 14 is optional and will be determined by the investigator. Whenever possible, the CT scan performed as part of the PET-CT scan should be of diagnostic quality (performed with contrast and with slice thickness ≤5 mm). If the CT scan performed in the PET-CT scan is not of diagnostic quality, a diagnostic quality CT scan is required to be performed at the same time as the PET-CT scan.

8.5. BMA/bone marrow biopsy and analysis

Bone marrow aspiration (BMA) and/or biopsy (unless clinically contra-indicated, or against institutional guidelines) should be performed during the Screening Period before lymphodepletion to determine if cytopenias are related to leukemic infiltration of the marrow in study subjects with CLL/SLL.

On Day 28, BMA and biopsy (unless clinically contra-indicated) should be performed to measure the tumor burden and to assess the presence of PBCAR20A cells in bone marrow in all CLL/SLL study subjects according to the timepoints indicated in the study schedule in Section 3.2. A marrow biopsy is mandatory to confirm a CR in CLL/SLL subjects (see Section 3.2). During study visits at 1, 2, 3, 6, 9, and 12 months or at the time of disease relapse, BMA and biopsy (unless clinically contra-indicated) will be performed in all subjects with previous evidence of bone marrow disease and if it is clinically indicated.

The BMAs/biopsies will be analyzed using smears and flow cytometry by the local laboratories. If BMA/biopsy samples are available and sent to the central laboratory, they will be tested for the presence of PBCAR20A.

In addition, the bone marrow aspirates collected at each time point will be analyzed by the central laboratory for MRD in study subjects with CLL/SLL with a CR (see Section 8.1).

8.6. Tumor biopsy

Core needle biopsies (ideally 4 will be obtained) may be performed in study subjects with mass lesions at any time at least 14 days post-treatment and/or as clinically indicated. For lymph nodes, an excisional biopsy is preferred.

A tumor biopsy may be performed to confirm imaging changes as clinically indicated. Additional biopsies may be performed pending Sponsor approval. Any tumor tissue that remains following a biopsy may be sent to the central laboratory. Please consult the Laboratory Manual for specific sample requirements and shipping information.

9. STATISTICS

9.1. General statistical methods

This is a Phase 1/2a, multicenter, nonrandomized, single-dose, open-label study that will employ the 3 + 3 dose-escalation (Phase 1) design and subsequent dose expansion (Phase 2a).

Results of statistical analyses, descriptive statistics will be presented by PBCAR20A Phase 1 Dose or by Phase 2 Arm. In addition, descriptive statistics will be calculated for subjects across all PBCAR20A Phase 1 dose levels. Supporting listings will be sorted by Phase, Subject ID and Dose/Arm.

Statistical analysis for all safety and efficacy parameters will be primarily descriptive in nature. Categorical variables will be summarized by frequency distributions (number and percentages of study subjects). Continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, and time-to-event variables will be summarized using Kaplan-Meier methods and figures for the estimated median time. No formal statistical hypothesis testing is

planned; however, if exploratory analyses are conducted and confidence intervals (CIs) are provided for estimates, the 95% CIs are consistent with a 2-sided 5% significance level. All analyses, summaries, and listings will be performed using SAS® (Cary, North Carolina) software (version 9.4 or higher).

A detailed methodology for summary and statistical analysis of the data collected in this study will be documented in an SAP that will be finalized prior to database lock. The SAP may modify the data analysis plans outlined in the protocol; any modifications will be clearly documented in the SAP. Any major modifications of the study design or study endpoints and/or its analysis will also be reflected in a protocol amendment.

9.2. Sample size considerations

Phase 1 (dose escalation):

Subjects will be enrolled in dose groups with 3 to 6 subjects for each dose. Dose escalation of PBCAR20A will follow a standard 3 + 3 design with sequential groups of 3 subjects treated with incrementally higher doses of PBCAR20A until a DLT is observed and the MTD is established (see Section 3.1). Per the standard oncology 3 + 3 Phase 1 dose-escalation design, the total number of subjects to be enrolled cannot be precisely determined because the sample size is dependent upon the observed safety profile, which will determine the number of subjects per dose group and the number of dose escalations required to achieve the MTD.

For Phase 1, 4 dose levels may be tested. It is anticipated that approximately 9-30 study subjects will be required to reach the MTD.

Phase 2a (dose expansion):

Enrollment in Phase 2a will begin once the MTD has been determined in Phase 1. A sample of 20 subjects per Arm will evaluate clinical benefit and further characterize safety and pharmacologic properties in specific populations of subjects and allow for the estimation of an ORR within 22% using a 95% CI.

A total of up to 60 subjects will be enrolled for Phase 2a dose optimization. The data collected from subjects enrolled in the dose expansion will be used to confirm safety, explore potential biomarkers, and evaluate potential signals of activity of PBCAR20A.

Under Simon's two stage the minimax design calculation in nQuery, assuming the minimum meaningful clinical response rate is defined as 40% versus maximum ineffective rate of 15%, a sample size of 19 is required to test a null hypothesis of H_0: $\pi \leq 0.15$ versus an alternative hypothesis of H_1: $\pi \geq 0.4$ with a one-sided significance level of 0.05 and 81.32% power, where π is the true proportion of response.

If the number of responses is less than or equal to 1 out of 9 subjects in the first stage then the Arm will be stopped. If the Arm proceeds to the second stage, 19 subjects in total will be needed for evaluation. If 5 or less responses are observed, then that dose is rejected.

For safety, the probabilities of observing at least 1 AE given the true event rate are shown in Table 13.

Table 13: Probability of detecting AE rates by sample size

True event rate	Probability of observing ≥1 event in 20 subjects
1%	18.2%
5%	64.2%
10%	87.8%
15%	96.1%
20%	98.8%
25%	99.7%

Abbreviations: AE=adverse event.

9.3. Analysis population sets

For purposes of planned analysis, the following analysis populations are defined:

- **Intent-to-Treat analysis population** includes all subjects who are eligible for treatment based on inclusion and exclusion criteria and enrolled into the study.
- **Safety analysis population** includes all subjects who receive study treatment. This population will be used to summarize the demographic and baseline characteristics and safety data.
- **Response Evaluable analysis population** includes all subjects who received study treatment PBCAR20A and have at least 1 post-Baseline efficacy assessment. Subjects who discontinue due to disease progression, have a transplant, die, or treatment-related toxicity prior to having a disease assessment will be included in the Response Evaluable population.

9.4. Study participant description

9.4.1. Disposition

A detailed description of subject disposition will be provided. It will include the number of subjects who were enrolled, screen failures, completion/earlier termination status and reasons for termination; first screening date, dose starting and ending dates per dose, number of subjects in Safety and Response Evaluable Populations by Dose and by Arm for each phase.

More details will be provided in the SAP.

9.4.2. Demographic and Baseline characteristics

Demographic characteristics including age, gender, race, and ethnicity will be presented in the form of tabular descriptive statistics. Other Baseline characteristics including, but not limited to, weight, height, body mass index, initial stage of disease, prior therapies, and ECOG Performance Status will be presented similarly.

9.4.3. Concomitant medications

The number and proportion of study subjects using different concomitant medications will be tabulated and summarized by the World Health Organization Drug Anatomical Therapeutic Chemical and preferred term (PT).

9.4.4. Treatment administration/compliance

Study treatment administrations (include both LD and PBCAR20A) will be listed for each subject with drug name, dosing day, dose and number of cells for PBCARCD20A with compliance information, and summarized by Dose, and by Arm for each phase.

9.5. Safety analysis

All subjects who receive at least one dose study treatment (any dose of LD regimen or PBCAR20A) will be included in the summaries and listings of safety data. All analyses will be descriptive.

9.5.1. AEs

The AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system version 20.0 or higher. The severity of the toxicities will be graded according to the NCI CTCAE version 5.0.

In all summaries, emphasis will be placed on TEAEs, namely those with initial onset or those that worsen in severity after the first dose of PBCAR20A. The AEs will be summarized by the frequency of study subjects experiencing TEAEs corresponding to body systems and the MedDRA PT and by worst NCI CTCAE (version 5.0) grade. Summaries will also be provided of treatment-related TEAEs, namely those judged by the investigator to be related or likely related to PBCAR20A.

The SAEs, AEs Grade ≥3, and AEs resulting in discontinuation of PBCAR20A treatment, withdrawal from the study, and deaths occurring during the study will be tabulated.

All DLTs in Phase 1 will be summarized and listed by PBCAR20A dose.

All AESIs, as defined in Section 7.2.1.3, and infections will be assessed and analyzed separately from AEs from the administration of PBCAR20A to end of study participation.

9.5.2. Laboratory tests

Laboratory data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes from Baseline (the value obtained prior to dosing on Day 1) using descriptive statistics.

For those analytes with CTCAE version 5.0 severity criteria, abnormal laboratory values will be summarized by shift tables displaying numerical values and percentages classified by Baseline grade (i.e., grade prior to dosing on Day 1) and maximum grade on treatment. All laboratory data will be presented in listings.

9.5.3. ECGs

The ECG parameters (PR interval, QRS duration, QT, QTc, and QTcF) will be summarized descriptively by Dose or by Arm and overall.

9.5.4. Vital signs and physical examination findings

Vital signs data will be summarized using descriptive statistics by the observed valued at each scheduled assessment and the corresponding changes from Baseline.

Physical examination findings will be presented in data listings.

9.6. Efficacy analysis

Since the primary objective of this study is to determine the safety and tolerability of PBCAR20A, an appropriate dose to optimize safety and efficacy, and to optimize the treatment regimen, an estimation approach will be applied to efficacy data analyses. ORR to treatment with PBCAR20A through Day 360 will be noted using the Lugano criteria for NHL and iwCLL for CLL/SLL (Section 8.1). The ORR is defined as the proportion of study subjects meeting the definition of response (PR+CR for both Phase 1 and 2a Arm C NHLs and PR+CR for Phase 1 CLL/SLL subtype). The ORR will be summarized by number and percentage of subjects meeting the definition of ORR along with the corresponding exact 95% CIs for all Phase 1 dose level and for Phase 2a Arm B and C, where CR with corresponding exact 95% CI will be presented for Phase 2a Arm A.

DoR, defined as the duration (days) from initial response to disease relapse or progression or death; PFS, defined as the duration (days) from Day 0 to disease relapse, progression, or death will be descriptively analyzed using Kaplan-Meier methods. Exploratory efficacy analyses include changes from Baseline in CBC counts, CAR T cells, cytokines, and CRP levels, and the number of subjects who have received allogeneic stem cell transplant. Exploratory efficacy endpoints and detailed analyses will be included in the SAP.

9.7. Interim analysis

A formal interim analysis is planned for the Phase 1 data when the last subject completed the study.

Dose escalation investigator calls consisting of the investigators, the medical monitor, and sponsor representative(s) will provide safety oversight during the study. The group will review safety data at regular intervals to discuss any unexpected significant toxicities and to determine whether dose escalation is appropriate.

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10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

10.1. Study monitoring

Before a study center can enter a study participant into the study, a representative of the sponsor will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the sponsor or its representatives. This will be documented in a Clinical Study Agreement between the sponsor and the investigator.

During the study, a medical monitor from the sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the study participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each study participant (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the sponsor.
- Confirm AEs and SAEs have been properly documented in the eCRFs and confirm any SAEs have been forwarded to the sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The medical monitor will be available between visits if the investigator(s) or other staff needs information or advice.

10.2. Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

10.3. IRB

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval and all materials approved by the IRB for this study, including the ICF and recruitment materials, must be maintained by the investigator and made available for inspection.

10.4. Data protection

Study subjects will be assigned a unique identifier by the sponsor. Any study participant records or datasets that are transferred to the sponsor will contain the identifier only; study participant names or any information that would make the study participant identifiable will not be transferred.

The study participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the study participant.

The study participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

11. QUALITY CONTROL AND QUALITY ASSURANCE

All study participant data relating to the study will be recorded in the eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Medical monitors will perform ongoing source data verification to confirm that data entered in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of study subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12. ETHICS

12.1. Ethics review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to the sponsor before he or she can enroll any study participant into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendments to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit study subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

12.2. Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, applicable regulatory requirements, and the sponsor's policies.

12.3. Written informed consent

The Principal Investigator(s) at each center will ensure that the study participant is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Study subjects must also be notified that they are free to discontinue from the study at any time. The study participant should be given the opportunity to ask questions and allowed time to consider the information provided.

The study participant's signed and dated ICF must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the study participant.

13. DATA HANDLING AND RECORDKEEPING

13.1. Inspection of records

The sponsor will be allowed to conduct site visits to the study centers for the purpose of monitoring any aspect of the study. The investigator agrees to allow the medical monitor to inspect the drug storage area, study treatment stocks, drug accountability records, study participant charts and study source documents, and other records relative to study conduct.

13.2. Retention of records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

14. PUBLICATION POLICY

This study is registered on the US National Institute of Health's web site www.clinicaltrials.gov.

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16. APPENDICES

Appendix 1. Contraceptive guidance and collection of pregnancy information

Definitions

Woman of childbearing potential (WOCBP)

A WOCBP is defined as any woman who is not postmenopausal or who has not had a hysterectomy. Postmenopausal is defined as being over the age of 55 and not having had a menstrual period for at least 1 year.

Contraception guidance

Male study subjects

Male study subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study treatment period (Day 0 through Day 90):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a highly effective contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male study subjects must refrain from donating sperm for the duration of the study.

Male study subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study treatment period.

Female study subjects

Female study subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception.

Highly effective contraceptive method

At least 1 of the methods below should be used in combination with male condoms:

- Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation, delivered orally, intravaginally, or transdermally.
- Progestogen-only hormonal contraception associated with inhibition of ovulation, delivered orally, via injection, or implanted.
- An intrauterine device.
- An intrauterine hormone-releasing system.

Pregnancy testing

The WOCBP should only be included after a negative pregnancy test at screening.

Pregnancy test will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of pregnancy information

Male study subjects with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male study participant's female partner who becomes pregnant while the male study participant is in this study. This applies only to male study subjects who receive PBCAR20A.

After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female study subjects who become pregnant

The investigator will collect pregnancy information on any female study participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a study participant's pregnancy. The study participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the study participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 7.2.5. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female study participant who becomes pregnant after receiving PBCAR20A will be followed through after giving birth or after the pregnancy is terminated.

Appendix 2. ASTCT consensus grading

Table 14: ASTCT CRS consensus grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/Or[b]		
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by oxygen delivery	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubations, mechanical ventilation)

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome.

[a] Fever is defined as temperature ≥38°C not attributable to any other cause. In study subjects with CRS who then receive antipyretic or anticytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

Source: Lee et al, 2019.

Table 15: ASTCT ICANS consensus grading for adults

	Neurotoxicity domain				
	ICE score[a]	**Depressed level of consciousness**[b]	**Seizure**	**Motor findings**[c]	**Elevated ICP/cerebral edema**
Grade 1	7 to 9	Awakens spontaneously	N/A	N/A	N/A
Grade 2	3 to 6	Awakens to voice	N/A	N/A	N/A
Grade 3	0 to 2	Awakens only to tactile stimulus	Any clinical seizure focus or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	N/A	Focal/local edema on neuroimaging[d]
Grade 4	0 (study participant is unarousable and unable to perform ICE)	Study participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to Baseline in between	Deep focal motor weakness such as hemiparesis or paraparesis	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviations: ASTCT=American Society for Transplantation and Cellular Therapy; CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICANS=immune effector cell-mediated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; N/A=not applicable.

[a] A study participant with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a study participant with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

[b] Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

[c] Tremors and myoclonus associated with IEC therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Note: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause. For example, a study participant with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

Source: Lee et al, 2019.

16.1. Protocol version summary of changes

16.1.1. Version 5.0

The following substantive changes were made from version 4.0 (dated 09 Sep 2020) to version 5.0 (dated 09 Feb 2021). Administrative and editorial changes were also made for correction and/or consistency throughout the document.

Global changes:

- Phase 2a arms A, B, and C were added along with rationale for associated lymphodepletion and PBCAR20A treatment regimens
- Primary and secondary objectives and endpoints for Phase 2a arms were added
- Inclusion/exclusion criteria were updated for clarity and to reflect specific cohorts to be enrolled in each Phase 2a arm
- Enrollment for Phase 2a was increased to up to 20 subjects in each arm
- Dose Level 2 was changed to 240×10^6 cells
- Criteria for retreatment were clarified

16.1.2. Version 4.0

The following substantive changes were made from version 3.0 (dated 13 Jan 2020) to version 4.0 (dated 09 Sep 2020). Administrative and editorial changes were also made for correction and/or consistency throughout the document.

Global changes:

- In Phase 1 of the study, the NHL and CLL/SLL cohorts have been combined for safety evaluation. In Phase 2a, the study will enroll two separate cohorts (one for NHL and one for CLL/SLL).
- Clarification that subjects in Phase 2a will be dosed at or below the MTD determined in Phase 1.
- The number of subjects and study centers has been adjusted to account for protocol changes.
- Phase 1 Dose Level 3 has been changed to a flat dose of 480×10^6 cells with a maximum dose of 4.8×10^8 cells.
- Updates have been made to the inclusion/exclusion criteria, including removal of the exclusion criterion for subjects with active hemolytic anemia.
- Overall survival (OS) has been removed as a secondary endpoint.
- Retreatment criteria have been added for subjects who exhibit some evidence of therapeutic benefit following one dose of PBCAR20A.
- A timeframe has been specified for the DLT of Grade ≥3 neurotoxicity (per American Society for Transplantation and Cellular Therapy [ASTCT] ICANS such that if there is

resolution or reduction to Grade ≤2 within 72 hours of onset, it is no longer considered a DLT.

- Staggering between the first and second subject in a dose level has been reduced from 28 to 14 days.
- Clarification that BMA or bone marrow core biopsy will be collected.
- The Synopsis has been updated where relevant to reflect all changes.

Section	Original text	Revised text	Rationale
Table 1; Key study contact information	Precision BioSciences medical representative was originally [redacted]	Precision BioSciences medical representative has been updated to [redacted]	Update/ clarification
3.1, Overall study design	This is a Phase 1/2a, nonrandomized, open-label, parallel assignment, single-dose, dose-escalation, and dose-expansion study to evaluate the safety and clinical activity of PBCAR20A in adults with r/r $CD20^+$ B-cell NHL (Cohort A) or r/r $CD20^+$ CLL/SLL (Cohort B).	This is a Phase 1/2a, nonrandomized, open-label, parallel assignment, single-dose, dose-escalation, and dose-expansion study to evaluate the safety and clinical activity of PBCAR20A in adults with r/r $CD20^+$ B-cell NHL including r/r $CD20^+$ CLL/SLL. Starting with protocol version 4.0, as all subjects enrolled to date have been NHL subjects, the Phase 1 portion of the study will continue to enroll and treat all subjects as one cohort. The Phase 2 portion of the study will enroll two separate cohorts, 1 for NHL subjects and 1 for CLL/SLL subjects.	Phase 1 disease cohorts have been combined for safety evaluation.
3.1, Overall study design	New text added to clarify dosing cohorts and number of intended subjects.	If DLTs are found to occur predominantly in one subtype of NHL subjects (i.e., those with indolent lymphoma, including follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and marginal zone lymphoma or aggressive lymphoma, such as diffuse large B cell lymphoma, PMBCL, Burkitt lymphoma, and other high grade T cell lymphomas), the possibility of separating the cohorts for dose escalation may be explored. For characterization of the pharmacology, safety profile, and clinical benefit profile, up to 18 subjects total may be enrolled in any given dose level for which safety has been established (i.e., ≤1 of 6 subjects experiences a DLT). These additional 12 subjects (any subjects after subject 6) will not be considered for determination of the MTD and can be	Clarification

<table>
<tr><th>Section</th><th>Original text</th><th>Revised text</th><th>Rationale</th></tr>
<tr><td></td><td></td><td>enrolled without delays into that dose level.</td><td></td></tr>
<tr><td>3.3, Number of study subjects</td><td>Part 1 (dose escalation):
Approximately 12 to 18 evaluable study participants are planned to be enrolled in each of the 2 disease cohorts for a total of 24 to 36 study participants.</td><td>Part 1 (dose escalation):
Approximately 9 to 30 evaluable subjects are planned to be enrolled in Phase 1 of the study.</td><td>Update/ clarification</td></tr>
<tr><td>3.4, Number of study centers</td><td>Approximately 4 study centers for Phase 1 and approximately 8 additional centers for Phase 2a in the United States.</td><td>Approximately 10-15 study centers in the United States.</td><td>Update/ clarification</td></tr>
<tr><td>3.6, cohorts and dose escalation</td><td>
<table>
<tr><th>Dose level</th><th>Number of CAR T cells/kg</th><th>Max cells/dose</th></tr>
<tr><td>Dose -1</td><td>3×10^5</td><td>3×10^7</td></tr>
<tr><td>Dose 1 (starting)</td><td>1×10^6</td><td>1×10^8</td></tr>
<tr><td>Dose 2</td><td>3×10^6</td><td>3×10^8</td></tr>
<tr><td>Dose 3</td><td>6×10^6</td><td>6×10^8</td></tr>
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<table>
<tr><th>Dose level</th><th>Number of CAR T</th><th>Max cells/dose</th></tr>
<tr><td>Dose -1</td><td>3×10^5 cells/kg</td><td>3×10^7</td></tr>
<tr><td>Dose 1 (starting)</td><td>1×10^6 cells/kg</td><td>1×10^8</td></tr>
<tr><td>Dose 2</td><td>3×10^6 cells/kg</td><td>3×10^8</td></tr>
<tr><td>Dose 3</td><td>480×10^6 cells</td><td>4.8×10^8</td></tr>
</table>
</td><td>Added flat dose for Dose Level 3 and adjusted maximum cells/dose.</td></tr>
</table>

Section	Original text	Revised text	Rationale
3.7, Retreatment criteria	New section added.	Retreatment refers to the specific scenario in which a subject receives all planned treatment and has some evidence of benefit followed by evidence of disease progression. All subjects will receive PBCAR20A as per the Schedule of Activities (SoA; Table 2). A subject may receive an additional dose of PBCAR20A if he/she meets retreatment criteria as determined by the investigator and agrees to be retreated. Subjects are eligible for retreatment only if the following criteria are met: • Subject has documented evidence of tumor response to initial dose of PBCAR20A followed by documented disease progression at subsequent visit. • Subject has biopsy-proven CD20+ tumor at progression. • Subject has no evidence of GvHD and no new disease-related central nervous system (CNS) involvement. • Subject has adequate bone marrow, renal, hepatic, pulmonary, and cardiac function as defined in Section 4.1. • Subject has not received another systemic treatment for NHL. Subjects who meet the retreatment criteria and have had a study visit within 30 days will undergo lymphodepletion chemotherapy and follow the SoA from the beginning. Subjects who meet the retreatment criteria and have discontinued the study will need to be re-enrolled into an open slot (Phase 1 or Phase 2a). Retreatment visits, starting from lymphodepletion visits, will be distinguished from initial visits in the electronic case report form (eCRF). Subjects eligible for retreatment may receive PBCAR20A at the highest dose level with established safety (see Section 3.1).	New addition to this protocol to allow a second dose of PBCAR20A in subjects who demonstrate some evidence of efficacy.

Section	Original text	Revised text	Rationale
3.8, Criteria for DLTs	• Any Grade ≥3 neurotoxicity (per American Society for Transplantation and Cellular Therapy [ASTCT] ICANS criteria provided in Table 15).	• Any Grade ≥3 neurotoxicity (per American Society for Transplantation and Cellular Therapy [ASTCT] ICANS criteria provided in Table 15) that does not resolve or reduce to Grade ≤2 within 72 hours of onset.	To ensure MTD is adequately evaluated.
3.10, Criteria for temporarily suspending treatment	In addition to the staggered dosing schedule (28 days between the first 2 study participants and 14 days between the second and third study participant in each dose group, including the dose de-escalation group if applicable).	In addition to the staggered dosing schedule (14 days between the first 2 study subjects in each dose group, including the dose de-escalation group if applicable).	Based on data collected in PBCAR0191-01; 14 day safety evaluation period is adequate.
4.1 and 4.2, Inclusion and Exclusion Criteria	Several updates have been made to the I/E criteria across NHL and CLL/SLL. The most notable changes are captured below:	Refer to track changes version of the protocol for a full comparison of changes made to the I/E criteria.	Clarifications
4.5, Study completion	A study participant is considered to have completed the entire study if the study participant is followed according to the protocol to the Day 360 visit, disease progression, death, or receiving a new treatment for MM (including stem cell transplant), whichever occurs first.	Subjects experiencing disease progression prior to day 28 should continue on the study through Day 28 to allow for completion of study's primary evaluation as long as another systemic therapy is not started. A subject is considered to have completed the entire study if the subject is followed according to the protocol to the Day 360 visit, disease progression, death, or receiving a new treatment for the diagnosed malignancy (including stem cell transplant), whichever occurs first.	To ensure subject monitoring and collection of data.

16.1.3. Version 3.0

The following substantive changes were made from version 2.0 (dated 04 Oct 2019) to version 3.0 (dated 13 Jan 2020). Administrative and editorial changes were also made for correction and/or consistency throughout the document.

Global changes:

- The dose levels were increased and a maximum number of cells (based on 100 kg subject) for each dose level was added.
- The Screening window was increased from 21 days to 28 days. Windows for Screening MRIs and lumbar punctures were added.
- Duration of response was removed as an endpoint.
- Additional secondary endpoints were added:
  - Progression-free survival
  - Overall survival
  - Incidence of AEs, SAEs, and DLTs related to the investigational product
- The dose escalation procedure was clarified.
- A window of -5 days was added to lymphodepletion chemotherapy.
- AEs and concomitant medications will be collected through Day 360

Section	Original text	Revised text	Rationale
Table 2, schedule of activities		A row for MRD assessment was added with the corresponding footnote: MRD assessment will be performed at Screening for all subjects. Please consult the Laboratory Manual for specific sample requirements at Screening. At subsequent visits, MRD assessment will only be performed for subjects who meet other standard response criteria (see Section 8.1). Please consult the Laboratory Manual for specific sample requirements at all subsequent visits. Note that these samples are disease-specific and may be different between Screening and all subsequent visits.	Clarification of procedures.

<table>
<tr><th>Section</th><th>Original text</th><th>Revised text</th><th>Rationale</th></tr>
<tr><td>3.6, cohorts and dose escalation</td><td><table><tr><td>Dose level</td><td>Number of CAR T cells/kg</td></tr><tr><td>Dose -1</td><td>3×10^4</td></tr><tr><td>Dose 1 (starting)</td><td>3×10^5</td></tr><tr><td>Dose 2</td><td>1×10^6</td></tr><tr><td>Dose 3</td><td>3×10^6</td></tr></table></td><td><table><tr><td>Dose level</td><td>Number of CAR T cells/kg</td><td><u>Max cells/dose</u></td></tr><tr><td>Dose -1</td><td><u>3×10^5</u></td><td><u>3×10^7</u></td></tr><tr><td>Dose 1 (starting)</td><td><u>1×10^6</u></td><td><u>1×10^8</u></td></tr><tr><td>Dose 2</td><td><u>3×10^6</u></td><td><u>3×10^8</u></td></tr><tr><td>Dose 3</td><td><u>6×10^6</u></td><td><u>6×10^8</u></td></tr></table></td><td>Increased dose level to improve efficacy.</td></tr>
<tr><td>4.1, inclusion criteria</td><td>Estimated glomerular filtration rate >60 mL/min/1.73 m^2</td><td>Estimated glomerular filtration rate >30 mL/min/1.73 m^2</td><td>Clarification.</td></tr>
<tr><td>4.2, exclusion criteria</td><td><u>Criteria for NHL:</u>
Active central nervous system (CNS) disease. A negative computed tomography (CT)/magnetic resonance imaging (MRI) is required at Screening if the study participant has a history of CNS lymphoma.

<u>Criteria for CLL/SLL:</u>
Active CNS disease. A negative lumbar puncture is required at Screening if the study participant has a history of CNS disease.</td><td><u>Criteria for NHL:</u>
<u>Any history</u> of central nervous system (CNS) disease. <u>If active CNS involvement is suspected,</u> a negative computed tomography (CT)/magnetic resonance imaging (MRI) is required at Screening.

<u>Criteria for CLL/SLL:</u>
<u>Any history</u> of CNS disease<u>. If active CNS involvement is suspected</u>, a negative lumbar puncture is required at Screening.</td><td>Clarification.</td></tr>
<tr><td>7.1.5, immunogenicity</td><td>Blood samples will be collected from all study participants according to Table 2 and shipped to the central laboratory, where they are archived as PBMCs and serum.</td><td>Blood samples will be collected from all study participants according to Table 2 and analyzed by the local laboratory.</td><td>Clarification of procedures.</td></tr>
<tr><td>7.2.1.1 AE</td><td>All AEs will be collected from the initiation of lymphodepletion chemotherapy through Day 28 and be recorded in the eCRF, regardless of whether or not</td><td>All AEs will be collected from the initiation of lymphodepletion chemotherapy <u>until death, disease progression, subsequent systemic therapy, withdrawal due to intolerable toxicity, withdrawal of consent, or Day 360, whichever occurs first</u> and be recorded in the</td><td>Clarification of procedures.</td></tr>
</table>

Section	Original text	Revised text	Rationale
	they are related to the study treatment.	eCRF, regardless of whether or not they are related to the study treatment. All AEs collected through Day 28 will be used for assessment of DLTs; any AEs occurring after Day 28 will be considered in dose-escalation decisions and monitoring procedures as appropriate.	

16.1.4. Version 2.0

The following substantive changes were made from version 1.0 (dated 30 Jul 2019) to version 2.0 (dated 04 Oct 2019). Administrative and editorial changes were also made for correction and/or consistency throughout the document.

Global changes

- "Data Safety Monitoring Board" was changed to "Safety Review Committee" for Phase 1
- The dose escalation algorithm and DLT definition were clarified

Section	Original text	Revised text	Rationale
2.3, exploratory objectives and endpoints		Removed RECIL assessment from exploratory objectives.	Clarification.
3.1, overall study design	The first treated study participant in each dose group (including the dose de-escalation group, i.e., Dose 1) will be observed for 14 days for safety before any subsequent study participant receives any study treatment to provide an adequate safety monitoring window. Once the first study participant in each cohort has completed Day 14 of dosing with no DLTs, the second and third study participants can be enrolled simultaneously at the same dose.	The first treated study participant in each dose group (including the dose de-escalation group, i.e., Dose 1) will be observed for 28 days for safety before any subsequent study participant receives any study treatment to provide an adequate safety monitoring window. There will be a staggered interval of 14 days between the second and third study participants. If no DLTs are observed, then subsequent study participants at that dose level can be treated without a formal stagger delay. Cohorts A and B will proceed with dose escalation separately. The following paragraph was added: During Part 2, a Data and Safety Monitoring Board (DSMB) will meet regularly to review safety and efficacy data during Part 2 of the study. A DSMB charter will be established before Part 2 of the study commences.	Modified staggered dosing intervals and clarification of procedures.
3.2, Table 2 schedule of activities		Tumor/liquid biopsy ~~(NHL only)~~ is optional from Day 14 to Day 360. Footnote m was modified: m. Screening tumor biopsy may be omitted if a study participant has had a biopsy showing $CD20^+$ disease within 6 months before Screening and has not received any anti-$CD20^+$ therapy since then. Note: If the tumor is CD20-negative by flow cytometry, it should be evaluated by immunohistochemistry as flow assays may result in false negatives due to competition with	Clarification of procedures.

Section	Original text	Revised text	Rationale
		CD20 targeting treatment antibodies (e.g. rituximab). Footnote n was added: Tumor biopsy may be performed to confirm imaging changes as clinically indicated. Additional biopsies may be performed pending Sponsor approval.	
3.7, criteria for DLTs	• CRS (per American Society for Transplantation and Cellular Therapy [ASTCT] consensus grading; see Section 7.3.1): Grade ≥3 that does not resolve or reduce below Grade 3 within 7 days. • Grade ≥3 toxicity of vital organs (heart, lung, liver, and kidney) associated with CRS that does not decrease to Grade ≤2 within 7 days or is not clinically manageable. • Any Grade 4 neurotoxicity (per American Society for Transplantation and Cellular Therapy [ASTCT] ICANS criteria provided in Table 16), regardless of duration, or Grade 3 neurotoxicity that shows no evidence of improvement for >72 hours after onset or that extends beyond 7 days. Evidence of improvement at 72 hours includes at least 1 of the following: – Increase in ICE score from worst score – Improvement in depressed level of consciousness to Grade	• CRS (per American Society for Transplantation and Cellular Therapy [ASTCT] consensus grading; see Section 7.3.1): – Any Grade 4 – Any Grade 3 that does not resolve or reduce to Grade ≤2 within 72 hours of onset • Any Grade ≥3 neurotoxicity (per American Society for Transplantation and Cellular Therapy [ASTCT] ICANS criteria provided in Table 15) • Any seizure • Grade 3 or 4 infusion reactions related to the study treatment that does not resolve or decrease to Grade ≤2 within 48 hours • Any Grade 4 hematologic toxicity, except lymphopenia, that does not resolve or decrease to Grade ≤2 within 42 days – Any Grade 4 non-hematologic toxicity – Any Grade 3 toxicity involving heart and lungs – Any Grade 3 toxicity involving kidney and liver	Clarification of DLTs.

Section	Original text	Revised text	Rationale
	1 or 2 level, if previously Grade 3 – No evidence of ongoing seizure events if seizure events were recorded – Improvements of motor weakness if any previously identified – Resolution of elevated intracranial pressure or cerebral edema if any observed • Any Grade 3 neurotoxicity lasting >3 consecutive days despite medical management, except for intermittent Grade 3 headache or isolated motor deficits, such as aphonia, that do not significantly affect activities of daily living. • Any Grade 4 hematologic toxicity, except lymphopenia, that does not resolve or decrease to Grade ≤2 within 42 days. • Any non-CRS related TEAE Grade ≥3 to vital organs (heart, lung, liver, and kidney) that does not decrease to Grade ≤2 within 4 days and is clinically meaningful. • Any Grade 5 CRS or any Grade 5 toxicity that was not due to underlying malignancy.	that does not resolve or reduce Grade ≤2 within 7 days of onset – Any Grade 3 toxicity to other organs that does not resolve or reduce Grade ≤2 within 72 hours of onset • Any Grade 5 toxicity that was not due to underlying malignancy	

Section	Original text	Revised text	Rationale
	• Other Grade 3 or 4 toxicities, unless there is a clear alternative explanation.		
3.8, criteria for treatment interruption	Previously Section 4.4.2.	No changes to text.	Clarification.
3.9, criteria for temporarily suspending treatment	In addition to the 14-day staggered dosing schedule between the first 2 study participants in each dose group (including the dose de-escalation group if applicable), dosing in all study participants, regardless of cohort and dose group, will temporarily stop if any of the following events occur: • Grade 4 toxicities related to CRS • Grade ≥3 GvHD • Any death that is possibly or probably related to the study treatment	In addition to the staggered dosing schedule (<u>28 days between the first 2 study participants and 14 days between the second and third study participant in each dose group</u>, including the dose de-escalation group if applicable), dosing in all study participants, regardless of cohort and dose group, will temporarily stop if any of the following events occur: • Any Grade 4 toxicity that is <u>possibly or probably related to the study treatment</u> • Grade ≥3 GvHD • Any death that is possibly or probably related to the study treatment	Clarification of procedures.
4.1, inclusion criteria	5. Study participants with CLL/SLL must have previously failed/tolerant to at least 2 prior lines of systemic targeted therapy of known benefit. 7. Total bilirubin <2.0 mg/dL, except in study participants with	5. Study participants with CLL/SLL must have previously failed/tolerant to at least 2 prior lines of systemic targeted therapy <u>including a Bruton tyrosine kinase inhibitor and venetoclax ± rituximab</u>. <u>6. Study participant has $CD20^{+}$ tumor. Note: If the tumor is CD20-negative by flow cytometry, it should be evaluated by immunohistochemistry as flow assays may result in false negatives due to competition with CD20 targeting treatment antibodies (e.g., rituximab).</u>	Clarification.

Section	Original text	Revised text	Rationale
	Gilbert's syndrome, who must have total bilirubin ≤5 × ULN.	8. Total bilirubin <2.0 mg/dL, except in study participants with Gilbert's syndrome, who must have total bilirubin ≤3 × ULN	
4.2, exclusion criteria	29. Study participant must not have received systemic corticosteroid therapy for at least 1 day prior to initiating lymphodepletion chemotherapy. Titration may be managed by the investigator.	30. Study participant must not have received systemic corticosteroid therapy for at least 7 days prior to initiating lymphodepletion chemotherapy. Titration may be managed by the investigator.	Clarification.
4.4, study discontinuation or withdrawal		"Study participant noncompliance/protocol violation," "study terminated by sponsor," "study participant withdrawal," and "lost to follow-up" were added to the reasons for study discontinuation or withdrawal.	Clarification of procedures.
5.1.3, hospitalization		The following was added: Study participants with Burkitt lymphoma or high tumor burden DLBCL/Richter's transformation CLL should receive prophylaxis for tumor lysis syndrome (including rasburicase, if indicated) and be hospitalized to undergo frequent monitoring (chemistries, LDH, and uric acid every 6 hours for up to 96 hours post-treatment). If tumor lysis does occur, there should be aggressive correction of electrolytes.	Clarification of procedures.
7.3.1, Table 8, CRS grading and management recommendations		Footnote was added: a. Tocilizumab 8 mg/kg IV over 60 min or per institutional standards. If no clinical improvement in signs/symptoms of CRS after first dose, up to 3 additional doses may be administered with at least 8 hours between consecutive doses.	Clarification of procedures.

Section	Original text	Revised text	Rationale
8.1, assessment of response		The following text was moved from Section 8.5 and Section 8.6 and applies to all study participants. The MRD assessment method and status for study participants with a CR will be determined as clinically indicated using flow cytometry, qPCR, Next Generation Sequencing, or by local institutional standard.	Clarification.
8.6, tumor biopsy ~~for NHL study participants~~	Core needle biopsies (minimum of 4 should be obtained) will be performed in study participants with NHL at time points in Table 2 or as clinically indicated. For lymph nodes, an excisional biopsy is preferred. A core biopsy at Day 14 is optional for restaging and analysis of T-cell infiltration, which will be performed in selected study participants based on the investigator's judgment and discussion with the study participant.	Core needle biopsies (ideally 4 will be obtained) may be performed in study participants with mass lesions at any time at least 14 days post-treatment and/or as clinically indicated. For lymph nodes, an excisional biopsy is preferred. A tumor biopsy may be performed to confirm imaging changes as clinically indicated. Additional biopsies may be performed pending Sponsor approval.	Clarification of procedures.