University of Pennsylvania

UPCC03712: DOSE OPTIMIZATION TRIAL OF AUTOLOGOUS T CELLS ENGINEERED TO EXPRESS ANTI-CD19 CHIMERIC ANTIGEN RECEPTOR (CART-19) IN PATIENTS WITH RELAPSED OR REFRACTORY CD19+ CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Principal Investigator:	*Noelle Frey, MD* *Department of Medicine* *Perelman School of Medicine* *Philadelphia, Pennsylvania 19104*
Sub-Investigators:	*Stephen Schuster, MD* *Sunita Nasta, MD* *Selina Luger, MD* *Alison Loren, MD, MSCE* *Elizabeth Hexner, MD* *Jakub Svoboda, MD* *Edward Stadtmauer, MD* *Marcela Maus, MD, PhD* *James Mangan, MD, PhD* *Anthony Mato, MD*
Laboratory Investigators:	*Bruce Levine, PhD* *Simon Lacey, PhD*
Regulatory Sponsor:	*Carl June, MD* *Department of Pathology and Laboratory Medicine* *Perelman School of Medicine* *Smilow Center for Translational Research, Room 08-123* *Philadelphia, PA 19104-51560* *215-746-5133*
Funding Organization:	*Novartis Pharmaceuticals Corp* *One Health Plaza* *East Hanover, NJ 07936*
Study Product:	*CD19 redirected autologous T cells (CART-19-T Cells)*
Protocol Numbers:	IRB #816556, UPCC 03712, CTL019A2201
IND Number:	BB-IND 13960

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Date: **Aug 7, 2012**
Sept 28, 2012
October 24, 2012
November 20, 2012
January 21, 2013, January 29, 2013
March 11, 2013
May 28, 2013
September 30, 2013
March 24, 2014
July 18, 2014
November 12, 2014
March 5, 2015

Medical Monitor Susan Rheingold, MD
Children's Hospital of Philadelphia

STUDY TEAM

Clinical Trial Site - University of Pennsylvania

Principal Investigator
Noelle Frey, MD

Clinical Team
Stephen Schuster, MD
Selina Luger, MD
Sunita Nasta, MD
Alison Loren, MD, MSCE
Elizabeth Hexner, MD
Edward Stadtmauer, MD
Jakub Svoboda, MD
Marcela Maus, MD, PhD
James Mangan, MD, PhD
Anthony Mato, MD

Protocol Advisor
David Porter, MD

Statistical Team
Wei-Ting Hwang, PhD

Quality Assurance for Manufacturing
Phil Cross Associates

Immune Correlative Studies
Simon Lacey, PhD

Sponsor Cell Manufacturing – University of Pennsylvania
Bruce Levine, PhD, Laboratory Director

CONFIDENTIAL
This document is confidential and the property of the University of Pennsylvania. No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorization from the study sponsor.

STUDY MANAGEMENT

Clinical Management Questions

For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact David.Porter@uphs.upenn.edu or Noelle.Frey@uphs.upenn.edu. Include the protocol number in the subject line and patient identification number (PID) and a brief relevant history in the message.

Laboratory Questions

For questions specifically related to clinical laboratory tests, contact the Project Managerat trpctu@mail.med.upenn.edu; for questions related to research laboratory tests, contact the Translational Correlative Sciences Laboratory (TCSL) at Simon.Lacey@uphs.upenn.edu. For questions related to cell manufacturing, contact the CVPF Laboratory Director at levinebl@mail.med.upenn.edu.

Data Management Questions

For nonclinical questions about inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, transfers, delinquencies, and other data management issues, contact the Project Manager at trpctu@mail.med.upenn.edu. For statistical questions, contact the Protocol Statistician. Send an e-mail message to Wei-Ting Hwang (whwang@mail.med.upenn.edu). Include the protocol number, PID, and a detailed question.

Protocol Document Questions

For questions concerning the protocol document, contact the Project Manager at trpctu@mail.med.upenn.edu.

Copies of the Protocol

To request hard copies of the protocol contact the Project Manager at trpctu@mail.med.upenn.edu.

Study Drug/Cell Manufacturing Questions

For questions related to cell manufacturing, contact the CVPF Laboratory Director at levinebl@mail.med.upenn.edu.

IND Number or Questions

Contact the Project Manager at trpctu@mail.med.upenn.edu.

Adverse Event Reporting/Questions

Contact the Project Manager at trpctu@mail.med.upenn.edu.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Table of Contents

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

List of Abbreviations

aAPC	Artificial APC
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
APC	Antigen presenting cell
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
B-ALL	B-lineage acute lymphoblastic leukemia
cAIX	Carbonic anhydrase IX
CAR	Chimeric antigen receptor
CART-19 cells	CD19 redirected autologous T cells
CD137	4-1BB co-stimulatory molecule
CFR	Code of federal regulations
CHOP	Children's Hospital of Philadelphia
CI	Confidence Interval
CIR	Chimeric immune receptor, interchangeable with CAR
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete Response
CRi	Complete Response with incomplete marrow recovery
CRF	Case report form
CRP	C-Reactive Protein
CSR	Clinical study report
CTC	Common toxicity criteria
CTL	Cytotoxic T lymphocyte
CTRC	Clinical and translational research center
CVPF	Clinical cell and vaccine production facility
DFS	Disease free survival
DIC	Disseminated intravascular coagulation
DMC	Data monitoring committee
DOCM	ACC Department of Compliance and Monitoring
DSMC	Data Safety Monitoring Committee
DSMB	Data safety and monitoring board
DSMP	Data safety monitoring plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report forms
EDC	Electronic data capture

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GVHD	Graft versus host disease
HAMA	Human anti-murine antibody
HIV	Human immunodeficiency virus
HLA	human leukocyte antigen
HUP	Hospital of the University of Pennsylvania
IBC	Institutional Biosafety Committee
Ig	Immunoglobulin
IRB	Institutional Review Board
IVIG	Intravenous immunoglobulin
IWCLL	International Workshop Group on Chronic lymphocytic leukemia
MAS	Macrophage activation syndrome
MED	Minimal efficacious dose
MEDRA	Medical dictionary for regulatory activities
MHC	Major histocompatibility complex
MOI	Multiplicity of infection
MOP	Manual of procedures
MRD	Minimal residual disease
mTOR	Mammalian target of Rapamycin
NHL	Non-Hodgkin's Lymphoma
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PFS	Progression-free survival
PHI	Protected health information
PID	Patient identification number
PLL	Prolymphocytic leukemia
PR	Partial Response
PRi	Partial Response with incomplete marrow recovery
Q-PCR	Quantitative polymerase chain reaction
Q-RT-PCR	Quantitative reverse transcriptase polymerase chain reaction
RAC	NIH Office of Biotechnology Recombinant DNA Advisory Committee
RCR/L	Replication competent retrovirus/lentivirus
RIC	Reduced intensity conditioning
RSA	Research Subject Advocate

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

RVP	Respiratory virus panel
scFv	Single chain variable fragment
SCID	Severe combined immunodeficiency
SCT	Stem cell transplant
SD	Stable disease
SLL	Small lymphocytic lymphoma
STR	Short tandem repeat analysis
SUSAR	Suspected unexpected serious adverse reaction
Tcm	Central Memory T cells
TCR	T cell receptor
TCRζ	Signaling domain found in the intracellular region of the TCR zeta, gamma and epsilon chains
TCSL	Translational Correlative Sciences Laboratory
Tem	Effector memory T cells
TLS	Tumor lysis syndrome
Treg	Regulatory T cells
UPenn	University of Pennsylvania
VSV-G	Vesicular Stomatitis Virus, Glycoprotein
Vβ	A rearranged T cell specific gene that can be used to determine clonality of a T cell population

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

CART-19 Study Synopsis

Title	**DOSE OPTIMIZATION TRIAL OF AUTOLOGOUS T CELLS ENGINEERED TO EXPRESS ANTI-CD19 CHIMERIC ANTIGEN RECEPTOR (CART-19) IN PATIENTS WITH RELAPSED OR REFRACTORY CD19+ CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)**
Short Title	CD19 redirected autologous T cells
Protocol Numbers	IRB #816556, UPCC 03712, IND #13960, CTL019A2201
Phase	2
Study Population	Adult patients who have relapsed or refractory CLL or SLL (3rd line)
Methodology	This is a randomized, open-label, parallel group study to determine the optimal dose of CART-19 cells (autologous T cells expressing CD19 chimeric antigen receptors expressing tandem TCRζ and 4-1BB costimulatory domains) of the two dose levels being assessed (1-5x10^8 vs. 1-5x10^7 CART-19 cells). This trial will be conducted in two stages. In Stage I, subjects will be randomized into one of the two dose cohorts with 1:1 ratio as below: 1) Arm 1: Target dose of 1 x10^8 to 5x10^8 CART-19 transduced cells 2) Arm 2: Target dose of 1 x10^7 to 5x10^7 CART-19 transduced cells In Stage I, approximately 30 subjects are expected to be randomized to ensure a total of 24 subjects (approximately 12 evaluable subjects in each arm) are evaluable for primary efficacy analysis. Safety, tolerability, and clinical response rates will be evaluated to determine a dose cohort for expansion. Subjects with cell doses less than the stated range will receive their cells, but will be scored as "manufacturing failures". They will be evaluated for safety endpoints and followed in the same way as subjects that have received the target dose, but will not be evaluable for primary endpoints and will be replaced for the purposes of the study. We will target the upper dose level but accept the lower dose range as a "successful" manufactured product. Anything below the lower limit will be considered a manufacturing failure, will follow the study protocol and will be monitored for safety and disease response, but will not be evaluable for the other endpoints (other than feasibility) on this protocol. Subjects with cell doses less than cell doses above will be replaced for analysis. No more than 20% of the total enrollment may be manufacturing failures. If this is exceeded a separate modification will

CONFIDENTIAL
This document is confidential and the property of the University of Pennsylvania. No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorization from the study sponsor.

	be submitted for IRB review. If appropriate, an additional dose level may be explored prior to the start of Stage 2. In Stage 2, the selected dose cohort will be expanded to enroll additional subjects, to ensure that a total of 20 evaluable subjects are treated at that dose level. Based on the Stage 1 analysis performed in November 2014, Arm 1 was chosen for expansion in Stage 2. Therefore, the Stage 2 dose will be 1-5x10^8 transduced CART-19 cells. The dose of 1-5 x 10^8 T-cells in Stage 2 will be administered via split dosing: 10% on Day 1 (1-5x10^7), 30% on Day 2 (3x10^7-1.5x10^8), 60% on Day 3 (6x10^7-3x10^8). Evaluable subjects are defined as those who were able to receive the viable product at the intended dose level and have completed at least 3 months of follow-up after the first infusion, or have discontinued early due to disease progression, initiation of a new cancer therapy, or death. This protocol also allows for the retreatment of any subject who had an initial response to their 1st infusion, lost detectable CART19 cells, and has subsequently relapsed. The target dose for this retreatment cohort is 1-5 x 10^8 CART19 cells. The minimum acceptable dose for infusion is 1 x 10^7 CART19 cells. Subjects originally treated under Stage 1 will receive a single infusion, if sufficient CART19 product remains. For patients from Stage 1 who do not have a sufficient dose remaining, subjects will be remanufactured under Stage 2 conditions and receive the split dose. Subjects originally treated under Stage 2 will also receive the split dose for retreatment.
Study Duration	Enrollment: • Stage 1: Approximately 18 months* • Stage 2: Approximately 12 months* Follow-up: 12 months Total study duration: approximately 42 months * Assumes adequate manufacturing and clinic capacity Safety and clinical response will be assessed every month for the first six months, followed by every three months for a total of 12 months. Tumor response will be assessed at 1 month post-infusion, and then every 3 months for a total of 12 months. The same schedule for evaluations will be applied for the retreatment cohort. Post-study follow-up: annual follow-up for lentiviral vector safety will continue under a separate destination protocol for 15 years post infusion in accordance with FDA guidelines for retroviral vectors.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Study Center(s)	Single-center
Objectives	**Endpoint**
Primary	
• Estimate efficacy of each CART 19 cell dose level	• Complete response (including complete response with incomplete marrow recovery) within 3 months (in evaluable patients).
Secondary	
• Assess safety and tolerability profile of each dose level	• Frequency and severity of adverse events and other safety data as considered appropriate.
• Dose (Manufacturing) Feasibility	• Number of manufacturing failures due to issues with in vitro (pre-infusion) cell expansion, T cell and product purity, viability, sterility, and tumor contamination.
• Evaluate additional efficacy parameters and other clinical outcomes	• Best overall response, progression free survival, overall survival, time to response, duration of response, time to alternative therapy
• Characterize CART-19 cell levels, function, and host responses	• Fold- and kinetics- of expansion, persistence and homing to marrow of infused cells. • Development of humoral and /or cellular immunity to CART-19 cells.
• Follow subjects infused with less than protocol-specified doses	• Exploratory analyses to inform on dose-response activity
Exploratory	
• Understand modulation of systemic levels of soluble immune and inflammatory factors by CART-19 cells	• Systemic soluble immune factors in serum before and after treatment
• Determine incidence of CD19 escape mutants	• Assess residual tumor in peripheral blood, bone marrow and lymph node aspirates for CD19 expression, and compared to base line tumor samples.
• Patient Reported Outcomes	• EORTC QLQ-C30 and CLL-16 questionnaires at baseline, chemotherapy week, end of treatment (day 28), 3, 6, 9, and 12 months post infusion.
• Assess safety and efficacy of re-infusion of CART19	• Frequency and severity of adverse events and other safety data • Expansion and persistence of CART19 cells, in comparison to their original infusion

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

cells in previously treated patients	• Overall response, time to response, duration of response and time to alternative therapy, in comparison to their original infusion
Number of Subjects	Stage 1: Approximately 30 subjects are expected to be randomized to ensure a total of 24 subjects (approximately 12 evaluable subjects in each arm) are evaluable for primary efficacy analysis. Stage 2: The arm (Arm 1) identified to have the optimal dose will enroll additional patients to ensure that a total of 20 evaluable subjects are treated at that dose level. Retreatment: The number of patients in the retreatment cohort will be no more than the number of infused patients in Stage 1 and 2 combined.
Study Product, Dose, Route, Regimen	CART-19 cells transduced with a lentiviral vector to express anti-CD19 scFv TCRζ:41BB administered via a single i.v. infusion on Study Day 1. A single lot of vector and a single manufacturing site will be used for all subjects enrolled into this study. The two dose levels to be tested are: 1) Target dose of 1-5x10^8 CART-19 cells 2) Target dose of 1-5x10^7 CART-19 cells In Stage I, subjects will be randomized into one of these two dose cohorts with 1:1 ratio. In Stage 2, the selected dose cohort will be expanded to enroll additional subjects, to ensure that a total of 20 evaluable subjects are treated at that dose level. Based on the Stage 1 analysis performed in November 2014, Arm 1 was chosen for expansion in Stage 2. Therefore, the Stage 2 dose will be 1-5x10^8 transduced CART-19 cells. The dose of 1-5 x 10^8 T-cells will be administered via split dosing: 10% on Day 1 (1-5x10^7), 30% on Day 2 (3x10^7-1.5x10^8), 60% on Day 3 (6x10^7-3x10^8).
Dose Rationale	Manufacturing success rates decline when targeting more than 10^8 CART-19 cells. Patients with CLL who have responded to CART-19 therapy have all received a magnitude of 10^7 or higher CART-19 cells. Therefore, the target dose level ranges of 1-5x10^8 and 1-5x10^7 CART-19 cells have been selected. If appropriate, an additional dose level may be explored.
Duration of administration	Based on the total volume to be infused and the recommended infusion rate of 10-20mL per minute
Reference therapy	None. This protocol will be given to subjects with unmet medical needs for whom there are no effective therapies known at this time.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Eligibility Criteria	• Documented CD19+ CLL or SLL • Successful test expansion of T-cells • Patients who progress within 2 years after the second or higher line of therapy will be eligible. For instance, patients who had progressions < 2 years after second or greater line therapy, but who have responded to their most recent treatment (3rd line of higher) will be eligible. • At least 2 prior chemotherapy regimens (not including single agent monoclonal antibody (Rituxan) therapy. Single agent of ofatumumab will be counted as a regimen. Patients with high risk disease manifested by deletion chromosome 17p will be eligible if they fail to achieve a CR to initial therapy or progress within 2 years of 1 prior regimen • Subject has not appropriate candidate for a potentially curative SCT due to the state of disease, co-morbid illness, lack of an available donor, or patient declines • Performance status (ECOG) 0 or 1 • Age >/= 18 years • Adequate organ system function including: o Creatinine < 1.6 mg/dl o ALT/AST < 3x upper limit of normal o Total Bilirubin <2.0 mg/dl • Any relapse after prior autologous SCT will make patient eligible regardless of other prior therapy • Patients with relapsed disease after prior allogeneic SCT (myeloablative or nonmyeloablative) will be eligible if they meet all other inclusion criteria and: o Have no active GVHD and require no immunosuppression o Are more than 6 months from transplant • No contraindications for leukapheresis • Left Ventricular Ejection Fraction ≥40% • Gives voluntary informed consent <u>Retreatment Cohort:</u> • Subjects previously infused with CART19 cells as part of this protocol and who experienced an initial response (either CR, CRi or PR) to therapy, but have subsequently progressed within 2 years of their initial response. 1. Subjects have undergone the 3 month efficacy endpoint evaluation. Subjects who achieve an initial response, but relapse prior to this Month 3 timepoint will be eligible. 2. Subjects have <5% CART19 cells in the CD3+ population by flow cytometry on PBMCs 3. Subjects have recovered from any toxicity attributed to the initial CART19 infusion, such as CRS.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Statistical Methodology	Safety population includes all patients who receive the T cell infusion. Safety population will be used to analyze safety-related endpoints. All adverse events will be described. Evaluable patients are defined as those eligible patients who receive the T cell infusion at the intended dose level by randomization and have completed at least 3 months of follow-up after the first infusion, or have discontinued early due to disease progression, initiation of a new cancer therapy, or death. This population will be the basis for the primary analysis in this study. The primary objective will be evaluated by calculating the CR rate by 3 months as the proportion of patients who reach CR or CRi within 3 months from the time of the first CART-19 infusion among the total evaluable patients. The exact 90% confidence interval (CI) will also be computed. Data from the two dose groups will be analyzed separately. All evaluable patients per arm will be included for the analysis. If 4 of 12 planned evaluable patients achieve CR or CRi within 3 months post infusion (i.e., an observed 3-month CR rate of 33%), then the lower bound of the 90% CI will exclude 10%. Specifically, the 90% exact CI would be (12%, 61%). At the end of the expansion cohort, the width of the exact 90% CI will be less than 20% based on 20 patients. For an observed 3-month CR rate of 30% (i.e., 6 out of 20 had CR or CRi), the 90% exact CI would be (14%, 51%). Analysis of other secondary or exploratory endpoints will be descriptive and may include summary statistics such as means and standard deviations or Kaplan-Meier curves for time-to-event survival information if appropriate. Safety and efficacy analyses for patients in retreatment cohort will be exploratory and used to generate hypotheses for future studies. Feasibility endpoints will be analyzed using all patients who are evaluated for cell expansion.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Figure 1a-Dose Finding Study Design Schema – Stage 1

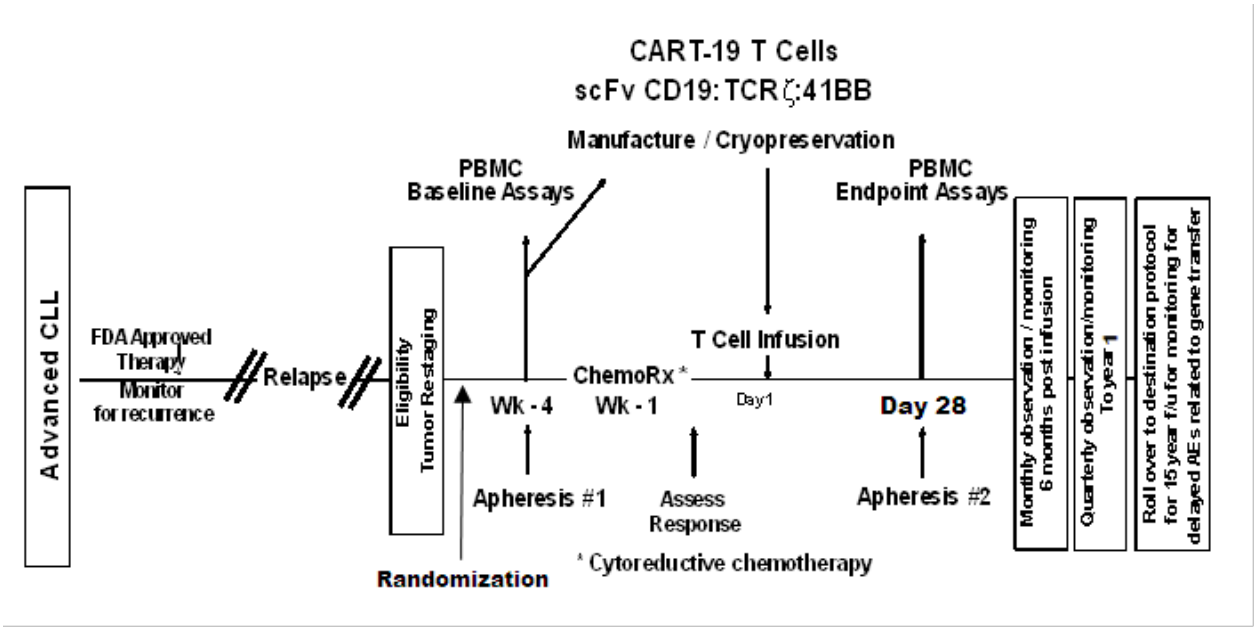
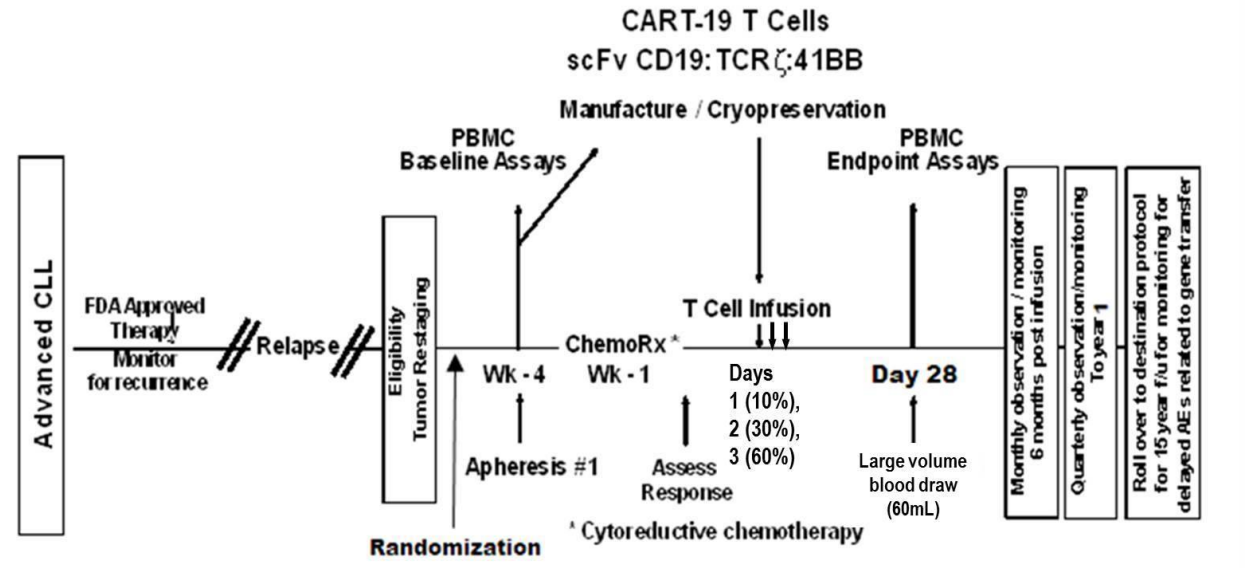


Figure 1b-Study Design Schema – Stage 2



This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

1 Introduction

1.1 *Background*

CLL is the most common leukemia in Western countries accounting for approximately 30 percent of all leukemias in the United States[1]. CLL is considered to be mainly a disease of the elderly, with a median age at diagnosis of 70 years[2]; however, it is not unusual to make this diagnosis in younger individuals from 30 to 39 years of age[3]. The incidence increases rapidly with increasing age. It is estimated that 16,060 new cases of CLL will be diagnosed in 2012, 9490 in males, and 6570 in females[1].

Patients who have relapsed or refractory CLL represent a population with high unmet need. With the exception of allogeneic hematopoietic cell transplantation, treatment options for CLL are almost never curative. About 60% of first-line patients will go on to receive second-line therapy including ~ 20% of patients who do not respond to first-line therapy (the refractory pool) and those patients who relapse after achieving a response. About one-half of second-line patients will either die before receiving the next line of chemotherapy or may be alive and not receive the next line of therapy either due to age, comorbidities or lack of available options[4].

CLL is a B-cell neoplasm. In most cancers, tumor-specific antigens for targeting are not well defined, but in B-cell neoplasms, CD19 is an attractive target. CD19 is a 95kDa glycoprotein present on B cells from early development until differentiation into plasma cells[5-7]. It is a member of the immunoglobulin (Ig) superfamily and a component of a cell surface signal transduction complex that regulates signal transduction through the B cell receptor[7-9]. Mice lacking CD19 have a decreased number of B cells in peripheral lymphoid tissues, a decreased B cell response to oral vaccines and mitogens, and decreased serum Ig levels[7, 10].

CD19 is not present on most normal tissues, other than normal B cells, including pluripotent blood stem cells[11], which makes CD19 a relatively safe target presenting a minimal risk of autoimmune disease or irreversible myelotoxicity. Anti-CD19 antibodies and scFvs either native or conjugated to radioisotopes or toxins are currently being developed and have demonstrated promise in both mouse models[12-16] and human and non-human primates[17-27].

1.2 *Investigational Agent*

The investigational agent in this protocol is CART-19 cells. CART-19 is the most recent adaptation of adoptive cellular immunotherapy that uses the patient's own peripheral blood T cells that have been genetically re-directed to kill CD19+ cells. As shown in Figure 2, the CAR approach uses genetically programmed, patient-derived lymphocytes transfected with chimeric receptor genes to combine the effector functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner[28, 29]. These receptors have the ability to recognize intact membrane proteins independent of antigen processing. CARs or T-bodies typically encode an extracellular domain to bind tumor or virus linked to an intracellular

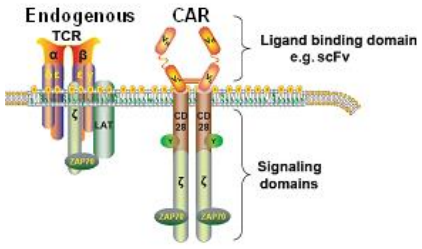


Fig. 2. CAR design. Bispecific T cells are created by the introduction of genes encoding CAR proteins that recognize target surface antigens in an MHC-independent fashion.

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

signaling domain that mediates T cell activation (reviewed in[30, 31]). In principle, universal targeting vectors can be constructed because the scFv bind to native cell surface epitopes and bypass the requirement for MHC restriction. The tumor binding function of CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) antibody, containing the V_H and V_L chains joined by a peptide linker of about 15 residues in length[32]. First generation CARs contain a minimal TCR signaling domain consisting of TCRζ. Second generation CARs contain double costimulatory signaling domains either CD28 and TCRζ or 4-1BB and TCRζ. The 3rd generation CARs contain further advancements such as triple costimulatory modules comprised of CD28, 4-1BB, and TCRζ. See reviews of CARs for details[33-35].

Autologous T cells will be engineered using a lentiviral vector to express an extracellular single chain antibody (scFv) with specificity for CD19. This will be expected to redirect specificity of the transduced T cells for cells that express CD19, a molecule that is restricted in expression on the surface of the malignant cells and on normal B cells. In addition to the CD19 scFv, the cells will be transduced to express an intracellular tandem signaling domain comprised of 4-1BB and TCRζ signaling modules. Clinical grade CD19 TCRζ/4-1BB lentiviral vector will be manufactured at the Children's Hospital of Philadelphia (CHOP) and City of Hope Center for Applied Technology Development. The extracellular single chain antibody (scFv) with specificity for CD19 was previously reported[21]. The scFv is derived from a mouse monoclonal antibody using hybridoma cell line FMC63 described in Nicholson et al.[21]. The signaling domains are entirely of the native human sequences[36, 37].

The CART-19 cells will be manufactured in the Clinical Cell and Vaccine Production Facility at the University of Pennsylvania. CART-19/4-1BB cells are resuspended in cryopreservation media containing 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 10% Dextran 40, 20% Human Serum Albumin, and 7.5% DMSO. Cells are frozen in bags using a controlled-rate freezer. Cryopreserved CART-19 products are stored in a monitored freezer at ≤-130°C. The target dose of CART-19 cells is calculated based on the scFv percent transduction efficiency (see section 5.4 for unthawing and infusion instructions).

Absorption, distribution and metabolism. Lymphocytes have complex trafficking and survival kinetics, and after adoptive transfer several fates have been demonstrated: 1) margination; 2) exit from the peripheral blood trafficking to lymphoid tissues; and 3) death by apoptosis. Following an intravenous dose, retrovirally modified and adoptively transferred T cells have been shown to persist in the circulation for at least 10 years in immunodeficient SCID patients due to the replicative competence of T cells[71]. Human CD8 CTLs have an elimination half life from the peripheral blood of about 8 days, and this increases to about 16 days when low doses of IL-2 are given[72]. In patients with HIV infection, we found that the mean half life of lentivirally modified CD4 T cells in the circulation of 5 patients following a single infusion was 23.5 (± 7.7) days in patients. Adoptively transferred human T cells have been shown to traffic to tumor and secondary lymphoid tissues[38-41].

Drug interactions. CART-19 cells are expected to retain many of the properties of natural T cells. As such, they will be expected to be susceptible to immunosuppressive agents such as corticosteroids, immunophilins such as cyclosporine and tacrolimus, methotrexate, mycophenolate mofetil, mTOR inhibitors such as rapamycin, alemtuzumab, daclizumab, denileukin difitox, and

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

everolimus. Lymphocytes are especially susceptible to cytotoxic and chemotherapeutic agents that are commonly administered for hematologic malignancies such as cyclophosphamide and fludarabine.

Immune elimination. An important consideration is that the CAR can be immunogenic, either because foreign sequences such as antibiotic selection genes or mouse antibody sequences are expressed, or because of novel epitopes that are created at the fusion joint of human signaling domains that are not normally juxtaposed. Immunogenicity of the CAR can lead to the rejection of the adoptively transferred T cells. The basis for this supposition is that human retrovirally-modified CTLs expressing a fusion protein consisting of hygromycin:HSV thymidine kinase were eliminated by host CTLs in patients with advanced HIV infection[42]; importantly, this immune mediated elimination was not accompanied by adverse effects and required 6 to 8 weeks to occur. There is one report where CAR containing a scFv with mouse sequences has been given to cancer patients. Following a single dose of CAR T cells (0.6 to 4 x 10^9 T cells), the CAR T cells were detected in circulation from 23, 32, and 53 days after infusion in three patients with renal cell carcinoma[43]. All three patients developed low levels of anti-scFv antibodies between 37 and 100 days after the CAR T-cell infusion. It is important to note that it is possible the CART-19 T cells will be rejected in our patients. We expect the cells to persist for a sufficient period of time to determine safety, T cell subset specific persistence, and effects on tumor burden and tumor specific immunity at 4 weeks following the first infusion.

Lymphocyte costimulation. Extensive research in the past two decades has documented that maximal activation, proliferation and persistence of T cells responding to antigenic stimuli is dependent on receipt of two discrete signals mediated by cell surface receptors. The primary "activation" signal is generated by ligation of the TCR with antigen (typically in the form of peptides presented in the groove of HLA class I molecules) and the second signal by ligation of a costimulatory molecule with its cognate ligand. T cell costimulatory molecules which have been identified to date include members of the immunoglobulin super-family (CD28), members of the tumor necrosis factor (TNF) super-family (e.g. CD40L, CD134 [OX-40], CD137 [4-1BB][44].

One issue that needs to be addressed with CARs is that signaling through the cytosolic domain of the usual scFv-TCRζ single chain construct does not fully replicate the multichain TCR signaling complex[45, 46]. Chimeric receptors bearing TCRζ signaling modules are sufficient to trigger sustained proliferation in T cell hybridomas and clones but are not sufficient to drive proliferation or cytokine production in peripheral T cells[45]. 4-1BB is a T cell co-stimulatory receptor induced by TCR activation, and evokes various T cell responses[47]. We and others have observed that 4-1BB signals are critical for long term proliferation of CD8 cells, and that CD28 is essential for sustained CD4 cell proliferation[48, 49]. We have begun to investigate the requirement for costimulation in our CD19-CAR by incorporating additional signaling modules in the cytoplasmic domain of the chimeric receptor. Our preclinical data are in accordance with the results from other laboratories[50, 51], and indicate that "bipartite receptors" comprised of TCRζ and either CD28 or 4-1BB signaling modules substantially improve the function and proliferation of T cells. The coalescence of improved T cell culture methods and lentiviral vector technology have made it possible to test this novel CD19 CAR- T cell concept, as we have done so in 3 patients and plan to continue to evaluate in this protocol with additional patients.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

1.3 *Preclinical Data*

Extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models[31, 52-55]. Others have used electroporation or retroviral vectors to create CART-19 T cells, and have shown in vivo safety and efficacy of adoptively transferred T cells in immunodeficient mouse models[25, 26, 56-58]. The incorporation of signaling modules such as CD28 and 4-1BB in 2nd generation CARs increases potency of the engineered T cells in pre-clinical studies[37, 50, 59-63]. The pre-clinical data supporting CART-19 has been published[36, 64].

1.4 *Previous Clinical Data with CART-19 cells*

Autologous CART-19 cells in CLL,ALL and NHL: As of January 2015, we have now infused 123 patients with autologous lentiviral-modified CART-19 cells. These include indications in CLL, ALL and NHL (summarized in Table 1-1).

Table 1-1 Summary of lentiviral CART19 studies under BB-IND 13960

Study ID	Indication	Study Status	Number of Subjects		Overall response rate (% of CR+PR)	CART19 Dose, Frequency and Formulation
			Infused with CART-19	Evaluable		
UPCC04409 (Phase I)	**Adult CLL and ALL**	Closed to enrollment	20 (14 CLL, 6 ALL)	20 (14 CLL, 6 ALL)	CLL: 58% (8/14) ALL: 100% (6/6)	$1.5x10^7$ – $5.0x10^9$ CART-19 cells Day 0 (10%), Day 1(30%), Day 2 (60%)*
CHP959 (Phase I)	**Pediatric ALL**	Enrolling	43	43	91% (39/43)	Dose adjusted as appropriate for children. ≤ 10cc/kg of total volume Dose 1 (10%), Dose 2 (30%), Dose 3 (60%)
UPCC03712 (Phase II)[b]	**Adult CLL**	Enrolling on Stage 2; Stage 1 complete	28 (14 – low dose 14 – high dose)	24	42% (10/24)	Stage 1 - Randomized, two dose cohorts low dose: 1 to 5 x 10^7 CART19 or high dose: 1 to 5 x 10^8 CART19 (Single dose, randomized)
UPCC21413 (Phase II)	**Adult ALL**	Enrolling	12	8	50% (4/8)	1 to 5 x 10^8 CART19 (first 6 subjects) 1 to 5 x 10^7 CART19 (remaining 18 subjects); single dose
UPCC13413 (Phase IIa)	**Adult NHL**	Enrolling	20[a]	14	11/14 (79%)	1 to 5 x 10^8 CART19; single dose

* earlier protocol version had a 4th dose, 100% at Day 11; only 04409-03 received this dose

[a]7th subject was infused with humanized CART19 under BB-IND 15801

[b]Results for Stage 1

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

UPCC04409 is the original adult CLL and ALL clinical protocol where $1.5x10^7$-$5x10^8$ CART-19 cells are infused in a split dosing regimen (10%, 30% and 60%) on Day 0, 1 and 2. An additional dose can be administered on Day 11 ($1.5x10^7$-$5x10^8$ CART-19) if able to be manufactured and tolerated by the patient. Only one patient 04409-03 received the Day 11 dose. CHP959 is the pediatric ALL trial in which $1.5x10^7$-$5x10^9$ ($0.3x10^6$-$1.0x10^8$/kg) CART-19 are administered in a split dosing regimen (10%, 30% and 60%).

Two phase II studies have opened. One for adult ALL under UPCC21413 and the other for NHL histologies including Diffuse Large B Cell, Mantle Cell and Follicular Lymphoma under UPCC13413. Both trials administer a single infusion of 1-$5x10^8$ CART19 cells. While this dose has been well tolerated in the NHL patient population, three of the six adult ALL subjects infused thus far died as a result of refractory-Cytokine Release Syndrome (CRS) in the setting of intercurrent infections (discussed in detail below). Thus, the dose for the remaining subjects has been reduced to 1-$5x10^7$ CART19 cells

Taken together under both adult protocols, UPCC04409 and UPCC03712, 38 CLL subjects are evaluable as of January 2015 to give an overall response rate of 18/38 (47%). Based on the small number of evaluable UPCC03712 patients, it appears that CART-19 dose continues to not correlate with response as patients treated with either dose can achieve disease remission. Under CHP959, 43 patients with pediatric ALL have been infused and evaluable subjects have an overall response rate of 39/43 (91%). A recent publication (Grupp et al., *NEJM* 2013) details the responses of CHP959-100 and -101. Additionally, the first pediatric patient treated, CHP959-100, remains in complete remission as of her 30 month follow-up visit on October 13, 2014. Six CRs have also been observed for the 6 ALL patients treated under UPCC04409, suggesting that the efficacy seen in the pediatric populations is replicated in the adult population.

The most significant SAE seen in adult and pediatric patients treated with CART-19 has been on target CRS. CRS is described in details below (section 1.5.2) but typically begins up to 2 weeks after CART-19 infusion. The CRS typically starts with several days of fevers. In all cases, evaluation for infections is done. Fevers tend to be spiking and can be associated with rigors, anorexia, nausea, diarrhea, diaphoresis, capillary leak, hypoxia and hypotension. In several cases ICU level care, ventilator support and pressors have been needed. Observations have noted experimentally very high levels of IL6 during the CRS. In addition, the reaction typically appears to be associated with MAS. This can be manifested by evidence of hemolysis, cytopenias, elevated ferritin, altered mental status, and other complications.

CRS/MAS was managed in 1 patient initially with corticosteroids. Subsequently, as more data became available, it has been successfully managed with supportive care and when needed, tocilizumab therapy. Tocilizumab is an anti-IL6 receptor antibody, and has been administered as a single dose of 4 to 8 mg/kg. This may be preferable to systemic immunosuppression with corticosteroids. In many cases, the CRS has been severe, but reversible. However there have been several cases of refractory CRS that resulted in death on UPCC#21413. It is hypothesized this may be related to tumor burden, so that treating patients with less tumor burden may result in less severe cytokine release syndrome. However, additional contributory patient and CART-19 related factors cannot be ruled out.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Since CRS mechanistically is a required part of the antitumor mechanism of *in vivo* CART-19 cell expansion and tumor killing, tocilizumab was administered for CRS with worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation or hemodynamic instability despite intravenous fluids and moderate vasopressor support or rapid clinical deterioration. Steroids following CART-19 infusion were avoided and given only under life threatening situations due to the known lymphocytic effects.

Historical Clinical Data with CARs

Completed clinical studies are limited to phase I studies evaluating first generation CARs targeting the folate receptor in ovarian cancer[65], carbonic anhydrase in renal cancer[43], CD20 in lymphoma[66], and GD2 in neuroblastoma[67, 68]. According to available literature, the clinical responses have overall been very modest, with the exception of one partial response in one of the neuroblastoma studies. Immunogenicity of CARs was observed in the first two studies, but not the latter two. However, two serious adverse events have recently been reported. The first occurred in a patient with bulky CLL and extensive prior therapies. The patient received autologous T cells modified to express a CD19-targeted CAR at a dose of 3x 10^7 cells/kg after lymphodepletion with high-dose cyclophosphamide. This patient developed fever, hypotension, and dyspnea 20 hours after infusion, which rapidly progressed. Elevated cytokine levels were seen before the T-cell infusion, and an autopsy failed to reveal an obvious cause of death. It was concluded that low grade sepsis, which was likely present before the initiation of therapy, was the most likely trigger in this heavily pretreated immunosuppressed patient[66]. The other adverse event occurred in a patient with colon cancer who received a high dose (> 10^{10}) of CAR T cells modified with a CAR targeting HER2 containing two costimulatory moieties (CD28 and 4-1BB) after intensive lymphodepletion. The subject developed pulmonary toxicity within 15 minutes in association with very high cytokine levels, followed by cardiac arrest, and died 4 days later. This patient is thought to have died from an on-target cytokine storm resulting from high numbers of cells localizing in the lung after infusion and recognizing low levels of the antigen on lung tissue[67]. Another example of on-target, off-organ toxicity occurred in a clinical trial in which patients were given T cells engineered to express a chimeric antigen receptor that was specific for carbonic anhydrase IX (cAIX), a transmembrane protein that is overexpressed by cancerous kidney cells[67]. In all three patients, severe liver toxicity ensued within 1 week following infusion of the gene-modified T cells. Subsequent investigation revealed that the cAIX protein was also expressed in the biliary tract of the liver. These events illustrate the potent effects of engineered lymphocytes and the need to carefully select the target. Trials with second generation CARs are just beginning as several centers.

CART-19 appears to have greater success than previous CAR constructs, since *in vivo* these cells proliferate more and persistent longer, and retain effector functions, therefore amplifying and sustaining effective anti-tumor responses. For recent reviews of CAR T cell trials, see PMID 22818942, 22308288, 22538493, 22262649, 21358705, 22781680.

1.5 *Rationale for the study design*

This is a randomized, open-label, parallel group study to determine the optimal dose of CART-19 cells of the two dose levels being assessed (1-5x10^8 vs. 1-5x10^7). This trial will be conducted in two stages. In the first stage, approximately 30 patients are expected to be randomized to ensure a

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

total of 24 subjects (approximately 12 evaluable subjects in each arm) are evaluable for primary efficacy analysis. Randomization will allow for a greater degree of comparability between the two arms than if there were two independent trials. Safety, tolerability, and clinical response rates will be evaluated to determine a dose cohort with a minimum of 30% three-month complete response (CR) rate for expansion. If appropriate, an additional dose level may be explored.

In the second stage, the selected dose cohort will be expanded to enroll additional subjects to ensure that a total of 20 evaluable subjects are treated at that dose level. Having at least 20 evaluable subjects treated at the same dose level will provide enough confidence in the estimated efficacy and safety assumptions that will be used in future trials for patients with refractory or relapsed CLL.

1.6 *Rationale for dose and regimen selection*

Based on the current manufacturing limitations and recent clinical experience from ongoing trials (UPCC04409, UPCC13413 and UPCC21413), the target dose levels of 1-5x10^8 and 1-5x10^7 CART-19 cells have been selected for this study.

Patients with heavily pretreated CLL frequently have a significantly lower percentage of CD3+ cells in leukapheresis products than subjects with other types of hematologic malignancy. Lentiviral transduction and expansion therefore could be limited in the setting of fewer CD3+ cells. As was observed in clinical protocol UPCC04409, manufacturing success rates declined to approximately 50% when targeting 10^9 or more CART-19 cells. Targeting 10^8 or fewer cells is not anticipated to be an issue from a manufacturing standpoint.

With the first 3 patients with CLL treated with CART-19 in UPCC04409, durable clinical activity was observed at doses ranging from 1.4x10^7 to 1.1x10^9 CART-19 cells. This two-log-fold difference did not support an obvious dose response relationship. Unlike standard drugs that are metabolized, CAR T cells can have a wide dose response range. This is most likely because the CAR T cells are able to proliferate extensively in the patients, and thus the actual *in vivo* amount of CART-19 T cells after engraftment and expansion will vary from patient to patient.

The upper range of the target dose was chosen because it is anticipated to be safe based on recent clinical experience from the ongoing trials as mentioned above, and because it will permit sufficient engraftment in order to evaluate the primary and secondary endpoints of this study.

Based on the Stage 1 interim analysis performed in November 2014, Arm 1 (1-5x10^8 CART-19 cells) was chosen for expansion in Stage 2. At the beginning of Stage 2 of this trial, IND-approved manufacturing changes were instituted. The first subject treated in Stage 2 (03712-51), experienced early CRS within 12 hours of receiving T-cells, and received anti-cytokine therapy with tocilizumab and steroids within 24 hours of infusion. The subject's clinical status improved in response to anti-cytokine therapy.

Based on this clinical experience and efforts to improve subject safety, the subsequent CLL subjects enrolled in Stage 2 of this study will be treated with the selected dose of 1-5 x 10^8 T-cells administered via split dosing: 10% on Day 1, 30% on Day 2, 60% on Day 3. Our initial pilot trial of CAR T cells in CLL (UPCC 04409) gave a similar dose of T cells split over 3 days. Additionally,

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

in our companion trial for subjects with ALL (UPCC 21413), CART-19 cells are being administered via split dosing over three days. This reflects an altered schedule of administration due to early and severe CRS experienced after single dose administration.

1.7 *Rationale for pre-treatment lymphodepletion*

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation[69], a recent finding that naive T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naive T cells are reduced below a certain threshold[70, 71]. Lymphodepletion eliminates regulatory T-cells and other competing elements of the immune system that act as "cytokine sinks", enhancing the availability of cytokines such as IL-7 and IL-15 [72]. This hypothesis has been tested clinically in patients with metastatic melanoma refractory of conventional treatments[39]. The patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide (60 mg/kg x 2 days) and fludarabine (25 mg/m^2 x 5 days) prior to adoptive transfer of T cells. We have treated patients with myeloma and lymphopenia after lymphodepleting chemotherapy, and observed improved engraftment[73, 74].

In this protocol CART-19 cells will be transfused into subjects who are rendered lymphopenic as a result of cytotoxic chemotherapy. Recent data indicates that the increased antitumor efficacy of adoptive transfer following host conditioning is more than simply "making room" because the quantitative recovery of adoptively transferred T cells in mice reveals that in vivo proliferation following adoptive transfer is identical in mice with or without previous irradiation.

1.8 *Benefit and Risk Assessment*

General safety. Participation in this study will expose the patient to genetically engineered autologous T cells. The risk of the cells alone is low based on clinical experience. The unknown risk is that of the signaling domains in the CAR. T cell proliferation could be uncontrolled; however we have not observed this in our pre-clinical models. In this case, corticosteroids and chemotherapy would be given to eradicate the CAR cells; this has worked in previous cases[43].
At the University of Pennsylvania we have treated >20 patients with HIV infection with autologous T cells modified with lentiviral vector. In the first protocol, each subject received a single i.v. infusion of 1x10^{10} lentiviral modified T cells; in the second protocol, each subject received up to 6 doses of 0.5-1 x 10^{10} cells. The lentiviral engineered T cells were well tolerated in all patients, with follow up of up to 5 years. Doses of up to 5x10^{10} autologous *ex vivo* non-gene modified and expanded T cells have been administered in five protocols to 128 patients with hematologic malignancies and HIV, and have found this to be well tolerated[73-76 95].

Immunogenicity. It is possible the cells may be immunogenic, and that the patients will have an immune response directed against the scFv; this has not had clinical consequences in previous trials. If an immune response to the cells occurs, it is possible that the cells will be rejected. Three of 3 subjects developed HAMA and loss of T cell engraftment in the Lamers study[47], but this has generally not been an issue in patients with B cell malignancies.

Immunoglobulin depletion. Transient or permanent host B cell depletion is also a potential risk with CART-19 cells, since normal B cells express CD19. This is expected to resolve when the CART-19 cells are cleared. In the meantime, patients may require periodic infusions of immunoglobulin.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Transformation. There is a risk that people who receive gene transfer may develop new tumors derived from their genetically modified cells. This risk is primarily associated with viral gene transfer vectors that integrate into the cellular DNA where they may dysregulate genes controlling proliferation. Transformation has not been observed following adoptive T cell transfer in hundreds of cancer and HIV patients receiving gamma retroviral modified T cells treated on multiple protocols at many academic centers[34], and in the 21 HIV patients treated with lentiviral modified T cells treated at University of Pennsylvania[77].

Risk of tumor lysis syndrome (TLS) related to cytoreductive chemotherapy or CAR T cells. The risk of TLS is dependent on the disease and burden of disease, but in most cases, this risk will be low. These are not front line CLL patients. Patients will be closely monitored both before and after chemotherapy and CART-19 infusions including blood tests for potassium and other relevant chemistries. Patients will receive hydration and allopurinol or rasburicase to minimize any toxicity should signs of significant acute tumor lysis begin to occur.

Cytokine release syndrome and Macrophage Activation Syndrome. Patients treated with CART-19 may experience a cytokine release syndrome (CRS), which has correlated with disease response. Clinical manifestations have included high fevers, fatigue, anorexia, nausea, vomiting, headache, rash, hypotension (occasionally requiring pressor support), tachypnea, hypoxia (occasionally requiring ventilator support), delirium and confusion (in several patients), evidence of disseminate intravascular coagulation as well as macrophage activation syndrome (MAS). In some cases CRS, TLS and hypotension have led to acute kidney injury and several patients have required at least transient dialysis. The CRS has been effectively abrogated with anti-cytokine directed therapy including tocilizumab in most patients. As of July 2014, three patients on another CART-19 trial have died of complications related to refractory CRS and intercurrent infections. It is unclear if treating the CRS adversely impacts the anti-tumor response.

Features consistent with MAS or HLH have been observed in patients treated with CART 19, coincident with clinical manifestations of the CRS. MAS appears to be a reaction to immune activation that occurs from the CRS, and therefore should be considered a manifestation of CRS.

Macrophage activation syndrome is similar to Hemophagocytic lymphohistiocytosis (HLH); it is a reaction to immune stimulation by infection, autoimmune diseases or other precipitants, but is distinguished from familial or genetically mediated HLH. There are no definitive diagnostic criteria for MAS, but it is typically diagnosed by meeting HLH criteria.

Some but not all features of MAS are typically observed. The clinical syndrome of MAS is characterized by high grade non-remitting fever, cytopenias affecting at least two of three lineages, and hepatosplenomegaly. It is associated with biochemical abnormalities, such as high circulating levels of serum ferritin, soluble interleukin-2 receptor (sCD25), and triglycerides, together with a decrease of circulating NK activity. Other findings include variable levels of transaminases up to signs of acute liver failure and coagulopathy with findings consistent with DIC. A pathologic feature of MAS is the presence of hemophagocytic CD163+ macrophages (HPC) in bone marrow or lymph-node aspirates.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Diagnosis is based on the fulfillment of criteria established in 2004[78] for HLH associated with autosomal recessive disorders (familial HLH, fHLH).

A diagnosis of non-familial HLH/MAS is made by having 5/8 criteria:

- Fever
- Splenomegaly
- Cytopenias (affecting 2 or more lineages in the peripheral blood; hemoglobin <9 g/dL, platelets <100,000/μL, Absolute neutrophil count <1000/μL)
- Fasting triglycerides >265 mg/dL , Fibrinogen < 1.5 g/L
- Hemophagocytosis in bone marrow or spleen or lymph nodes
- Low or absent NK-cell activity
- Ferritin > 500 g/L
- Soluble CD25R > 2400 U/L

Supportive clinical criteria include neurologic symptoms and cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia, and transaminitis, hypoalbuminemia and hyponatremia. Typically high fevers, cytopenias, and when performed hemophagocytosis in the bone marrow is observed (though marrow specimens at the time of the reaction are not often taken). Soluble CD25R and NK cell activity are not standard tests, though samples are taken for retrospective CD25R analysis. Therefore, patients may not meet strict definition of HLH/MAS, but given the constellation of findings, and the consistent dramatic elevation in Ferritin, this is indeed the reaction associated with the CRS.

At this time it is still unknown whether CRS/MAS is beneficial or harmful to the antitumor response. Research monitoring data showed that IL6 levels were extraordinarily high during the CRS, prompting us to use an anti-IL6 receptor antibody tocilizumab to treat the CRS/MAS. Four adult patients have been treated with tocilizumab for CRS and MAS. The majority of patients treated with tocilizumab for CRS and MAS had rapid (within hours) resolution of dramatic fevers, and continuous improvement in hypotension and hypoxia over hours to several days, and showed improvement in biochemical evidence of CRS and MAS within 48 hours. Adult patients were treated with tocilizumab 4mg/kg or 8mg/kg. It is unclear if early treatment will negate the antitumor response. Treatment and timing of treatment of this toxicity will be at the discretion of the patient's physician and the study investigator, and occur in the setting of hemodynamic instability.

Pediatric ALL patients treated with CART-19 on CHP9595 have experienced a similar CRS and MAS. CHP959-100 experienced a severe CRS and had high fevers, hypotension, acute vascular leak syndrome and acute respiratory distress. The patient was treated with etanercept and tocilizumab, as described in *Grupp et al., NEJM, 2013*, and all associated adverse events resolved. CHP959-104 and CHP959-105 received the 10% dose only and experienced CRS. CHP959-103 received the 10% and 30% doses, respectively, and experienced a mild CRS after the 10% dose, with no CRS experienced after the 30% dose. None of these patients experienced were severe enough CRS (i.e. there were no instances of more than transient oxygen requirements, or hypotension requiring pressor support) requiring treatment with steroids or cytokine blockade.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Fatal SAEs with CARs: Two studies have reported fatal SAEs following CAR infusion in patients with malignancy. Brentjens et al designed a retrovirally-transduced CAR against the CD19 molecule for patients with B cell lymphoma. The **CD19** CAR was the second generation design containing CD28 and CD3ζ signaling domains. A total of 7 subjects have been treated on this protocol, 6 without SAE. However, subject four in this study was a 69 year old man with refractory CLL and who had a significant past medical history of myocardial infarction, coronary artery disease, hypertension, and chronic renal failure. This was the 4th patient in the study and the first one on the cohort undergoing lymphodepletion. This subject received pre-T cell conditioning with 1.5g/m^2 of cyclophosphamide followed 2 days later by infusion with genetically modified CD19 CAR T cells at 1.2-3x10^7 cells/kg. Twenty hours following T cell infusion, the patient developed persistent fever (transient fever was observed in the first 3 subjects on the study too) and hypotension that was rapidly followed by respiratory distress despite negative chest x-ray, hypoxemic respiratory failure, and acute renal failure. The family decided to remove further life sustaining therapies and the patient expired 44h post-T cell infusion. The post-mortem pathology report failed to support a diagnosis of tumor lysis syndrome as the primary source of renal failure. Analysis of serum cytokines revealed elevated levels of IL-2, IL-7, IL-15, and IL-12 following cyclophosphamide therapy which may have been secondary to a prior subacute infection exacerbated by the immune suppression associated with cyclophosphamide-mediated lymphodepletion. The authors concluded that concomitant sepsis was the most likely cause of death and attributed the etiology of the death as "possibly related" to CAR T cell infusion[79].

The second case of a fatal SAE related to CAR T cells was reported by the NCI group (Morgan et al. 2010). This study attempted to treat cancer patients with overexpressing ERBB2 tumors with an anti-**ERBB2 CAR** of 3rd generation (containing CD28, 41BB and CD3ζ signaling domains). The first subject in the study was a 39-year-old female with colon cancer metastatic to lungs and liver. The patient received lymphodepleting regimen (60mg/kg cyclophosphamide daily for 2 days followed by fludarabine 25mg/m^2 for the next 5 days) followed the next day by retrovirally-transduced 10^{10} ERBB2 CAR T cell (transduction efficiency 79%). At 15min post-infusion, the patient began to develop dyspnea and hypoxia with pulmonary infiltrates on chest X-ray. The patient progressed into hypoxemic respiratory failure requiring mechanical ventilatory support, vasopressor-dependent hypotension, and cardiopulmonary arrest. The patient was initially resuscitated and started on high dose steroids, but despite aggressive supportive care, the patient expired 5 days after infusion. Serum cytokine measurements demonstrated a dramatic rise in pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6, GM-CSF) within 4 hours of infusion consistent with a cytokine storm initiating multi-system organ failure. Dr. Morgan postulates that upon first pulmonary circulation passage[80], the CAR ERBB2 T cells bound to native low level expression pulmonary epithelial cell ERBB2 proteins[81], leading to CAR activation and pulmonary microvascular injury.

Other fatal SAEs have been reported. Two events occurred at the Memorial Sloan Kettering Cancer Center using CD19 specific CAR redirected T cells. Five fatal events occurred at the University of Pennsylvania using CART-19 T-cells (a CD19-specific CAR using a lentiviral vector) in patients with acute lymphoblastic leukemia. These SAEs are still under investigation.

Grading of CRS: The CTC grading system was originally developed to capture a cytokine syndrome occurring during infusional therapy; therefore, it is inadequate to capture the delayed

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

CRS that occurs after CART19 infusions. We propose to modify the CTC grading specifically to capture toxicity for protocols using CART-19 cells. MAS/HLH observed signs and symptoms are a manifestation of CRS and will therefore not be graded separately (See Table 9-1 in Section 9.2).

Uncontrolled T cell proliferation. CART-19 cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies, CART-19 cells have only proliferated in response to physiologic signals or upon exposure to CD19. In the context of this protocol it is possible that the T cells will proliferate in response to signals from the malignant tumor or normal B cells. This could be beneficial or harmful depending on the extent of proliferation. Clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials[39, 82]. If any subject develops excessive CART-19 cell accumulation, corticosteroids will be administered to eradicate the infused cells.

GVHD. The chance of GVHD occurring is low, but it is a potential risk with CTL019 therapy. A prior study of activated donor lymphocyte infusions (ex vivo activated cells collected from the donor and grown in the same fashion as CART-19 but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4)[83]. Eight ALL patients treated to date with autologous CART-19 therapy had prior allogeneic hematopoietic SCT with residual donor chimerism. None of these patients have developed GVHD after autologous CART-19 infusion

Potential benefits. Based on inclusion criteria and published literature [84, 85], we believe eligible patients will have a median anticipated survival of <2 years without allogeneic SCT. The risks associated with allogeneic SCT are high and include at least 20% treatment related mortality. At best, RIC allogeneic SCT results in a 50% 2 years DFS for patients with CLL but is also associated with extensive morbidity and mortality [86, 87]. Patients not eligible for allogeneic SCT have limited treatment options. Treatment with CART-19 could be potentially curative for an otherwise fatal disease. Taken together under both adult protocols, UPCC04409 and UPCC03712, 30 CLL subjects are evaluable as of November 2013 and include 7 CRs and 7 PRs to give an overall response rate of 14/30 (47%). In the patients with the longest follow-up, responses have persisted beyond 2 ½ years. Therefore we believe the risk benefit ratio for this study remains quite favorable.

2 Study Objectives and Endpoints

Objectives	Endpoint
Primary	
• Estimate efficacy of each CART 19 cell dose level	• Complete response (including complete response with incomplete marrow recovery) within 3 months (in evaluable patients).
Secondary	
• Assess safety and tolerability profile of each dose level	• Frequency and severity of adverse events and other safety data as considered appropriate.

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Objectives	Endpoint
• Dose Feasibility	• Number of manufacturing failures due to issues with in vitro (pre-infusion) cell expansion, T cell and product purity, viability, sterility, and tumor contamination.
• Evaluate additional efficacy parameters and other clinical outcomes	• Best overall response, progression free survival, overall survival, time to response, duration of response, time to alternative therapy
• Characterize CART-19 cell levels, function, and host responses	• Fold- and kinetics- of expansion, persistence and homing to marrow of infused cells. • Development of humoral and /or cellular immunity to CART-19 cells.
• Follow subjects infused with less than protocol-specified doses	• Exploratory analyses to inform on dose-response activity
Exploratory	
• Understand modulation of systemic levels of soluble immune and inflammatory factors by CART-19 cells	• Systemic soluble immune factors in serum before and after treatment
• Determine incidence of CD19 escape mutants	• Assess residual tumor in peripheral blood, bone marrow and lymph node aspirates for CD19 expression, and compared to base line tumor samples.
• Patient Reported Outcomes	• EORTC QLQ-C30 and CLL-16 questionnaires at baseline, chemotherapy week, end of treatment (day 28), 3, 6, 9,and 12 months post infusion.
• Assess safety and efficacy of re-infusion of CART19 cells in previously treated patients	• Frequency and severity of adverse events and other safety data • Expansion and persistence of CART19 cells, in comparison to their original infusion • Overall response, time to response, duration of response and time to alternative therapy, in comparison to their original infusion

Duration of *in vivo* survival of CART-19 cells is defined as "engraftment". The primary engraftment endpoint is the # DNA vector genomic copies per ml blood of CART-19 cells on week 4 after the first infusion. Q-PCR for CART-19 vector sequences will also be performed at baseline and on Study Day -1, 1, 2, 3, 4, 7, 10, every week up to one month, monthly up to 6 months, and every 3 months thereafter until any 2 sequential tests are negative documenting loss of CART-19 cells.

Efficacy endpoints will be based on information from the following: history & physical exam, CBC with differential, bone marrow aspirate, lymph node biopsy, and CT scans. Assessments will be performed at baseline and end of months 1, 3, 6, 9, and 12 after CART-19 cell infusion.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

The International Workshop Group on CLL (IWCLL) has published a revised version of the guidelines for evaluating disease response that were published in 1996 by the National Cancer Institute Working Group (NCI/WG)[84, 88, 89]. Please refer to Section 7 for definitions of complete response, partial response, progressive disease, and stable disease.

3 Study Design

3.1 *General Design*

This is a randomized, parallel group study to determine the optimal dose of CART-19 cells of the two dose levels being assessed (1-5x10^8 vs. 1-5x10^7). This trial will be conducted in two stages.

In Stage I, subjects will be randomized into one of the two dose cohorts with 1:1 ratio as below:

1) Arm 1: Target dose of 1 x10^8 to 5x10^8 CART-19 transduced cells
2) Arm 2: Target dose of 1 x10^7 to 5x10^7 CART-19 transduced cells

In Stage I, approximately 30 patients are expected to be randomized to ensure a total of 24 subjects (approximately 12 patients in each arm) are evaluable for primary efficacy endpoint analysis. Primary efficacy evaluable patients are those who have received CART-19 cells at the protocol-specified dose for the Arm they have been randomized to (1-5x10^8 and 1-5x10^7 CART-19 cells for Arms 1 and 2, respectively). These patients will be evaluable for primary efficacy endpoints. Safety, tolerability, and clinical response rates will be evaluated to determine a dose cohort with a minimum of 30% three-month complete response (CR) rate for expansion.

Subjects with a manufactured cell dose that is less than the protocol-specified dose will be scored as a manufacturing failure. These subjects will receive their cell infusion, provided that the manufactured dose is above the CVPF minimum acceptable dose for infusion (2x10^6 CART-19 cells) and all other manufacturing release criteria are met. The subjects that are infused with lower than the protocol specified dose for their randomized arm are primary efficacy non-evaluable patients. They will not be included in the primary efficacy endpoint analysis. However, they will be included for secondary efficacy, safety, manufacturing, correlative and exploratory endpoint analyses.

For the purposes of the study, primary efficacy non-evaluable patients will be replaced with primary efficacy evaluable patients. Both primary efficacy evaluable and non-evaluable patients will be followed in the same manner according to the Schedule of Study Procedures for all evaluations, including clinical, research (correlative) and safety.

All patients receiving $\geq$2x10^6 CART-19 will be assessed for clinical response according to the criteria discussed in Section 7. Again, patients scored as manufacturing failures and receiving less than the dose for their randomized arm will not be included in primary efficacy endpoint analysis (see Section 8.3). **Table 3-1** summarizes nomenclature, endpoint analysis and clinical evaluations for all possible CART-19 dose manufacturing and infusion scenarios.

Table 3-1 Subject Dose, Infusion and Endpoint Analysis Summary- Stage 1

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Manufactured CART-19 Dose	Released from CVPF*? (Y/N)	Can subject be infused**? (Y/N)	Included in endpoint analysis? (Y/N)				Analysis Population Assigned to for Efficacy Endpoints (Section 8.3)
			Primary Efficacy	Secondary Efficacy	Correlative and Safety	Manufacturing Feasibility	
Arm 1: 1-5x10^8 Arm 2: 1-5x10^7	Y	Y	Y	Y	Y	Y	Evaluable Population
≥2x10^6	Y	Y	N	Y	Y	Y	Safety Population
<2x10^6	N	N	N	N	N	Y	N/A

***Provided that all other manufacturing release criteria are met**
****If subject does not receive dose, then they are only assessed for manufacturing feasibility**

All subjects will follow the same general protocol schema as shown above in **Figure 1**. After signing informed consent, patients will undergo screening tests and procedures to determine eligibility. Once patient eligibility is confirmed, patients will be staged for apheresis (leukapheresed) to obtain peripheral blood mononuclear cells (PBMC) for CART-19 manufacturing. The T cells will be purified from the PBMC, transduced with CD19 TCRζ/4-1BB lentiviral vector, expanded *in vitro* and then frozen for future administration. The number of patients who have inadequate T cell collections, expansion or manufacturing compared to the number of patients who have T cells successfully manufactured at each of the dose levels will be a primary measure of dose feasibility in this study.

In Stage 2, the selected dose cohort will be expanded to enroll additional subjects, to ensure that a total of 20 evaluable subjects are treated at that dose level. See Section 8 for expansion rules and statistical considerations. Based on the Stage 1 analysis performed in November 2014, Arm 1 was chosen for expansion in Stage 2. The interim analysis revealed that the response rates of Arm 1 and Arm 2 are comparable with a trend towards greater efficacy in Arm 2. There is not enough evidence to suggest that the two dose arms have statistically significant differences in CRS. There is some evidence to suggest that the two dose arms have statistically significant differences in TLS, but none of these cases were clinically unmanageable. TLS also contributed to the incidence of renal failure. However it should be emphasized that TLS is also a manifestation of response and not simply a toxicity that must be avoided. In sum, the analyses revealed that high dose has a favorable safety profile with similar or possibly higher efficacy, Therefore, the Stage 2 dose will be 1-5x10^8 transduced CART-19 cells.
At the beginning of Stage 2 of this trial, manufacturing changes were instituted in line with the FDA IND. The first subject treated in Stage 2 (03712-51), experienced early CRS within 12 hours of receiving T-cells, and received anti-cytokine therapy with tocilizumab and steroids within 24 hours of infusion. The subject responded well to anti-cytokine therapy. Our initial pilot trial of CAR T cells in CLL (UPCC 04409) gave a similar dose of T-cells but split over 3 days. Currently, in our companion trial for subjects with ALL (UPCC 21413), we altered the schedule of administration to give the cell dose via split dosing over 3 days (10% given on Day 1; 30% on Day 2; and 60% on Day 3), due to early and severe CRS experienced after single dose

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

administration. Subjects who develop fevers or CRS symptoms but who have not received all 3 infusions, will not receive subsequent infusions. As of March 5, 2015, two subjects have been treated using this split dosing regimen on UPCC#21413, and our preliminary experience suggests that this administration schedule results in a more delayed and responsive CRS.

Therefore, we plan to treat subsequent CLL subjects enrolled in Stage 2 of this study with the selected dose of 1-5 x 10^8 T-cells administered via split dosing: 10% on Day 1 (1-5x10^7), 30% on Day 2 (3x10^7-1.5x10^8), 60% on Day 3 (6x10^7-3x10^8).

Table 3-2 Subject Dose, Infusion and Endpoint Analysis Summary- Stage 2

			Included in endpoint analysis? (Y/N)				
Manufactured CART-19 Dose	**Released from CVPF*? (Y/N)**	**Can subject be infused**? (Y/N)**	**Primary Efficacy**	**Secondary Efficacy**	**Correlative and Safety**	**Manufacturing Feasibility**	**Analysis Population Assigned to for Efficacy Endpoints (Section 8.3)**
1-5x10^8	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Evaluable Population**
≥2x10^6	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Safety Population**
<2x10^6	**N**	**N**	**N**	**N**	**N**	**Y**	**N/A**

***Provided that all other manufacturing release criteria are met**
****If subject does not receive dose, then they are only assessed for manufacturing feasibility**

Evaluable patients are defined as those who were able to receive viable product at the intended dose level by randomization and have completed at least 3 months of follow-up after the first infusion or who have discontinued early due to disease progression, initiation of a new cancer therapy, or death.

It is anticipated that many patients have been receiving chemotherapy for relapse or resistant disease. Prior to CART-19 cell infusion, an additional chemotherapy cycle for lymphodepletion is planned. The regimen of chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden and histology (see section 6.6).

All subjects will have blood tests to assess safety, and engraftment and persistence of the CART-19 cells at regular intervals during the first 4 weeks after treatment, monthly up to 6 months, and quarterly up to 12 months following treatment. The subsets of circulating T-cells that contain the two constructs will be assessed at various times after infusion and compared to the baseline sample. Trafficking of CART-19 cells will be assessed in bone marrow aspirates. Following the 6 months of intensive follow-up, subjects will be evaluated quarterly for 1 year with a medical history, a physical examination, and blood tests. Following this evaluation, subjects will enter a destination protocol (UPCC 10908/IRB #815699) for follow-up by phone or mail and questionnaire for up to

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

15 years from initial infusion to assess for the diagnosis of long-term health problems, such as development of new malignancy.

3.2 *Primary Efficacy Non-Evaluable Patients*

A primary efficacy non-evaluable patient is defined as any patient who is infused with the CART-19 cells at less than the protocol-specified dose for which a manufactured product has been released. The minimum CART-19 dose for this protocol that will be released from CVPF for infusion is $2x10^6$; therefore, this is the lowest dose that will be administered to subjects under this protocol. Patients who choose to receive their released CART-19 dose that falls below the protocol-specified dose will be clinically followed for safety and efficacy exactly the same as those patients who receive their CART-19 dose that falls within the protocol-specified range (i.e. the primary efficacy evaluable patients). The only difference between the primary efficacy evaluable and non-evaluable patients is that only the primary efficacy evaluable patients will be used for primary efficacy endpoint analysis. Both primary efficacy evaluable and non-evaluable patients will be used in secondary efficacy, safety, manufacturing feasibility, correlative and exploratory analyses. The statistical analysis sets are detailed in Section 8.3.

3.3 *Retreatment Cohort*

3.3.1 Overview

Based on available clinical trial data as of February 1, 2014, sustained persistence of CART19 cells are directly correlated with ongoing response. Thus, several subjects who have lost detectable CART19 cells have subsequently relapsed. Relapsed subjects have been retreated with additional CART19 cell infusions and, in some cases, the initial responses were reestablished. Given the clinical evidence that will be described in depth below, we would like to allow for the retreatment of subjects who had an initial response to their 1st infusion, lost detectable CART19 cells and have subsequently relapsed.

Retreatment with CART19 cells has already been performed in two adult CLL subjects on UPCC#04409 as well as 5 pediatric ALL subjects on CHP959.

Subject #04409-05: This subject initially received all three split dose fractions (10%, 30% and 60%) for a total dose of $7.50x10^8$ CART19 cells. This subject displayed limited CART19 expansion and no persistence after his initial infusion. An exception to retreat this subject approximately one year after his initial treatment with remanufactured cells was granted by the Penn CTSRMC and IRB. The subject again received all three split dose fractions ($6.27x10^8$ CART19 cells) but did not exhibit T cell expansion or a significant response. While there was no persistence, there was also no infusional toxicity associated with the second round of infusions indicating that reinfusion after a year since first exposure was well-tolerated.

Subject #04409-10: This CLL subject was infused with the 10% and 30% split dose fractions ($3.75x10^8$ CART19 cells), experienced cytokine release syndrome which was treated with tocilizumab. The cytokine release syndrome resolved; however, there was no detectable disease response. Since this was early in the clinical development, there was concern that the administration of tocilizumab could have impaired CART19 activity and/or response. Therefore, approval was sought and granted to reinfuse the subject with the remaining 60% dose ($3.0x10^9$

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

CART19) 2 months later. The subject's infusion was well tolerated and once again followed by a cytokine release syndrome, which was treated with tocilizumab 10 days after this infusion. However, a durable complete remission was induced and continues 15 months post-reinfusion.

As of February 1, 2014, five pediatric subjects experiencing complete responses to their 10% CART19 dose have relapsed or lost CART19 cells with evidence of B cell recovery at ≥8 weeks since the infusion. Upon relapse or B cell recovery, these subjects were retreated with either their remaining 30% or 30% and 60% CART19 doses. Infusional toxicities were not seen in any of these cases. Two of the five subject retreated with their 30% dose experienced complete responses; CHP959-105 went on to receive a bone marrow transplant at 2 months and CHP959-121 remains in an ongoing CR at 2 months post-reinfusion.

Table 3-1. Retreated CHP959 subject summary as of February 1, 2014

Subject ID	Reason for Retreatment	Time elapsed since 10% dose prior to retreatment	Dose fractions given for retreatment	Response after retreatment
CHP959-101	Relapse	3 months	30%, 60%	NR
CHP959-105	Relapse	9 months	30%	CR ongoing, went to BMT at 2 months
CHP959-110	Relapse	3 months	30%, 60%	NR
CHP959-111	Relapse	2 months	30%	NR
CHP959-121	CART19 cell loss and B cell recovery	3 months	30%	CR, 2 months, ongoing

Taken together, there have been no severe or unexpected toxicities observed in any subject upon retreatment with CART19 cells ranging from 2-12 months after the initial infusion(s) retreated with CART19 cells as of February 1, 2014. Given the currently available safety data, there is no suggestion that retreatment of these targeted subjects will pose risks to the subject greater than that of their original infusion. Additionally, 3 of the 7 subjects retreated have experienced clinical benefit with few alternative treatment options available. Therefore, retreatment with additional CART19 doses carries potential benefit with no observable increased risk associated with the current data.

3.3.2 Retreatment Objectives

This cohort of subjects will be analyzed separately in order evaluate the following exploratory objectives:

- Assess the frequency and severity of adverse events and other safety data including development of cytokine release syndrome
- Evaluate the expansion and persistence of CART19 cells, in comparison to their original infusion
- Evaluate overall response, time to response, duration of response and time to alternative therapy, in comparison to their original infusion.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

3.3.3 Retreatment Dose

Three types of subjects will be eligible for retreatment.

- The first group are subjects initially treated in Stage 1 of this trial (who receive a one-time bulk dose infusion), who have previously manufactured cells available and meet criteria for retreatment. These subjects will receive retreatment with a one-time dose of previously manufactured cells as described here.
- The second group of subjects are those treated in Stage 2 on an amended version of the protocol (As of Protocol Version 12. 03-05-2015) and will have received split dose infusions as described (10% on Day 1; 30% on Day 2; 60% on Day 3), and meet eligibility criteria for retreatment. They will be retreated in the same manner as their initial treatment and receive split dose infusions as described.
- The third group of subjects are subjects initially treated in Stage 1 of this trial (who receive a one-time bulk dose infusion), and who meet criteria for retreatment, but do not have previously manufactured cells available. These subjects will undergo a new T-cell collection for manufacturing, and will receive cells split dosing fashion (10% on Day 1; 30% on Day 2; 60% on Day 3).

Up to one retreatment dose (either single or split) will be allowed per eligible subject. The target dose for this retreatment cohort is 1-5 x 10^8 CART19 cells. The minimum acceptable dose for infusion is 1 x 10^7 CART19 cells. The target dose corresponds to that of Arm 1 in Stage I of this protocol. Both the target and minimum acceptable dose have been safe and effective in ongoing trials evaluating this therapy in patients with both ALL and CLL. Previously manufactured cells for this dose level are also readily available in the CVPF for many previously enrolled subjects.

All prerequisites for eligibility to receive CART19 outlined in Section 5.2 must be met prior to retreatment. The study drug will be prepared and administered per the guidelines set forth in Section 5. All required pre-medications, prophylaxis monitoring guidelines from the initial infusion will apply for retreatment.

Additional information related to retreatment eligibility and procedures, is outlined in Section 6.13 below.

4 Subject Selection and Withdrawal

Patient Population

4.1 *Inclusion Criteria*

1) Documented CD19+ CLL or SLL
2) Successful test expansion of T-cells (as described in Section 6.1)
3) At least 2 prior chemotherapy regimens, not including single agent monoclonal antibody (rituxan) therapy. Single agent ofatumumab will be counted as a regimen. Patients with high risk disease manifested by deletion chromosome 17p will be eligible if they fail to achieve a CR to initial therapy or progress within 2 years of 1 prior regimen.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

4) Patients who progress within 2 years after the second or higher line of therapy will be eligible. For instance, patients who had progression < 2 years after second or greater line therapy, but who have responded to their most recent treatment (3rd line or higher) will be eligible.
5) Subject is not appropriate candidate for a potentially curative allogeneic SCT due to the state of disease, co-morbid illness, lack of an available donor, or patient declines
6) ~~Expected survival > 12 weeks~~RETIRED FROM PROTOCOL VERSION 12
7) Performance status (ECOG) 0 or 1
8) Age >/= 18 years
9) Adequate organ system function including:
    a. Creatinine < 1.6 mg/dl
    b. ALT/AST < 3x upper limit of normal
    c. Total Bilirubin <2.0 mg/dl
10) Any relapse after prior autologous SCT will make patient eligible regardless of other prior therapy
11) Patients with relapsed disease after prior allogeneic SCT (myeloablative or nonmyeloablative) will be eligible if they meet all other inclusion criteria and:
    a. Have no active GVHD and require no immunosuppression
    b. Are more than 6 months from transplant
12) No contraindications for leukapheresis
13) Left Ventricular Ejection fraction ≥40%
14) Gives voluntary informed consent

4.2 *Exclusion Criteria*

1) Pregnant or lactating women. The safety of this therapy on unborn children is not known. Female study participants of reproductive potential must have a negative serum or urine pregnancy test performed within 48 hours before infusion.
2) Uncontrolled active infection
3) Active hepatitis B or hepatitis C infection
4) Concurrent use of systemic steroids or chronic use of immunosuppressant medications. Recent or current use of inhaled steroids is not exclusionary. For additional details regarding use of steroid and immunosuppressant medications, please see Section 5.6.
5) Any uncontrolled active medical disorder that would preclude participation as outlined
6) HIV infection
7) Patients with active CNS involvement with malignancy. Patients with prior CNS disease that has been effectively treated will be eligible providing treatment was >4 weeks before enrollment.
8) Class III/IV cardiovascular disability according to the New York Heart Association Classification (see Appendix 3).

Please see Section 6.13 for eligibility criteria for the Retreatment Cohort.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

4.3 *Subject Recruitment and Screening*

Subjects will be identified through the clinical practices of the investigator or sub-investigators and through referrals from outside hospitals and physicians. No direct-to-patient advertising will be performed. The clinical trial will be listed on the clinicaltrials.gov website.

To be eligible, the subjects must have an adequate number of T cells that can be successfully transduced and expanded with the CD19 TCRζ/4-1BB lentiviral vector (≥ 4-fold expansion needed), as determined from a sample of PBMC obtained by phlebotomy at the first screening visit (~week -8). The purpose of this screening procedure is to exclude subjects from participation who would otherwise undergo a futile apheresis and restaging, without the possibility of having the source T cells obtained by apheresis returned as redirected CAR T cells. There will be a minimum of 6-8 weeks in between test expansions should the first test expansion fail because of insufficient starting T cell numbers, up to a maximum of three test expansions per subject to determine eligibility.

Female subjects of reproductive potential (women who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone a sterilization procedure [hysterectomy or bilateral oophorectomy]) must have a negative serum or urine pregnancy test within 48 hours prior to entry.

Due to the high risk level of this study, while enrolled, all subjects must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization). Additionally, if participating in sexual activity that could lead to pregnancy, the study subject must agree to use a reliable method of contraception during their participation in the study.

Acceptable birth control includes one of the following methods:

- Condoms* (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormonal-based contraception

Subjects who are not of reproductive potential (women who have been post menopausal for at least 24 consecutive months or have undergone hysterectomy, salpingectomy, and/or bilateral oophorectomy or men who have documented azoospermia) do not require the use of contraception. Acceptable documentation of sterilization, azoospermia, and menopause is specified below:

Written documentation by clinician or clinician's staff through one of the following:

- Physician report/letter
- Operative report or other source documentation in the subject record (a laboratory report of azoospermia is required to document successful vasectomy)
- Discharge summary of sterilization procedure or hysterectomy, and/or salpingectomy, oophorectomy
- Laboratory report of azoospermia
- Follicle stimulating hormone measurement elevated into the menopausal range

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

4.4 *Early Withdrawal of Subjects*

4.4.1 When and How to Withdraw Subjects

Subjects who do not complete the study protocol will be considered to have prematurely discontinued the study. The reasons for premature discontinuation (for example, voluntary withdrawal, toxicity, death) must be recorded on the case report form. Final study evaluations will be completed at the time of discontinuation.

Potential reasons for premature discontinuation include:

1. The subject is lost to follow-up.

2. The judgment of the principal investigator.

3. Patient noncompliance with study therapy and/or clinic appointments.

4. Pregnancy: Withdraw patient if pregnancy occurs prior to the CART-19 T-cell infusion

5. Voluntary withdrawal; a patient may remove himself/herself from the study at any time without prejudice. A patient may withdraw from the study at any time they wish to withdraw consent.

6. Significant and rapid progression of malignancy, requiring alternative medical, radiation or surgical intervention including, but not limited to, the development of CNS metastasis if this occurs prior to the CART-19 T-cell infusion.

7. A serious adverse event that requires the patient's being withdrawn from the trial if the SAE occurs prior to the CART-19 T-cell infusion.

8. Technical difficulties are encountered in the T cell genetic modification and expansion procedure that precludes the generation of clinical cell doses that meet all Quality Control release criteria as specified by FDA.

9. Termination of the study by the principal investigator, the sponsor, the study funder, the IRB, or the FDA.

Once a subject has received a CART-19 T-cell infusion, subjects should continue to be followed until the subject withdraws consent, dies or are lost to follow up. Subjects are encouraged to enroll into a 15 year long term follow up protocol to evaluate specific long term adverse events related to the study product.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Follow-up data collection after gene modified cell therapy clinical trials is specified by the FDA. As long as patients have detectable cells transduced with the lentiviral vector, they should be followed for toxicity, immune reactions, and any long-term adverse events. Therefore, subjects will continue to be followed for 1) engraftment as long as patients are at risk (until evidence of

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

loss of detectable transduced T cells), 2) DFS until there is disease progression or they begin a new cancer therapy, and 3) survival until the time of death; until the patient withdraws consent for clinical data collection or the end of the study (Last Patient/Last Visit).

Patients who are followed at other institutions or practices, because of preference or geographical concerns will have follow-up via notes from their local physician and/or phone interviews with periodic study assessments done at HUP. An example would be a patient referred from out of state but cared for at another center. We will obtain toxicity and other clinical assessments from the treating physician, and follow the patient as described in the table in Appendices 1 and 2. In numerous previous cell therapy trials at the University of Pennsylvania, loss of follow-up is estimated to occur in less than 5% of cases. Every effort will be made to contact subjects who appear to be lost to follow-up in order to at least obtain survival data. In the event a subject fails to complete the follow-up requirements, documentation of all attempts to contact the subject includes at least 3 telephone contacts (on different days and at different times of the day), and a certified letter.

After subjects' complete or prematurely discontinue participation in this study, subjects will also be asked to participate in a separate 15 year long-term follow-up destination protocol.

5 Study Drug

5.1 *Description*

CART-19 cells are autologous T cells that have been engineered to express an extracellular single chain antibody (scFv) with specificity for CD19 linked to an intracellular signaling molecule consisting of a tandem signaling domains comprised of the TCRζ signaling module linked to the 4-1BB costimulatory domain. The CART-19 cells are cryopreserved in infusible cryomedia and will be administered as one bag on Day 1. Each bag will contain an aliquot (volume dependent upon dose) of cryomedia containing the following infusible grade reagents (% v/v): 31.25% Plasmalyte-A, 31.25% dextrose (5%), 0.45% NaCl, up to 7.5% DMSO, 1% dextran 40, 5% human serum albumin.

Expected toxicities associated with infusion of CART-19 cells include transient fever, chills nausea, rigors, hypotension, tumor lysis syndrome, and cytokine release syndrome. In order to minimize these events, patients will receive premedication as instructed below. Toxicities that could potentially occur but are unprecedented are primarily related to the gene transfer and are described in the Risk and Benefit section (refer to section 1.8). These include generation of a replication competent lentivirus (RCL), insertional oncogenesis, and uncontrolled proliferation of the CART-19 cells.

5.2 *Patient Eligibility to Receive CART-19 Transduced T Cells*

Day 1 CART-19 Infusion:

1. All patients must undergo a Respiratory Virus Panel (RVP) within 10 days prior to the first planned CART-19 infusion. If the patient is positive for influenza, Tamiflu® or equivalent, should administered for 10 days as preventative treatment. The patient must complete their 10 day preventative treatment course **prior** to receiving CART-

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

19. The test does not need to be repeated prior to the first CART-19 infusion, however if influenza sign and symptoms are present, the CART-19 infusions should be delayed until the patient is asymptomatic. If the patient is positive for another virus on the RVP, the CART-19 infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the infusion will be delayed until resolution of these symptoms.

2. Patient should not experience a significant change in performance status or clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, increase the risk of experimental cell infusion.
3. Patients experiencing laboratory abnormalities after enrollment, that in the opinion of the treating investigator or PI may impact subject safety or the subjects' ability to receive CART-19 T-cells, may have their infusion delayed until both the treating investigator and PI determine it is clinically appropriate to proceed with the CART-19 infusion.
4. Patients experiencing toxicities from their preceding cytoreductive chemotherapy can have their infusion schedule delayed until these toxicities have resolved. **Note:** If patients CART-19 infusion is delayed > 4 weeks from cytoreductive chemotherapy, the cytoreductive chemotherapy should be repeated. The specific toxicities warranting delay of T cell infusions include:
    a. Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 95% or presence of radiographic abnormalities on chest x-ray that are progressive
    b. Cardiac: New cardiac arrhythmia not controlled with medical management
    c. Hypotension requiring pressor support
    d. Active Infection(s): as evident by positive blood cultures for bacteria, fungus, or virus within 48 hours of CART-19 cell infusion.

Day 2 CART-19 Infusion:

1. Patient should not experience a significant change in performance or clinical status compared to their previous study visit that would, in the opinion of the treating physician, increase the risk of experimental cell infusion.
2. Patients experiencing new laboratory abnormalities, that in the opinion of the treating investigator or PI may impact subject safety or the subjects' ability to receive CART-19 T-cells, may have their infusion delayed until both the treating investigator and PI determine it is clinically appropriate to proceed with the CART-19 infusion.

Day 3 CART-19 Infusion:

1. Patient should not experience a significant change in performance or clinical status compared to their previous study visit that would, in the opinion of the treating physician, increase the risk of experimental cell infusion.
2. Patients experiencing new laboratory abnormalities, that in the opinion of the treating investigator or PI may impact subject safety or the subjects' ability to receive CART-19 T-cells, may have their infusion delayed until both the treating investigator and PI determine it is clinically appropriate to proceed with the CART-19 infusion.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

5.3 *Treatment Regimen*

CART-19 transduced T cells will be administered at a dose of 1-5x10^8 given via split dosing on Days 1, 2 and 3. The first CART-19 infusion will be scheduled to occur approximately 1 to 4 days following lymphodepleting chemotherapy but may be delayed as outlined above (Section 5.2).

5.4 *Preparation and Administration of Study Drug*

Cell manufacturing is done according to Figure 3 under INDs 13960 at the University of Pennsylvania Clinical Cell and Vaccine Production Facility (CVPF). The CART-19 T cells are prepared in the CVPF and are not released from the CVPF until FDA approved release criteria for the infused cells (e.g., cell dose, cell purity, sterility, average copy number of vectors/cell, etc.) are met. Upon release, the cells are administered at the bedside.

Cell thawing

The cells will be transported by CVPF personnel to the subject's bedside. The cells will be thawed at the bedside or in the CVPF by trained personnel using a water bath maintained at 36°C to 38°C. The bag will be gently massaged until the cells have just thawed. There should be no frozen clumps left in the container by the time it is connected to the I.V. tube. If the CART-19 cell product appears to have a damaged or leaking bag, or otherwise appears to be compromised, it should not be infused, and should be returned to the CVPF.

Premedication

Side effects following T cell infusions include transient fever, chills, and/or nausea. It is recommended that the subject be pre-medicated with acetaminophen (650 mg) and diphenhydramine hydrochloride (25-50 mg IV/PO) at least 30 minutes prior to each infusion of CART-19 cells. These medications may be repeated every six hours as needed. A course of non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved by acetaminophen. Patients should not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol) or dexamethasone (Decadron) at any time, except in the case of a life-threatening emergency, since this may have an adverse effect on CART-19 cell expansion and function. If corticosteroids are required for an acute infusional reaction, an initial dose of hydrocortisone 100 mg is recommended.

Febrile reaction

In the event of febrile reaction, an evaluation for infection should be initiated, and patients managed appropriately with antibiotics, fluids and other supportive care as medically indicated and determined by the treating physician. In the event that the patient develops sepsis or systemic bacteremia following CAR T cell infusion, appropriate cultures and medical management should be initiated. If a contaminated CART-19 T cell product is suspected, the product can be retested for sterility using archived samples that are stored in the CVPF. Consideration of a CRS should be given.

Additional Safety Procedures prior to Administration

The on-site pharmacy must confirm that a dose of tocilizumab is on site and available for administration in order to manage suspected toxicities prior to infusion.

Emergency medical equipment (i.e., emergency trolley) must be available during the infusion in

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

case the patient has an allergic response, or severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, respiration rate, pulse, and blood pressure) will be taken before infusion.

Packaging and Labeling

CART-19 transduced T cells will be administered at a dose of 1-5x10^8 given via split dosing on Days 1, 2 and 3. Each infusion bag will contain an aliquot (volume dependent upon dose) of cryomedia containing the following infusible grade reagents (% v/v): 31.25% plasmalyte-A, 31.25% dextrose (5%), 0.45% NaCl, up to 7.5% DMSO, 1% dextran 40, 5% human serum albumin.

Each infusion bag will have affixed to it a label containing information regarding the dose, the method of manipulation, the vector and "FOR AUTOLOGOUS USE ONLY." In addition the label will have the following unique identifiers patient name, study ID, and patient birth date. Prior to each infusion, two individuals will independently verify all unique identifier information in the presence of the patient and to confirm that the information is correctly matched to the patient.

5.5 *Infusion of CART-19 Product*

Trained study staff will administer the CART-19 product via i.v. infusion using precautions for immunosuppressed patients. A physician from the research team will be readily available during the complete duration of the infusion. The transduced T cells will be infused at a flow rate of approximately 10 to 20 mL per minute through an 18-gauge latex free macrodrip i.v. tubing without a leukocyte filter or equivalent. A leukoreduction filter **must not be used for the infusion of the T cell product**. The duration of the infusion will be based on the total volume to be infused and the recommended infusion rate. Vital signs (temperature, respiration rate, pulse, blood pressure, and oxygen saturation by pulse oximetry) will be measured within 10 minutes prior, during and within 10 minutes after the infusion, and then every 15 minutes for the first hour and then every hour for the next 2 hours until these signs are satisfactory and stable. In the event that an infusion takes longer than 15 minutes, vital signs will be taken every 15 minutes until the infusion is completed. If the subject's vital signs are not satisfactory and stable three hours post-CART-19 infusion, vital signs will continued to be monitored at a minimum of every hour or as clinically indicated until stable. The subject will be discharged after the physician managing their care on the day of each infusion has determined that they are in satisfactory condition.

5.6 *Prior and Concomitant Therapy*

All prescription and nonprescription medication, vitamins, herbal and nutritional supplements, taken by the subject during the 30 days prior to screening will be recorded at the screening visit. At every visit following the CART-19 infusions through 1 year, concomitant medications will be recorded in the medical record and on the appropriate CRF. Any additions, deletions, or changes of these medications will be documented. The following guidelines must be adhered to during the study:

- GM-CSF should be avoided due to potential to worsen CRS symptoms. G-CSF would be the preferred myeloid growth factor over GM-CSF, if medically indicated. The effects of G-CSF are unknown and can be used at the physician's discretion.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

- Steroids or other immunosuppressant drugs should NOT be used within 10 days prior to the apheresis procedure
- Steroids or other immunosuppressant drugs should NOT be used within 24 hours prior to the CART-19 infusions (refer to Section 5.4) or following CART-19 infusion unless under life threatening circumstances or at the physicians' discretion to manage CRS.
- Patients with severe signs and symptoms attributable to cytokine release syndrome (i.e. CRS) should be managed with administration of tocilizumab or other anti-cytokine directed therapies (Refer to Section 9.5.2 for administration details).

5.7 *Subject Compliance Monitoring*

The investigator-initiated phase I/II trials at the UPenn Abramson Cancer Center (ACC) are subject to routine auditing in accordance with their high risk policy. Ongoing monitoring of each patient is performed by the monitor designated by the Sponsor.

6 Study Procedures

The study consists of 1) a screening phase, 2) a randomization and arm assignment stage (Stage 1 only), 3) an intervention/treatment phase consisting of apheresis, chemotherapy (to be determined according) to the investigator and dependent on the patient's disease burden and histology), infusions of CART-19 cells, CT scans and tumor collection by bone marrow aspiration or lymph node biopsy (optional, depending on availability), and 4) follow up. Schedule of evaluations and infusion are included in **Appendix 1**.

6.1 *Pre-Entry Evaluations (Screening) and Subject Number Assignment (Week -8 to -12)*

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Sponsor to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available to the investigator. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the subject is re-screened.
If the subject fails screening for any reason, the reason will be entered into the Screening Disposition page.

After informed consent and demographic information are obtained, blood tests to determine eligibility are performed, and a blood sample is sent to the CVPF to determine T cell manufacturing feasibility. Adverse events and concomitant medications will be recorded beginning from the time the patient's informed consent has been obtained. In approximately 1 week, the CVPF will return a result as to whether the subject's PBMC are likely to be adequate for large scale CART-19 T cell manufacturing process. At the discretion of the Principal Investigator, subjects who have had a successful test expansion of T-cells prior to enrollment in this study may not be required to have a second test expansion. During the screening period, inclusion and exclusion criteria will be assessed. Also, subjects will be tested for Human Immunodeficiency Virus (HIV).

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

6.2 *Enrollment and Baseline Assessment (Week -6 to -8)*

Eligible subjects who have signed an informed consent and have adequate pre-screening evaluation will undergo a routine lymphoma/leukemia staging workup including:

a) Eligibility form and randomization (Stage 1 Subjects Only)
b) Relevant medical history, current medical conditions, and physical examination (including vital signs, height, weight, body surface area)
c) Concomitant medications
d) Adverse events
e) Performance status assessment
f) CT scans of the chest, abdomen, and pelvis done within 42 days of study entry
g) Hematology (Complete blood count, differential and platelet count)
h) Chemistry panel (Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid)
i) β2 Microglobulin Level
j) Serum immunoglobulin levels
k) Serum pregnancy test (qualitative)
l) Viral serologies (CMV, EBV, Hepatitis B/C). If the HCV antibody is positive, a screening HCV RNA by any RT-PCR or bDNA assay must be performed. Eligibility will be determined based on the screening value. The test is not required if documentation of a negative result of a HCV RNA test performed within 60 days prior to screening is provided
m) Autoimmune screen (ANA, ESR)
n) Leukapheresis screening (assessment of the suitability of venous access)
o) Bone marrow biopsy/aspirate and lymph node biopsy (if accessible). Samples are sent to hematopathology for MRD assessment, p53 mutation analysis and CD19 expression.
p) Blood will be sent for flow cytometry to confirm CD19 expression if this has not been done in the past 6 months
q) MUGA/ECHO
r) Quality of Life Questionnaires (EORTC QLQ-C30 and CLL-16)
s) Research labs: Molecular (including p53 and VSV-G), cytokine, Immunogenicity (HAMA/HACA), and cellular assessments

Correlative Research Labs: For molecular and cell engraftment studies (Q-PCR and Q-RT-PCR), immune phenotyping and functional assays, peripheral blood and marrow samples will be collected in Lavender top (K2EDTA) tubes. For cytokine analyses, such as IL-6 and IL-2, peripheral blood and marrow samples will be collected in red top (no additive) tubes. Samples will be collected according to the protocol Schedule of Study Procedures (Appendices 1 and 2). Samples will be delivered, processed, and frozen as per SOP to the Translational and Correlative Studies Laboratory (TCSL) (University of Pennsylvania). Samples will be stored in the TCSL at the University of Pennsylvania for storage and bulk analyses. Documentation for sample -receipt, -processing, and storage and primary data from the research analyses will be collected and stored in the TCSL. All research analyses will be performed based on principles of Good Clinical Laboratory Practice, with assay-specific SOP using qualified and if possible validated assays.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Translational and Correlative Studies Laboratory
University of Pennsylvania Perelman School of Medicine
Translational Research Center, 9-188
3400 Civic Center Boulevard, Building 421
Philadelphia, PA 19104-5157

In the event that the time between the above baseline assessments and the Day 1 CART-19 T cell infusion exceeds the 8 week Enrollment/Baseline Window, the following clinical tests/procedures will be repeated: Physical Examination, Performance Status Assessment, Complete Blood Count, Differential and Platelet Count, Chemistry Panel, Pregnancy test, HIV, and Hepatitis B/C.

6.3 *Enrollment Process*

To enroll a subject on this study, provide the documents listed below to:

Protocol Monitor and Sponsor Project Manager Translational Research Program Email: trpctu@mail.med.upenn.edu Fax: 215-615-2869

Documents required:

- Complete Enrollment Form (including patient past medical history, laboratory, radiological reports, documentation of consent, physical exam, concomitant medications and any other source documentation to support subject meets eligibility criteria and has completed all required screening assessments)
- Copy of signed patient consent and HIPAA form

Upon informed consent completion and receipt of screening and eligibility documentation, the Sponsor Protocol Monitor will review and provide documentation that the monitoring visit for eligibility has been completed. This documentation must be received prior to cell product manufacturing.

For enrollment into Stage 1, randomization assignments will be performed centrally by Novartis using Treatment Allocation Cards. A full set of 40 cards will be maintained by the site. Each card will have a specific Randomization Number printed on it. The treatment information on each card is hidden and will only become visible after it is scratched-off.

When a confirmed eligible patient requires randomization into Stage 1 of the study, designated site staff will complete the Randomization Number Request Form and submit it to the Randomization Coordinator (NVS). The Randomization Coordinator will provide the next available Randomization Number to the site using the Randomization Number Assignment Form. The site will then provide the Treatment Allocation Card corresponding ONLY to the assigned Randomization Number to the Investigator/ designee for use in randomizing the eligible patient. More details on randomization are available in the study specific Novartis Randomization Document.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

All patients will be enrolled into Stage 1 until the dose cohort for Stage 2 has been selected for expansion, per section 8.1. After the dose cohort for Stage 2 has been selected, all subsequent patients will be enrolled into Stage 2. If deemed appropriate by the Investigator, an additional dose level may be explored prior to the start of Stage 2.

No more than 20% of the total enrollment may be manufacturing failures. If this is exceeded, a separate modification will be submitted for IRB review.

6.4 *Apheresis (Week -4)*

Subjects will undergo the additional following assessments:

a) Current medical conditions
b) Concomitant medications
c) Adverse events
d) Leukapheresis (as mentioned below)
e) Research labs: Cytokine assessments

A large volume (12-15 liters or ~2-3 blood volumes) apheresis procedure is carried out at the apheresis center. PBMC are obtained for CART-19 during this procedure. From a single leukapheresis and due to the low percentage of T cells in CLL study subjects, the intention is to harvest at least 5 x 10^9 white blood cells to manufacture CART-19 T cells. Baseline blood leukocytes for FDA look-back requirements and for research are also obtained and cryopreserved (1 x 10^8 cells from apheresis to TCSL). The cell product is expected to be ready for release approximately 4 weeks later. Baseline cytokines will be measured. If T cells were previously collected on another research study, and are acceptable to use to manufacture T cells for this study, they may be used in lieu of repeating apheresis.

6.5 *Cytoreductive chemotherapy (Week -1)*

In preparation for cytoreductive chemotherapy (detailed below), the subjects will undergo the following assessments:

a) Current medical conditions
b) Concomitant medications
c) Adverse events
d) Cytoreductive chemotherapy (as mentioned below)
e) Quality of Life Questionnaires (EORTC QLQ-C30 and CLL-16)

It is anticipated that many patients have been receiving chemotherapy for relapse or resistant disease. Patients referred with stable disease on no recent therapy will be eligible. Prior to the first CART-19 cell infusion, an additional chemotherapy cycle for lymphodepletion is planned if clinically indicated. The regimen of chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden and histology. The preferred chemotherapy and lymphodepletion is fludarabine 30 mg per meter squared per day for 3 days and cyclophosphamide 300 mg per meter squared per day on the same 3 days, as there is the most experience with the use of these agents in facilitating adoptive immunotherapy. Rituximab will not to be given. In the unusual circumstance that patients have a medical contraindication to either of these drugs, or a

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

failure to respond to previous fludarabine based regimen, bendamustine 90 mg per meter squared per day for 2 days will be preferred. Pentastatin/cyclophosphamide is another acceptable alternative if fludarabine cannot be given.

Chemotherapy is started approximately 1 week before the first infusion so that CART-19 cells may be given 1-4 days after completion of the chemotherapy. The timing of chemotherapy initiation therefore depends on the length of the regimen. The purpose of the chemotherapy is to induce lymphopenia in order to facilitate engraftment and homeostatic expansion of CART-19 cells. In addition, chemotherapy can potentiate the ability of T cells to kill tumor cells[91, 92]. The chemotherapy is not investigational and may be given by a patient's local oncologist within the specified time frame.

All patients must undergo a Respiratory Virus Panel (RVP) within 10 days prior to the first planned CART-19 infusion. If the patient is positive for influenza, Tamiflu® or equivalent, should administered for 10 days as preventative treatment. The patient must complete their 10 day preventative treatment course **prior** to receiving CART-19. The test does not need to be repeated prior to the first CART-19 infusion, however if influenza sign and symptoms are present, the CART-19 infusion should be delayed until the patient is asymptomatic. If the patient is positive for another virus on the RVP, the CART-19 infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the infusion will be delayed until resolution of these symptoms.

6.6 *CART-19 Pre-Infusion (Day -1)*

Subjects will undergo the following work-up including:

a) Current medical conditions and physical examination (including vital signs, height, weight, body surface area as clinically indicated)
b) Performance status assessment
c) Concomitant medications
d) Adverse events
e) Hematology (complete blood count, differential and platelet count)
f) Chemistry panel (Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid)
g) Urine pregnancy test
h) Baseline screens for HLH/MAS: triglycerides and haptoglobin
i) Baseline screen for coagulation factors: PT, PTT, INR, fibrinogen, D-dimer
j) Research labs: Molecular (including VSV-G), cytokine and cellular assessments

6.7 *CART-19 Infusions (Days 1, 2, and 3)*

The first CART-19 infusion should begin 1 to 4 days after completion of cytoreductive chemotherapy. The dose will be administered as a split infusion of 1 to 5 x 10^8 total CART-19 transduced cells: 10% on Day 1 (1-5x10^7), 30% on Day 2 (3x10^7-1.5x10^8), 60% on Day 3 (6x10^7-3x10^8). Patients will be infused and premedicated as described in Section 5.4.

Prior to each infusion, patients will undergo the following assessments:

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

a) Current medical conditions and physical examination (including vital signs, height, weight, body surface area as clinically indicated)
b) Performance status assessment
c) Concomitant medications
d) Adverse events
e) Hematology (complete blood count, differential and platelet count)
f) Chemistry panel (Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid). Potassium prior to infusion and 2 hours post infusion.
g) CD3, CD4 and CD8 lymphocyte counts
h) CART-19 infusion (as mentioned below)
i) Research labs: Molecular, cytokine and cellular assessments (pre & post infusion, as below)

The cells are thawed at the patient's bedside or in the CVPF by trained personnel. The thawed cells will be given at an infusion rate as quickly as tolerated so that the duration of the infusion will be approximately 2-20 minutes. In order to facilitate mixing, the cells will be administered simultaneously using a Y-adapter. Subjects will be infused and premedicated as described in Section 5.4. Vital signs (temperature, respiration rate, pulse, blood pressure, and oxygen saturation by pulse oximetry) will be measured within 10 minutes prior, during and within 10 minutes after the infusion and then every 15 minutes for the first hour and then every hour for the next 2 hours until these signs are satisfactory and stable. In the event that an infusion takes longer than 15 minutes, vital signs will be taken every 15 minutes until the infusion is completed. If the subject's vital signs are not satisfactory and stable three hours post-CART-19 infusion, vital signs will continued to be monitored at a minimum of every hour or as clinically indicated until stable. The subject will be discharged after the physician managing their care on the day of the infusion has determined that they are in satisfactory condition. Blood samples for determination of a baseline cytokines, molecular persistence and CART-19 levels are obtained any time prior to the first infusion. Additional blood samples are collected 20 minutes to 2 hours post each infusion for cytokine assessment and molecular persistence testing (and sent to the TCSL- please refer to Section 6.8).

Patients experiencing toxicities from their preceding cytoreductive chemotherapy will have their infusion schedule delayed until these toxicities have resolved. The specific toxicities warranting delay of T cell infusions include: 1) Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 95% or presence of radiographic abnormalities on chest x-ray that are progressive; 2) Cardiac: New cardiac arrhythmia not controlled with medical management. 3) Hypotension requiring pressor support. 4) Active Infection: Positive blood cultures for bacteria, fungus, or virus within 48-hours of T cell infusion.

A serum sample for potassium will be collected before each infusion (as part of the chemistry panel) as well as approximately two hours after each infusion (separate blood sample).

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

6.8 *Post infusion laboratories to assess engraftment, persistence and bioactivity (Days 4, 7, 10, 14, and 21)*

Subjects will return to the clinic at days 4, 7, 10, 14, and 21 after the CART-19 cell infusions. At these study visits, subjects will undergo the following assessments:

a) Current medical conditions and physical examination (including vital signs, height, weight, body surface area as clinically indicated)
b) Performance status assessment
c) Concomitant medications
d) Adverse events
e) Hematology (complete blood count, differential and platelet count)
f) Chemistry panel (Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid)
g) Vital signs
h) Coagulation factors: PT, PTT, INR, fibrinogen, D-dimer on Day 14
i) Research labs: Engraftment and persistence of CART-19 cells,
j) Research labs: Molecular, cytokine, and cellular assessments

6.9 *Day 28/End of Treatment*

At this study visit, subjects will undergo the following assessments:

a) Current medical conditions and physical examination (including vital signs, height, weight, body surface area as clinically indicated)
b) Performance status assessment
c) Concomitant medications
d) Adverse events
e) Hematology (complete blood count, differential and platelet count)
f) Chemistry panel (Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid)
g) CT scans of the chest, abdomen, and pelvis
h) Bone marrow biopsy/aspirate and lymph node biopsy (if accessible)
i) Serum immunoglobulin levels
j) HLH/MAS: triglycerides and haptoglobin
k) CD3, CD4 and CD8 lymphocyte counts
l) Research labs: Engraftment and persistence of CART-19 cells, Molecular, cytokine, and cellular assessments
m) 100mL peripheral blood draw
n) Quality of Life Questionnaires (EORTC QLQ-C30 and CLL-16)

Restaging is done in order to provide tumor burden measurements. Restaging testing is determined by disease type and may include imaging, MRD assessments by Dr. Bagg (or designee), bone marrow aspirate and biopsy and/or optional lymph node biopsy.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

6.10 *Monthly evaluations 2 to 6 months post infusion (Safety follow-ups 1 to 5)*

Subjects will return to the clinic on a monthly basis during months 2 to 6 post CART-19 cell infusion. At these study visits, subjects will undergo the following:

a) Current medical conditions and physical examination (including vital signs, height, weight, body surface area as clinically indicated)
b) Concomitant medications
c) Adverse events
d) Hematology (complete blood count, differential and platelet count)
e) Chemistry panel (Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid)
f) Performance status assessment
g) Quality of Life Questionnaires (EORTC QLQ-C30 and CLL-16) (only at months 3 and 6)
h) CT scans of the chest, abdomen, and pelvis (only at months 3 and 6)
i) Bone marrow biopsy/aspirate (only at months 3 and 6) and lymph node biopsy (if accessible and as clinically indicated at months 3 and 6 only)
j) Research labs: Engraftment and persistence of CART-19 cells, Molecular, cytokine, and cellular assessments (VSV-G at months 3 and 6 only)
k) CD3, CD4 and CD8 lymphocyte counts (only at months 3 and 6)
l) Serum immunoglobulin levels at months 3 and 6

6.11 *Months 9 (Safety follow-up 6) and 12 (End of Study) evaluations post infusion*

Subjects will be evaluated on a quarterly basis until 1 year post infusion (month 12 visit is the end of study visit). At these study visits, subjects will undergo the following assessments:

a) Current medical conditions and physical examination (including vital signs, height, weight, body surface area as clinically indicated)
b) Concomitant medications
c) Adverse events
d) Hematology (complete blood count, differential and platelet count)
e) Chemistry panel (Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid)
f) Performance status assessment
g) Quality of Life Questionnaires (EORTC QLQ-C30 and CLL-16)
h) CT scans of the chest, abdomen, and pelvis
i) Bone marrow biopsy/aspirate and lymph node biopsy (if accessible and as clinically indicated)
j) Serum immunoglobulin levels
k) CD3, CD4 and CD8 lymphocyte counts (only at month 12)
l) Research labs: Engraftment and persistence of CART-19 cells, Molecular, Immunogenicity (HAMA/HACA), cytokine, and cellular assessments (VSV-G at month 12 only)

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

6.12 *Secondary Follow-up*

For subjects who complete or prematurely discontinue from study follow-up while in remission, follow-up attempts will be made to assess the subject's relapse and survival status every 3 months post CART-19 infusion until the end of the study (Last Patient/Last Visit). Once subjects' relapse or they begin a new cancer therapy, additional follow-up for relapse will not be required, and subjects will be followed for survival only.

6.13 *Long-term Follow-up Protocol*

After subjects' complete or prematurely discontinue participation in this study, subjects will be asked to participate in a separate 15 year long-term follow-up destination protocol. This long-term follow-up protocol includes evaluations performed for up to 15 years on all subjects as recommended by the FDA for protocols utilizing integrating viral vectors. Evaluations will include: physical exam and medical history (including concomitant medications and adverse events) with careful attention to features possibly related to onco-retroviral diseases such as cancer, neurologic disorders or other hematologic disorders. In addition, labs will be drawn to evaluate engraftment, CART19 PCR and research labs. Blood for a VSV-G DNA test will be drawn yearly in order to detect RCL. If all VSV-G DNA tests are negative during the study period to the first annual evaluation, then future plasma samples may be archived for analysis on an as needed basis.

6.14 *Retreatment Cohort Procedures*

6.14.1 Eligibility for Retreatment

Up to one retreatment dose will be allowed per eligible subject.

1. Subjects previously infused with CART19 cells as part of this protocol and who experienced an initial response (either CR, CRi or PR) to therapy, but have subsequently progressed within 2 years of their initial response.
2. Subjects have undergone the 3 month efficacy endpoint evaluation. Subjects who achieve an initial response, but relapse prior to this Month 3 timepoint will be eligible.
3. Subjects have <5% CART19 cells in the CD3+ population by flow cytometry on PBMCs
4. Subjects have recovered from any toxicity attributed to the initial CART19 infusion, such as CRS.

In addition, subjects must also meet the following:

Retreatment Inclusion Criteria

1. Performance Status 0-1
2. Adequate organ system function including:
    - Creatinine < 1.6 mg/dl
    - ALT/AST < 3x upper limit of normal
    - Total Bilirubin < 2.0 mg/dl
3. Subject is not an appropriate candidate for a potentially curative allogeneic SCT due to the state of disease, co-morbid illness, lack of an available donor, or patient declines.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

4. ~~Expected survival > 12 weeks~~ Retired from Protocol Version 12
5. Left Ventricular Ejection Fraction ≥ 40%
6. No contraindications for leukapheresis (if required for retreatment)
7. Gives voluntary informed consent for retreatment

Retreatment Exclusion Criteria

1. Pregnant or lactating women. Female study participants must have a negative serum or urine pregnancy test performed within 48 hours before infusion.
2. Uncontrolled active infection
3. Active hepatitis or hepatitis infection
4. Concurrent use of systemic steroids. Recent or current use of inhaled steroids is not exclusionary.
5. Any uncontrolled active medical disorder that would preclude participation as outlined.
6. HIV infection
7. Patients with active CNS involvement with malignancy. Patients with prior CNS disease that has been effectively treated will be eligible providing treatment was >4 weeks before enrollment on the retreatment cohort.
8. Class III/IV cardiovascular disability according to the New York Heart Association Classification (see Appendix 3).

6.13.2 Retreatment Procedures

Subjects eligible for retreatment who consent to participate in this cohort will be enrolled on the retreatment cohort. To enroll a subject on the retreatment cohort, please provide the documents listed below to:

Protocol Monitor and Sponsor Project Manager Translational Research Program Email: trpctu@mail.med.upenn.edu Fax: 215-615-2869

Documents required:

- Copy of signed retreatment consent
- Completed Retreatment Cohort Enrollment Form- including documentation of retreatment consent, current physical examination, laboratory and radiological reports, current/past medical history and concomitant medications, and any other documentation to support the subjects' enrollment onto the retreatment cohort and has completed all required assessments.

Upon informed consent completion for retreatment and receipt of retreatment screening and eligibility documentation, the Sponsor Protocol Monitor will review and provide documentation that the monitoring visit for retreatment eligibility has been completed. This documentation must be rec

The same Subject Number previously assigned will be used to identify participants. Enrollment on the retreatment cohort will be tracked by adding "r" to the end of this existing subject identification number (i.e. 1000-00001R), however the same Subject Number previously assigned will be used in the clinical database.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Three types of subjects will be eligible for retreatment.

- The first group are subjects initially treated in Stage 1 of this trial (who receive a one-time bulk dose infusion), who have previously manufactured cells available, and who meet criteria for retreatment. These subjects will receive retreatment with a one-time dose of previously manufactured cells as described here.
- The second group of subjects are those treated in Stage 2 on an amended version of the protocol (As of Protocol Version 12. 03-05-2015) and will have received split dose infusions as described (10% on Day 1; 30% on Day 2; 60% on Day 3), and meet eligibility criteria for retreatment. They will be retreated in the same manner as their initial treatment and receive split dose infusions as described.
- The third group of subjects are subjects initially treated in Stage 1 of this trial (who receive a one-time bulk dose infusion), and who meet criteria for retreatment, but who do not have previously manufactured cells available. These subjects will undergo a new T-cell collection for manufacturing, and will receive cells split dosing fashion (10% on Day 1; 30% on Day 2; 60% on Day 3).

The target dose for this cohort is 1-5 x 10^8 CART19 cells. All prerequisites for eligibility to receive CART19 outlined in Section 5.2 must be met prior to retreatment. The study drug will be prepared and administered per the guidelines set forth in Section 5. All required pre-medications, prophylaxis monitoring guidelines from the initial infusion will apply for retreatment.

Subjects will be required to undergo the same baseline assessments outlined in Section 6.2. If there is an existing sufficient CART19 dose, leukapheresis screening to assess venous access will not be performed. However, if there is either an insufficient manufactured dose or starting material available in the CVPF, the subject will be asked to undergo apheresis to collect additional cells to manufacturer a sufficient dose for retreatment (per Section 6.4).

All other pre-infusion, on study and follow-up procedures will be completed as outlined in Sections 6.5 to 6.12 above and the Retreatment Cohort Schedule of Events in Appendix 2, including the administration of cytoreductive chemotherapy if clinically indicated.

7 Response Assessments

Tumor response assessments will be done according to standard care and practices at baseline (within 4 weeks prior to CART-19 infusion), limited assessment after chemotherapy, at day 28 following the infusion, 3, 6, 9, and 12 months after the first CART-19 cell infusions or until the patient requires alternative therapy for their disease. Tumor assessments will depend on the patients underlying disease as follows:

Response Definition After Treatment for CLL

Parameter	Complete response	Partial response	Progressive disease
Group A			
Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Parameter	Complete response	Partial response	Progressive disease
Hepatomegaly	None by CT	If enlarged prior to therapy, decrease ≥ 50% by CT	Increase ≥ 50%
Splenomegaly	None by CT	If enlarged prior to therapy, decrease ≥ 50% by CT	Increase ≥ 50%
Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules, Hypocellular marrow defines CR with incomplete marrow recover (Cri)	50% reduction in marrow infiltrate, or B-lymphoid nodules	N/A
Blood lymphocytes	< 4000/μ/L	Decrease ≥ 50% over baseline	Increase ≥ 50% over baseline
Group B			
Platelet count without growth factors or platelet transfusions	>100,000/μ/L	>100,000/μ/L or increase ≥ 50% over baseline	Decrease ≥ 50% over baseline secondary to CLL
Hemoglobin without transfusions or growth factors	> 11.0 g/dL	> 11.0 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils without growth factors	> 1500/μ/L	> 1500/μ/L or > 50% improvement over baseline	N/A

The above response criteria are consistent with NCCN Guidelines Version 2.2012 CLL/SLL, which is based on the 2008 International Workshop Group on CLL (IWCLL) revisions of the original guidelines for evaluating disease response released in 1996 by the National Cancer Institute Working Group (NCI/WG)[84].

Group A criteria define the tumor load. Group B criteria define the function of the hematopoietic system (or marrow).

Complete response (CR): all of the criteria must be met, and patients have to lack disease-related constitutional symptoms attributable to CLL (ie. ≥10 percent unintentional weight loss within the previous six months, fatigue that interferes with work or usual activities, fevers greater than 100.5ºF (>38ºC) for ≥2 weeks, or night sweats for >1 month).

Complete response with incomplete marrow recovery (CRi): CR in the setting of hypocellular marrow.

Partial response (PR): at least two of the criteria of group A plus one of the criteria of group B must be met.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Partial response with incomplete marrow recovery (PRi): PR in the setting of hypocellular marrow.

Stable disease (SD): Patients who do not meet the criteria for a complete remission, partial remission, or progressive disease, have stable disease. Stable disease is therapeutically equivalent to a nonresponse.

Progressive disease (PD): appearance of any new lesions; at least one of the above criteria of group A or group B have been met. Includes Richter's transformation (the development of an aggressive large-cell lymphoma) as documented by biopsy. Also, cytopenias that occur at least three months after the completion of therapy and are accompanied by an infiltrate of clonal CLL cells on bone marrow biopsy can be used to define disease progression. Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly of improvement in hemoglobin/platelets will not be considered PD.

Calculating Tumor Burden: Tumor burden at baseline is calculated as the sum of the volume of bone marrow involved with CLL, the peripheral blood CLL burden and the volume of tumor masses in spleen and nodal masses as determined in volumetric CT scans. Tumor burden reduction is calculated from the tumor assessments done post therapy, and the best overall response calculated by the difference from the baseline tumor burden and the residual tumor burden after therapy. The estimates of total CLL mass are then converted to total CLL cell number using 1 kg = 10^{12} cells[100].

8 Statistical Considerations

8.1 *Design Overview*

This is a single center, randomized, parallel group study to evaluate two dose levels of CART-19 cells. This trial will be conducted in two stages.

Stage 1

In the first stage, subjects will be randomized into one of the two dose levels (ARM 1: 1-5x10^8 CART-19 transduced cells vs. ARM 2: 1-5x10^7 CART-19 transduced cells) with 1:1 randomization ratio. Approximately twelve (n=12) evaluable subjects will be enrolled into each arm. Safety, tolerability, and rate of complete response by 3 month will be evaluated to determine a dose cohort for expansion based on the rule described below.

After the end of the first stage, the lower dose level associated with 3-month CR rate (including CRi) of ≥30% and manageable toxicity profile will be expanded to the second stage, unless the higher dose level has a 16.7% higher CR rate, or equivalently having ≥2 patients with CR or CRi within 3 month out of 12 evaluable subjects, compared to the low dose level and has a comparable toxicity profile, then the higher dose level will be expanded. If none of the dose levels have reached an observed 3-month CR rate of ≥30%, the study may be stopped.

Stage 2

The Stage 1 analysis performed in November 2014 led to choosing Arm 1 for expansion in Stage 2. Therefore, the Stage 2 dose will be 1-5x10^8 transduced CART-19 cells. The dose of 1-5 x 10^8

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

T-cells will be administered via split dosing: 10% on Day 1 (1-5x10^7), 30% on Day 2 (3x10^7-1.5x10^8), 60% on Day 3 (6x10^7-3x10^8). The selected Arm 1 dose cohort will be expanded to enroll additional subjects, for a total of 20 evaluable subjects at that dose level. At the end of the Stage 2, all data on safety, tolerability, and efficacy will be combined to determine a recommended dose level for future trials.

Retreatment Cohort
This protocol also allows for the retreatment of Stage 1 and Stage 2 subjects who had an initial response to their 1st infusion, lost detectable CART19 cells, and have subsequently relapsed. This retreatment cohort may include any previously evaluable subjects that meet the retreatment eligibility criteria, but is expected to be much smaller. On study and follow-up procedures for this cohort will be completed as outlined in Sections 6.5 to 6.12 above and the Retreatment Cohort Schedule of Events in Appendix 2.

8.2 *Sample Size Justification*

A total of 24 evaluable subjects (approximately 12 evaluable subjects per arm) will be targeted for the first stage of the study. Approximately 30 patients are expected to be randomized to ensure a total of 24 subjects are evaluable for primary efficacy analysis. With approximately 12 evaluable subjects at the end of the first stage, if 4 out 12 patients remained CR or CRi within three months post infusion (i.e., an observed 3-month CR rate of 33%), then the 90% exact confidence interval will exclude 10%, specifically, the 90% exact CI would be (12%, 61%). The following table presents the confidence interval given the observation of different complete responders out of 12 evaluable patients.

Complete responder (response rate)	Exact 90% CI (%)
10 (83.3%)	51.6 – 97.7
9 (75%)	42.8 – 94.5
8 (66.7%)	34.9 – 90.1
7 (58.3%)	27.7 – 84.8
6 (50%)	21.1 – 78.9
5 (41.7%)	18.1 – 68.5
4 (33.3%)	12.3 – 60.9
3 (25%)	7.2 – 52.7

At the end of the second stage after expansion with 20 evaluable subjects, for an observed 3-month CR rate of 30% (i.e., 6 out of 20 had CR or CRi), the 90% exact confidence interval would be (14%, 51%). The following table presents the confidence interval given the observation of different complete responders out of 20 evaluable patients.

Complete responder (response rate)	Exact 90% CI (%)
15 (75%)	55.4 – 89.6
14 (70%)	49.2 - 86.0
13 (65%)	44.2 - 82.3
12 (60%)	39.4 – 78.5
11 (55%)	34.7 – 74.1
10 (50%)	30.2 – 69.8
9 (45%)	25.9 – 65.3

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Complete responder (response rate)	Exact 90% CI (%)
8 (40%)	21.7 – 60.6
7 (35%)	17.7 – 55.8
6 (30%)	14.0 – 50.8
5 (20%)	10.4 - 45.6

Note: the 90% confidence intervals in above table were not adjusted for multiple stages.

8.3 *Analysis Population(s)*

Evaluable population are defined as all eligible patients who were able to receive the viable T cell infusion(s) at the intended dose level and have completed at least 3 months of follow-up after the infusion or have discontinued early due to disease progression, initiation of a new cancer therapy, or death. Patients receiving a lower than planned dose level due to manufacturing limitations will not be considered evaluable.

Full analysis set (FAS) population is defined as all patients who are randomized to each treatment arm. In addition, all patients enrolled in the 2nd stage will be included. If an additional arm is studied, the FAS will be defined as all patients enrolled at the dose. Sensitivity analysis for efficacy endpoints will be performed for FAS population. Patients will be classified by the intended treatment arm. Sensitivity analysis for efficacy endpoints will also be performed according to the actual dose level received.

Safety population is defined as all patients who were able to receive at least one T cell infusion. The safety analyses will be conducted by the actual dose received.

Definitions relevant to the Analysis Sets:

1) **Manufacturing failure** – Any patient who has manufactured CART-19 cells that do not meet the manufacturing release criteria or the minimum protocol-specified dose for their respective stage or randomized arm (as applicable).
2) **Primary efficacy evaluable patient** – Any patient who is infused with CART-19 cells at the protocol-specified dose for their protocol stage and assigned randomized arm (as applicable) and completed the response assessments for the primary efficacy endpoint as planned by the protocol. Efficacy evaluable patients also include those with disease progression or death prior to the primary efficacy endpoint response assessment.
3) **Primary efficacy non-evaluable patient** – Any patient who is infused with CART-19 cells at a less than the protocol-specified dose. These patients are considered also counted as manufacturing failures.

8.4 *Primary objective*

The primary objective is to assess the 3-month CR rate, which is defined as the proportion of patients, whose best overall response by the end of the first 3 months after the first CART-19 infusion after randomization, is CR among all evaluable patients. Stage 1 and Stage 2 patients will be evaluated independently. The 3-month CR rate will be summarized along with the Exact Clopper-Pearson 90% confidence intervals for each dose in evaluable population. As a sensitivity analysis, the 3-month CR rate and the respective 90% confidence interval will also be summarized for FAS population and safety population by stage, as described above.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

8.5 *Secondary Efficacy Objectives*

The secondary efficacy objective in this study is to assess each dose with respect to the overall response rate, progression free survival (PFS), overall survival, time to response, duration of response, and time to alternative therapy.

If a patient has not had an event of interest at the date of the analysis cut-off or when the patient received any further anti-neoplastic therapy, PFS will be censored at the time of the last adequate assessment before the cut-off date or the anti-neoplastic therapy start date.

Best overall response rate is defined as the proportion of patients with best overall response either complete response [CR, including CRi], or partial response [PR, including PRi].

Best overall response rate will be summarized along with the Clopper-Pearson 90% confidence intervals for each dose in evaluable population. The best overall response rate and its exact confidence interval will also be summarized for FAS population and safety population.

Progression free survival (PFS) is defined as the time from the date of the first CART-19 infusion to the date of first documented disease progression/relapse or death. If a patient has not had an event at the date of the analysis cut-off or when the patient received any further anti-neoplastic therapy, PFS will be censored at the time of the last adequate assessment before the cut-off date or the anti-neoplastic therapy start date.

Listing of PFS for all patients in each dose will be provided. The distribution function of PFS estimated using the Kaplan-Meier method and the median PFS along with 90% confidence intervals will be presented for two treatment groups if appropriate.

Overall survival (OS) is defined as the time from date of the first CART-19 infusion to the date of death from any cause. If a patient is not known to have died at the date of analysis cut-off, OS will be censored at the last date of contact.

Listing of OS for all patients in each dose will be provided. The distribution function of OS estimated using the Kaplan-Meier method and the median OS along with 90% confidence intervals will be presented for two treatment groups if appropriate.

Time to response is defined as the time from the date of the first CART-19 infusion to the date when the response criteria of PR/PRi/CR/CRi is first met for patients with the best overall response of PR/PRi or CR/CRi.

Time to response (CR/CRi or PR/PRi) will be summarized with descriptive statistics for evaluable patients in each dose and will also be summarized for FAS population and safety population.

Duration of response is defined as the time from the date when the response criteria of PR/PRi/CR/CRi is first met to the date of progression/relapse or death. If a patient has not had an event at the date of the analysis cut-off or when the patient received any further anti-neoplastic therapy, duration of response will be censored at the time of the last adequate assessment before the cut-off date or the new anti-neoplastic therapy start date. A listing of duration of response will be provided for all responders.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Time to alternative therapy is defined as the time from the date of the first CART-19 infusion to the date of alternative therapy. Alternative therapy is defined as any therapy for treatment of CLL excluding palliative care. For patients who did not receive any alternative therapy, their time to alternative therapy will be censored at the date of analysis cut-off.

A listing of duration of response will be provided for all evaluable population. The distribution function of time to alternative therapy estimated using the Kaplan-Meier method and the median time to alternative therapy along with 90% confidence intervals will be presented for each dose only if appropriate.

8.6 *Safety objectives*

For all safety analyses, the safety population will be used. All listings and tables will be presented by dose group.

The assessment of safety will be based mainly on the frequency of adverse events. Other safety data will be considered as appropriate. Vitals and ECGs will be collected as clinically needed. All safety data will be listed.

The safety summary tables will include only assessments collected no later than 30 days after study treatment discontinuation.

Adverse Events

All adverse events (AE) starting on or after study day 1 (i.e. on or after the day of the first infusion) and starting no later than 1 year after the end of treatment during the study will be summarized. All AEs will be listed. AEs starting prior to study day 1 and AEs starting later than 30 days after the last treatment date will be flagged in the listings.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, preferred term and maximum toxicity grade (based on CTCAE v4.03). A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. The frequency of CTC grade 3 and 4 AEs will be summarized separately. In addition, AEs related to study drug will be presented by primary system organ class, preferred term, and maximum CTC grade. Serious adverse events (SAEs) will be summarized separately.

8.7 *Manufacturing (Dose) Feasibility*

The frequency of manufacture failure will be calculated. Associations between patient characteristics and the likelihood of manufacture failure will be evaluated.

8.8 *Correlative Research Secondary and Exploratory Objectives*

Descriptive statistics will be provided for the correlative endpoints. Correlative secondary objectives will focus on the evaluation and quantification of the expansion, homing, persistence, phenotype, and functional properties of the infused CART19 cells as assessed by flow cytometry and QPCR endpoints. In addition, an assessment of the patient humoral or cellular immune response to their CART 19 cells will also be a key correlative secondary objective that informs

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

both efficacy and safety endpoints. These data will help describe the pharmacokinetics of infused CART 19 cells and highlight the incidence of CART 19 host immune responses.

Exploratory objectives focus on assessment of serum cytokine levels pre and post CART 19 infusion(s). In addition, the incidence of CD19 escape mutants will be determined in blood, bone marrow and lymph node aspirates by assessing CD19 expression, as compared to base line tumor samples. These data will help inform on CART 19 engraftment, cytokine side-effects, and optimal patient safety management strategies.

More detailed characterization of both pre-infusion CART-19 product and the in vivo persisting CART-19 cells may be carried out on a per subject basis for research purposes. Specifically, the T cell subsets of CART-19 T cells and the relative T cell subset ratio will be determined by flow cytometry. In addition, the pre-infusion product and in vivo persisting CART 19 cells may be further characterized by transcriptional profiling, flow cytometry-based phenotypic and functional assays. These data will help to inform potential predictive markers of CART-19 efficacy but are not formal study objectives

8.9 *Retreatment Cohort Analysis*

Safety and efficacy endpoints for those subjects participating in the retreatment cohort will include frequency and severity of adverse events, overall response, time to response, duration of response and time to alternative therapy, expansion and persistence of CART19 cells. Definition and statistical methods used for those endpoints will be the same as described in Sections 8.4 and 8.5 but with the start of the observation time as time of the re-infusion. Data analyses for the retreatment cohort will be exploratory and performed separately from the analyses for the initial infused subjects. In particular, we will use statistical methods appropriate for paired data (e.g., paired t-test, McNemar test) to compare endpoints from the same subject between the first and re-infusion. Results from these analyses will be used to generate hypotheses for future studies.

8.10 *Patient Reported Outcomes (PRO)*

EORTC QLQ-C30 and CLL16 raw summary scores will be generated by adding up the item responses on the questions which make up each domain in accordance with the respective scoring manual provided by the developers. Raw scores will be summarized using means and medians at each assessment time point and for each domain for each treatment group. Patients will be asked to complete the questionnaire at baseline, chemotherapy week, end of treatment (day 28), 3, 6, 9, and 12 months after treatment.

EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) contains 30 questions that incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included (dyspnea, insomnia, appetite, constipation, diarrhea, and financial impact). [Aaronson NK, et al. J Natl Cancer Inst 85: 365-376, 1993]

Chronic Lymphocytic Leukaemia (QLQ- CLL16)

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

This module is designed for patients with stage 0 to stage 4 chronic lymphocytic leukaemia. It is comprised of sixteen questions that address five domains of HRQoL important in CLL. There are three multi item scales on: - Fatigue (2 items), treatment side effects and disease symptoms 8 items), infection (4 items) and two single item scales on social activities and future health worries.

It was developed using the EORTC recommended guidelines, with additional patient interviews based on a grounded theory approach. Pilot testing was performed in England and Germany. The module development committee has approved the first three phases of development and a paper describing this process is awaiting publication. Phase four international field-testing has yet to be agreed

9 Safety and Adverse Events

Safety will be assessed by monitoring and recording potential adverse effects of the treatment using the Common Toxicity Criteria (CTCAE) version 4.03 at each study visit. Patients will be monitored by medical histories, physical examinations, and blood studies to detect potential toxicities from the treatment. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1-4, will be used. Subjects will be monitored by medical histories, physical examinations, and blood studies to detect potential toxicities from the treatment.

To the extent possible, adverse events should be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event. Do not list symptoms if a diagnosis can be assigned.

9.1 *Definitions*

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study that occur after the patient has signed the informed consent. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal laboratory values or test results of diagnostic procedures occurring after the informed consent are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Suspected Adverse Reaction (21 CFR 312.32(a))
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected Suspected Adverse Reaction (21 CFR 312.32(a))
An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, such as preplanned study visits and preplanned hospitalizations for study procedures or treatment administration
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the time the patient informed consent has been obtained to the end of the study treatment follow-up. For this study, adverse events will be collected until the subject is off study or until the end of study visit at 12 months. Events occurring during chemotherapy but prior to CART-19 infusion will be excluded from the adverse event reporting period. Patients experiencing toxicity from their preceding cytoreductive chemotherapy will have their schedule delayed until these toxicities have resolved.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition on the medical history eCRF. During the course of the study if any pre-existing conditions worsen or require additional intervention than these should be recorded as adverse events and indicated as worsening events. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the regulatory sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event. Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

Laboratory abnormalities due to underlying disease and chemotherapy regimen are **expected** and will not be reported as adverse events (e.g. abnormal hematology values, mucositis, etc.).

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event. As was noted above, events related to the cytotoxic chemotherapy will be excluded from adverse event reporting.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was planned, elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2 *Recording of Adverse Events*

At each contact with the subject, the investigator must seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events also may be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. To the extent possible, adverse events should be recorded as a diagnosis and

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

symptoms used to make the diagnosis recorded within the diagnosis event. Do not list symptoms if a diagnosis can be assigned.

All adverse events occurring during the adverse event reporting period (defined in Section 9.1 above) must be collected, however only the highest grade of the AE will be recorded in the CRF if there is a change in grade. Conditions that were already present at the time of informed consent should be recorded in the Medical History CRF. Any condition listed in a subjects' Medical History for which the severity of the grade increases at the time of, or post CART19 infusion, should be captured as an adverse event.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)- only the highest grade of the AE will be recorded in the CRF if there is a change in grade
2. Its duration (start and end dates)
3. Its relationship to the study treatment (Is there a reasonable possibility that the AE is related to the study treatment: No (unrelated) or Yes). If yes- is the event possibly, probably or definitely related to the investigational treatment (CART-19 T-cells) or the non-investigational treatment (i.e. lymphodepleting chemotherapy)?
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy taken (i.e. no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious as defined as in Section 9.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), documented appropriately in the medical records, should not be reported as a serious adverse event.

Adverse events that occur concurrently with the progression of malignancy but that are not related to disease progression (i.e. deep vein thrombosis or hemoptysis) will be reported as an adverse event as described above.

Serious adverse events that are still ongoing at the end of the adverse event reporting period must be followed to determine the final outcome. Any serious adverse event that occurs after the adverse event reporting period and is considered to be possibly related to the study treatment or study participation, should be recorded and reported immediately.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Modification of CTC Grading scale for Cytokine Release Syndrome (CRS)
The current CTCAE grading system developed to capture cytokine release syndrome (CRS) relates to acute infusional toxicity, within 24 hours. CRS due to CART-19 often occurs 1 or more days post-infusion. A proposed CTC grading system specifically to capture toxicity for protocols using CART-19 cell is described below (**Table 9-1)** and should be used to evaluate CRS events.

Recipients of CART-19 cells may develop a CRS. Data from a small number of patients shows marked elevations in IL6, IFN-g, and less intensely TNF. Elevations in clinically available markers of inflammation including ferritin and CRP have also been observed to correlate with the clinical CRS syndrome.

Symptoms usually occur 1-14 days after cell infusion, but the syndrome is not defined by the timing of the reaction. Patients developing any symptoms attributable by the investigator as related to cytokine release should be reported has having a CRS. Symptoms may include.

- High fevers
- Rigors
- Sweating
- Nausea
- Vomiting
- Anorexia
- Fatigue
- Headache
- Myalgia/arthralgia
- Hypotension
- Dyspnea
- Tachypnea
- Hypoxia
- Altered mental status
- End organ dysfunction
- Signs of macrophage activation syndrome including hemophagocytosis and hemolysis

For the purposes of reporting and grading on clinical trials using CART-19 cells, the following grading system is proposed. The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (i.e. sepsis). The stop date of CRS is defined as the date when the patient has been afebrile for 24 hours and off vasopressors for 24 hours.

Table 9-1: Amended CTCAE v4 criteria for CRS related to CART-19 infusion

Modified CRS Toxicity Grading System				
1	2	3	4	5
Mild reaction: Treated with supportive	Moderate reaction requiring IV fluids or parenteral nutrition; some	More severe reaction: Hospitalization required for management of symptoms related to	Life-threatening complications such as hypotension	Death

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Modified CRS Toxicity Grading System				
1	2	3	4	5
care such as anti-pyretics, anti-emetics	signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests ([LFTs] related to CRS and not attributable to any other condition). Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions; this excludes management of fever or myalgias. Includes hypotension treated with IVFs* or low-dose pressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP].). Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.	requiring high-dose pressors (see Table 9-2) or hypoxia requiring mechanical ventilation.	

*CRS Grade 3 language clarification: "hypotension treated with intravenous fluids" is further defined as hypotension requiring multiple fluid boluses for blood pressure support.

Table 9-2 High Dose Vasopressor Use

Definition of "High-Dose" Vasopressors	
Vasopressor	Dose for ≥ 3 hours
Norepinephrine monotherapy	≥ 20 mcg/kg/min
Dopamine monotherapy	≥ 10 mcg/kg/min
Phenylephrine monotherapy	≥ 200mcg/min
Epinephrine monotherapy	≥ 10 mcg/min

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Definition of "High-Dose" Vasopressors	
If on vasopressin	High-dose if vaso + Norepinephrine Equivalent (NE) of >10 mcg/min (using Vasopressin and Septic Shock Trial (VASST) formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 mcg/min (using VASST formula)

Vasopressin and Septic Shock Trial (VASST) Equivalent Equation:

Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10]

Criteria from Russell et al, 2008[93].

9.3 *Reporting of Serious Adverse Events and Unanticipated Problems*

Investigators and the regulatory sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

(see definitions, section 9.1)

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring during the adverse event reporting period defined in Section 9.1 above must be reported to the sponsor within 24 hours of learning of its occurrence. If a subject is taken off study within 30 days of the T-cell infusion, all SAEs experienced within 30 days after the T-cell infusion should be reported to the sponsor. SAEs experienced after this 30 days period should only be reported to the sponsor if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode when follow-up information is received. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. **Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported per section 9.3.4 below.**

9.3.1 Sponsor Notification by Investigator

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the sponsor by email within 24 hours of knowledge of the event.

Report serious adverse events by email to:

Attention: Clinical Safety Manager or designee
Translational Research Program
University of Pennsylvania
Fax: 215-615-2869
Email: trpsae@mail.med.upenn.edu

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

At the time of the initial notification, the following information should be provided:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 3 business days, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed SAE form, and any other diagnostic information that will assist the understanding of the event. The Investigator will keep a copy of this SAE Form on file at the study site. Significant new information on ongoing serious adverse events should be provided promptly to the regulatory sponsor.

Follow-up information on SAEs should be reported when received, on a copy of the original SAE Form, and should include both the follow-up number and report date. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

9.3.2 Investigator reporting: notifying the UPenn IRBs

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the IRB. The IRB requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Unanticipated problems posing risks to subjects or others as noted above will be reported to the IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths: more rapid reporting requirements
Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

- Report the event within 72 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm

For reportable deaths, the initial submission to the IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome)
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects

9.3.3 Reporting obligations to the DSMC of the Abramson Cancer Center

The Abramson Cancer Center (ACC) has developed a detailed data safety and monitoring program. The Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) serves as a rigorous scientific peer review mechanism for all cancer protocols conducted within the University of Pennsylvania. The CTSRMC's focus is the scientific merit, priorities, and progress of Cancer Center clinical research. The Data Safety and Monitoring Committee (DSMC) is responsible for the overall quality control and quality assurance of all cancer related studies conducted within the University, including data quality and subject safety monitoring and auditing. The guidelines governing both committees have been adapted from the NCI/NIH policies.

All events that meet the DSMC definition of reportable AE's must be promptly entered into Velos.

The DSMC requires AE/SAE submission as follows:

On-Site subjects (this includes any subjects enrolled at other sites on an in-house study)

- All grade 3 or higher events within 5 business days of knowledge of the adverse event. Grade 3 and 4 events that are typical in the disease population, with the exception of those that could be symptoms/early indicators of any of the toxicities defined in the Toxicity Management section of the protocol, signs/symptoms of an allergic response, severe hypotensive crisis or any other reaction to the infusion, do not require DSMC reporting. It is important to note that these events must be reported in the absence of a diagnosis of a specific toxicity. These events must be reported via e-mail to the assigned DOCM study monitor.
- All unexpected deaths within 24 hours of knowledge
- All others deaths within 30 days of knowledge (including death of subjects off-study)
- In the event of a grade 4 or 5 unexpected event regardless of attribution, the DSMC and ACC leadership require investigators and the study team to meet or have a teleconference within 24 business hours of the event to have a thorough discussion of the event. These types of events will not be vetted via e-mail. The sponsor should not be involved in discussions about attribution. The PI and Research Coordinator will schedule a meeting with the study team to discuss the grade 4 or 5 unexpected event. Meeting minutes capturing the review of any ongoing investigations of the grade 4 or 5 unexpected event, including next steps in the management of the subject and any proposed changes to the protocol will be forwarded to the DSMC

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

9.3.4 IBC Notification by Investigator

Notify the IBC prior to reporting any serious adverse event that meets expedited reporting requirements to the FDA and RAC. You must also submit a copy of your FDA cover letter and report summary to the IBC should a serious adverse event occur.

9.3.5 FDA Notification by Regulatory Sponsor

The regulatory sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The regulatory sponsor must report an IND safety reports as described in:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 Calendar Days***

  Any study event that is:

  - *Unexpected* fatal or life-threatening *suspected adverse reaction.*
  - Expected and unexpected Grade 3 or higher events of cytokine release syndrome per the modified CRS grading scale in Table 9-1
  - All fatal events occurring within 30 days of T-cell infusion, regardless of attribution and expectedness

- ***Within 15 Calendar Days***

  Any study event that is:

  - unexpected
  - Suspected adverse reaction that is serious, but not fatal or life-threatening

  -or-

  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:

  – suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.

  Increase in rate of occurrence of serious suspected adverse reactions:

  - any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Additional Reporting Requirements

Sponsors are also required to review all adverse events to make a causality determination on the basis of information from investigators and report these findings to the FDA in accordance with 21 CFR 312.32.

If the adverse event does not meet expedited reporting requirements, the regulatory sponsor will report the SAE as in the IND Annual Report.

9.4 *Pregnancies*

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to protocol sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the protocol sponsor Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug for any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.5 *Toxicity Management, Stopping Rules and Study Termination*

It is expected that AEs will occur frequently in this population based on the underlying advanced hematologic malignancy and that these can be SAEs. Therefore, there is no specific occurrence of SAEs that define a stopping rule, but the review of SAEs will form the basis for potential early stopping of the study. Only unexpected SAEs that are related to the CART-19 cells would define a stopping rule. The review of these adverse events, and any decision to prematurely stop subject enrollment, will be determined by the DSMB and reviewed by the IRB, Medical Monitor, ACC DSMC and FDA.

Premature termination of the clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB, the DSMB, Medical Monitor, ACC DSMC, or determination that there are problems in the cell product generation or safety at the discretion of the study investigators. Additionally, recruitment may be stopped for reasons of particularly low recruitment, protocol violations, or inadequate data recording.

9.5.1 Criteria for stopping or pausing the study

The study will be stopped if:

- Any subject develops uncontrolled T cell proliferation that does not respond to management.
- Premature study termination may occur if the Investigator, Study Funder, Sponsor, DSMB, Medical Monitor, ACC DSMC or any appropriate independent review board or regulatory body decides for any reason that subject safety may be compromised by continuing the study.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

- Premature study termination may occur if the Sponsor or Study Funder decides to discontinue the development of the intervention to be used in this study.

The study will be paused if:

- The protocol will be paused pending submission of the protocol pause to the FDA and review by the IRB, ACC DSMC, ACC CTSRMC, Medical Monitor and the DSMB if any patient experiences any of the following events within two weeks of the first CART-19 infusion
  - Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to protocol therapy. High fevers, hypotension, possible ICU admission and even mechanical ventilation are expected. These side effects can result in grade 4 liver toxicity, nephrotoxicity, and other organ involvement
  - Death

If the study is paused for the reasons above, the PI, members of the study team and Protocol Advisor will meet in person or by teleconference within 24 hours of the event to have a thorough discussion of the event. These types of events will not be vetted via e-mail. The sponsor should not be involved in discussions about attribution. Meeting minutes capturing the review of any ongoing investigations, including next steps in the management of subjects and any proposed changes to the protocol will be forwarded to the FDA, IRB, ACC DSMC, Medical Monitor, and DSMB. If all parties are in agreement as to the event resolution, then the pause will be lifted.

The protocol manufacturing will be paused to review the manufacturing process should there be ≥20% manufacturing failures [i.e. the manufacturing process fails to meet the protocol-specified dose range according to the protocol stage and randomized dose arm (as applicable)].
If the study is paused for manufacturing reasons, the PI, members of the study team, Protocol Advisor, Clinical Operations and Cell Manufacturing will meet to identify manufacturing failure. The team will make recommendations for process improvements to be implemented. Pending successful completion of a process validation run, the manufacturing pause will be lifted.

9.5.2 Toxicity management considerations

Replication-competent lentivirus (RCL) may be generated during the CART-19 manufacturing phase or subsequently after introduction of vector transduced cells into the patient. However, an RCL resulting from the production phase is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL before it can be released to a subject. Nevertheless, generation of an RCL following infusion of the vector product remains a theoretical possibility. The consequences of such recombination events in subjects without a known lentiviral infection are unknown, and therefore subjects with coexistent HIV infection are excluded from participation in this study in order to minimize this possibility. The development of RCL could pose a risk to both the subject and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial.

Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a subject. However, because the probability of developing,

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

and characteristics of an RCL are unknown, no guidelines have been put in place. Nevertheless, all agree that the subject must be isolated until an understanding of how to manage the subject becomes clear. Some considerations are

- Intensive follow-up of subject in consultation with gene therapy experts, study investigators, FDA and NIH.
- Inform local public health officials and CDC.
- Identify sexual partners and provide appropriate counseling and intervention.

RCL will be monitored by a suitable Q-PCR assay for the detection of the lentivirus (VSV-g DNA). If a positive VSV-g DNA assay result is obtained, the Investigator will be informed and the patient rescheduled for a retest for the DNA test. If the second DNA test is positive, then infusions will be temporarily halted. The patient will undergo a blood draw for isolation of HIV from his/her cells. The virus will be sequenced and compared to sequences of the transfer vector and packaging constructs, as well as to available HIV sequences to determine the origin of the virus. Determination of the origin of the virus can be easily performed by evaluation for HIV accessory genes such as vif, vpr and vpu which are not present in the packaging constructs. If the sequence is derived from wt-HIV then infusions for all patients can resume, and the patient will be referred to treatment for HIV. If an RCL is confirmed, or the virus cannot be isolated from the blood draw, the patient will be scheduled for apheresis and will undergo a full biological RCR/L testing for detection and/or characterization of the RCRL.

Clonality and insertional oncogenesis. Four of nine treated patients in a gene therapy trial for X-linked Severe Combined Immunodeficiency (SCID) developed T cell leukemia 31-68 months post-treatment. The T cell leukemias were attributable to clonal expansion conferred by gammaretroviral vector integration sites in the CD34+ bone marrow stem cell modification[94]. This represents the most severe adverse event caused by vector integration. However, there is also evidence for retroviral vector integration site dominance in a gene therapy trial of β-thalassaemia without malignancy[95]. The lentiviral vector used for CART-19 manufacturing is part of a vector class that may have a lower risk for integration in or near oncogenic regions than oncoretroviral vectors[96]. As of March 2014, none of the patients treated with CART-19 have developed a new malignancy, T cell or otherwise, related to lentiviral vector integration. Subjects will be monitored for evidence of unexpected CART-19 expansion by CART-19 transgene quantitation by qPCR and clinical monitoring for malignancy by complete blood count (CBC) as part of the study design. If an unexpected pattern of CART-19 expansion is observed (i.e. CART-19 expansion in the absence of CD19+ target), subjects will be closely monitored clinically for new malignancies, particularly T cell, and further studies, including insertion site analysis, will be considered to investigate the molecular basis of the expansion. Investigators should consult with the Regulatory Sponsor if an unexpected pattern of CART-19 expansion and/or a new malignancy arises. Subjects will continue to be similarly monitored for clonality and insertional oncogenesis when enrolled on the long term follow-up protocol.

Uncontrolled T cell proliferation. CART-19 cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies, CART-19 cells have only proliferated in response to physiologic signals or upon exposure to CD19. In the context of this protocol it is possible that the T cells will proliferate in response to signals from the malignant tumor or normal B cells. This could be beneficial or harmful depending on the extent of proliferation. If any subject develops

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

excessive CART-19 cell accumulation, corticosteroids will be administered to eradicate the infused cells.

Toxicity associated with allogeneic or autologous T cell infusions has been managed with a course of pharmacologic immunosuppression. CAR T cell associated toxicity has been reported to respond to systemic corticosteroids[43]. If uncontrolled T cell proliferation occurs (grade 3 or 4 toxicity related to CART-19 cells), subjects will be treated with corticosteroids. Subjects will be treated with pulse methylprednisolone (2 mg/kg i.v. divided q8 hr x 2 days), followed by a rapid taper.

B cell depletion. It is possible that B cell depletion and hypogammaglobulinemia will occur. This is common with anti-CD20 directed therapies[97]. In the event of clinically significant hypogammaglobulinemia (i.e. systemic infections), subjects will be given intravenous immunoglobulin (IVIG) by established clinical dosing guidelines to restore normal levels of serum immunoglobulin levels, as has been done with Rituximab.

Infusion reaction. Acetaminophen and diphenhydramine hydrochloride may be repeated every 6 hours as needed. A course of non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved by acetaminophen. It is recommended that patients not receive corticosteroids at any time, except in the case of a life threatening emergency, since this may have an adverse effect on CART-19 cells.

Febrile reaction. In the event of febrile reaction, an evaluation for infection should be initiated, and patients managed appropriately with antibiotics, fluids and other supportive care as medically indicated and determined by the treating physician. In the event that the patient develops sepsis or systemic bacteremia following CAR T cell infusion, appropriate cultures and medical management should be initiated. If a contaminated CART-19 T cell product is suspected, the product can be retested for sterility using archived samples that are stored in the CVPF. Consideration of a cytokine release syndrome (see below) should be given.

Cytokine Release Syndrome (CRS) / Macrophage Activation Syndrome (MAS)
CRS has been observed in patients after treatment with CART-19. Patients with clinical responses exhibited some level of CRS that ranged from mild to severe consisting of fevers, hypotension, capillary leak, hypoxia or other symptoms (See Section 1.5.2 and 8.2). All patients who have responded to CART-19 cells have experienced a CRS.

Cytokine production is required for the activation, expansion and cytolytic function of T cells and for CART-19 T cells. Therefore some degree of CRS may be a desired clinical outcome. Premature or early intervention with anti-cytokine therapy may therefore abrogate the anti-tumor efficacy of CART-19. Subsequent to this experience, selective tocilizumab (an anti-IL6-receptor antibody), therapy has been utilized (described below) with effective toxicity management and successful ongoing CART-19 T cell expansion in patients. Please note, steroids or other immunosuppressant drugs should **NOT** be used as pre-medication for CART-19 therapy but may be considered in the management of CRS.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

The moderate to severe cases of CRS observed required intervention with tocilizumab with or without high dose corticosteroids, between 2 and 9 days after T cell infusion to date. This resulted in rapid reversal of the high persistent fevers and hemodynamic instability associated with CRS in most but not all patients.

Given the dramatic clinical improvement of most patients treated with anti-cytokine therapy, patients with moderate to severe cytokine toxicities should be first managed with administration of tocilizumab.

Tocilizumab should be used as a single, weight-based dose of 8 mg/kg at the time of hemodynamic instability. This management approach is designed to avoid life-threatening toxicities, while attempting to allow the CART-19 cells to establish a proliferative phase that appears to correlate with anti-tumor efficacy. Thus, the timing of the tocilizumab should be individualized, in close consultation with the Principal Investigator and/or expert consultants for the trial. Steroids have not always been effective in this setting and may not be necessary given the rapid response to tocilizumab. Because steroids will interfere with CART-19 function and efficacy, if used, they should be rapidly tapered.

Upon developing the prodrome of high-persistent fevers following CART-19 infusion, patients should then be followed closely. Infection and tumor lysis syndrome work up should be immediately undertaken. The pharmacy should be notified of the potential need for tocilizumab. Patient management in an intensive care unit may be required and the timing is dependent upon local institutional practice. In addition to supportive care, tocilizumab may be administered in cases of moderate to severe CRS, especially if the patient exhibits any of the following:

- Hemodynamic instability despite intravenous fluid challenges and moderate stable vasopressor support
- Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow O2, and/or need for mechanical ventilation.
- Any other signs or symptoms of rapid deterioration despite medical management

The recommended dosing for tocilizumab is 8 mg/kg i.v. single dose. Not all Grade 4 CRS reactions following CART-19 have been immediately treated with tocilizumab and decisions are, in part, based upon the rapidity of the syndrome onset and underlying patient reserve.

Other anti-cytokine therapies, such as repeat administration of tocilizumab or use of siltuximab or etanercept, may also be considered if the patient does not respond to the initial dose of tocilizumab. If the patient experiences ongoing CRS despite administration of anti-cytokine directed therapies, anti T-cell therapies such as cytoxan, ATG, campath may be considered.

CRS has been associated with biochemical and physiologic abnormalities consistent with MAS. Moderate to extreme elevations in serum C-reactive protein (CRP) and ferritin have been seen with CART-19 associated CRS, however the magnitude and kinetics vary greatly between individual patients. CRS management decisions should be based upon clinical signs and symptoms and response to interventions, not these laboratory values *per se*.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

CTCAE grading of CRS relates to its occurrence with acute infusional toxicities, whereas the CRS associated with CART-19 therapy is not acute, but rather delayed. Refer to Section 9.2 and **Table 5** for modified definitions of grading of CART-19 delayed CRS events.

Tumor lysis syndrome. Patients will receive allopurinol prophylactically for 28 days to prevent complications from TLS. TLS resulting in insufficiency, or rapidly rising uric acid, or evidence of organ dysfunction will be managed with fluids and rasburicase as clinically indicated and determined by the treating physicians.

GVHD: The chance of GVHD occurring is low, but it is a potential risk with CTL019 therapy. A prior study of activated donor lymphocyte infusions (ex vivo activated cells collected from the donor and grown in the same fashion as CART-19 but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4). Eight ALL patients treated to date with autologous CART-19 therapy had prior allogeneic hematopoietic SCT with residual donor chimerism. None of these patients have developed GVHD after autologous CART-19 infusion

9.5.3 Criteria for discontinuing a subject's participation in the study:

If a subject develops a condition that precludes CART-19 infusion after enrollment but before infusion, the subject will be prematurely discontinued. This will be done at the judgment of the PI, and could include for example, the occurrence of an intercurrent illness requiring the institution of systemic immunosuppression.

9.6 *Protocol Exceptions and Deviations*

Exception

A one time, **intentional** action or process that departs from the IRB and CTSRMC approved study protocol, intended for **one** occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, **advance** documented IRB and DSMC approval is required.

No exception would be granted if the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, **advance** documented IRB and DSMC approval is required.

Exceptions will be approved by the Medical Monitor and Regulatory Sponsor prior to submission to the IRB and ACC DSMC. Documentation of approval by the Medical Monitor and Regulatory Sponsor will be submitted with the initial request for an exception to the IRB and ACC DSMC. All exceptions require **advance** documented IRB and ACC DSMC approval.

No exceptions to eligibility of any type will be granted for this study.

Deviation

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

A one time, **unintentional** action or process that departs from the IRB and ACC DSMC approved study protocol, involving one incident and **identified retrospectively**, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the ACC DSMC within 5 business days and the IRB within 10 business days.

Any departure from the protocol that meets the following criteria should be submitted to the regulatory sponsor, ACC DSMC and IRB:

- Impacts subject safety
- Impacts the integrity of the study design or outcome
- Based on the PI's judgment is reportable

Deviations identified retrospectively pertaining to manufacturing, treatment, eligibility or safety reporting will result in suspension of enrollment until the DSMC is satisfied with the corrective action plan.

Other deviations should be explained in a memo to file (such as a subject missing a visit is not an issue unless a critical/important treatment or procedure was missed and must have been done at that specific time).

Include the following information on the Sponsor supplied exception/deviation form: protocol number, subject study number, description of the exception/deviation and rationale. Ensure all completed exception/deviation forms are signed by the Principal Investigator (or a sub-investigator) and submitted to the Sponsor Project Manager and Medical Monitor for review.

Attention: Sponsor Project Manager
Translational Research Program
University of Pennsylvania
Fax 215-615-2869
Email: trpctu@mail.med.upenn.edu

The Sponsor Project Manager will submit the exception and/or deviation request to the Regulatory Sponsor for review and approval. Once approval of the exception request or acknowledgement of the deviation has been granted by the Regulatory Sponsor and Medical Monitor, the exception or deviation will be submitted to the IRB, ACC DSMC and all other applicable committees for review and approval.

Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the regulatory sponsor or its agents, if any, monitoring the study to request a protocol exception, as no authorized exceptions are permitted. If the investigator feels a protocol exception would improve the conduct of the study, this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the IRB/IEC at the study site should be informed to the local regulations (e.g., UK required the notification of urgent safety measures within 3 days) but no later than 10 working days.

9.7 *Medical Monitoring*

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 11 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

A protocol-specific independent medical monitor with appropriate expertise and experience has been recruited in addition to the DSMB to review subject safety data and ensure the safety of participants. The Medical Monitor will receive real-time reporting of any events that could potentially impact subject safety (including dose-limiting toxicities). The Medical Monitor will also receive all of the following:

- All Serious Adverse Events (regardless of expectedness/relatedness). The SAE will be reported to the Medical Monitor within 24 hours of becoming aware of the SAE.
- Deviations reported to the regulatory sponsor, ACC DSMC and IRB as they occur
- Exceptions prior to submission to the IRB and ACC DSMC
- IRB Continuing Review Reports
- All queries issued by the DSMC (including those related to grading, attribution and expectedness of adverse events).

The Medical Monitor will correspond via email to communicate:

- SAE acknowledgement and inquiries
- Deviation acknowledgement, inquiries, recommendations
- Exception acknowledgement, inquiries and approval/disapproval
- Continuing review acknowledgement, inquiries

The Medical Monitor will review and acknowledge the above, and make recommendations whether to continue with the study, amend the study, and/or stop/pause the study as needed. In addition, the Medical Monitor and Principal Investigator will meet approximately every 3 months to review cumulative AE data, the status of all enrolled subjects and the study progress.

Documentation of Medical Monitor review will be maintained in the study regulatory binder and sent to the ACC DSMC and Regulatory Sponsor as soon as a response is received from the Medical

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Monitor.

9.7.1 Independent Data and Safety Monitoring Board

An Independent Data and Safety Monitoring Board (DSMB) will be constituted prior to the randomization of the first patient. Please note that the DSMB is separate from the DSMC (refer to section 9.3.3). The DSMB will be comprised of a minimum of four individuals including physicians with experience in oncology and/or gene transfer therapy and a statistician. The DSMB will be assembled and will work under a charter specifically developed for safety oversight of this study. The DSMB will be responsible for reviewing available safety data. The DSMB will provide advice to the investigators, and consult with regulatory sponsor as necessary. The DSMB will evaluate patient-subject safety as specified in the Data Safety and Monitoring Plan. There will be a meeting with the DSMB describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of the interim analysis plan.

The results of the analysis following Stage I will also be presented to the DSMB for review and recommendations. The analyses will address efficacy and key safety data.

If necessary, additional meetings of the DSMB may be held if safety issues arise in between scheduled meetings.

It is envisioned that the DSMB may make four types of recommendations, namely:

- No safety or efficacy issues, ethical to continue the study as planned
- Serious safety concerns precluding further study treatment, regardless of efficacy
- Overwhelming evidence for futility, recommend stopping the study.
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

If the study is recommended to continue by the DSMB, no details about the results of the current interim analysis will be revealed prior to the next scheduled analysis. A Regulatory Sponsor representative will submit the DSMB report to the PI for submission to the ACC DSMC and IRB within 10 working days of receipt of the approved minutes.

9.7.2 Clinical Field Monitors

A representative appointed by the Regulatory Sponsor will be responsible for monitoring and reporting on the progress of the investigation for GCP compliance with FDA and ICH requirements and 21 CFR Part 11. The clinical field monitor will monitor GCP aspects of the study, including completeness and accuracy of the CRFs, eligibility, and informed consent.

Representatives of the regulatory sponsor will conduct a site initiation visit and periodically audit, at mutually convenient times during and after the study, all eCRFs and corresponding source documents for each subject. At the site initiation visit, monitors will assure that proper study-related documentation exists, provide training to investigators and other site personnel in study procedures and GCP guidelines, and assure that acceptable facilities and adequately trained staff are available to conduct the study.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Key study personnel must be available to assist the field monitor during these visits. The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

Periodic monitoring visits throughout the study provide the Sponsor with the opportunity to evaluate the progress of the study and inform the Sponsor of potential problems. The clinical field monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

The investigator must give the clinical field monitor access to all relevant source documents to confirm their consistency with the eCRF entries. The monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

At the end of the study, monitors will conduct a close-out visit and will advise on storage of study records and disposition of unused investigational products. Further details about clinical monitoring can be found in the Sponsor Data Safety Monitoring Plan (DSMP).

Data Collection

A PPD electronic database system will be used for data collection in this study. The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Database management and quality control

The designated CRO will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to a designated CRO.

After database lock, the investigator will receive a CD-ROM or paper copies of the CRFs for archiving at the investigational site.

In addition to the CRO created database, subject information will also be entered into the UPenn Velos database. The following Velos Forms will be filled out: Protocol Registration, Subject Registration, and Adverse Event/SAE CRF.

10 Data Handling and Recordkeeping

10.1 *Confidentiality*

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the funding sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to unauthorized personnel who have completed the prerequisite training.

If country rules or ethics committee standards do not permit collection of patient initials and the exact date of birth, generic initials will be used and only the year of birth will be collected.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

10.2 *Source Documents*

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinical medical records) containing demographic and medical information, laboratory data, electrocardiograms and the results of any other tests or assessments. All information recorded on the eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form, and a signed copy must be given to the patient.

10.3 *Case Report Forms*

For studies using electronic data capture (EDC), the designated investigator staff will enter the data required by the protocol into the electronic case report form (eCRFs). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The designated CRO will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the mature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments entered into the database will be coded using the WHO Drug reference list. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedRA) terminology.

At the conclusion of the study the occurrence of any protocol violations will be determined, and all unused supplies are to be returned. After this has been completed and the data has been verified to be complete and accurate, the database will be declared locked. After database lock, all investigators will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

The following CRFs are required to be completed in the ACC Velos electronic database:

- Protocol Registration form
- PRA Form

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

- Subject Registration form (for all subject who have signed the ICF)
- Adverse Event form. Information required to be reported to the DSMC (section 9.3.3)
    - All grade 3 or higher events within five business days of knowledge
      All unexpected deaths within 24 hours of knowledge
      All others deaths within 30 days of knowledge

11 Study Monitoring, Auditing, and Inspecting

11.1 *Study Monitoring Plan*

This study will be monitored according to the Sponsor Data and Safety Monitoring Plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities and has adequate space to conduct the monitoring visit.

11.2 *Auditing and Inspecting*

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Code of Federal Regulations Title 21 Part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the regulatory sponsor before commencement of this study. The investigator should provide current IRB FWA information and any other certifications to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject, and the investigator-designated research professional obtaining the consent.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

The protocol is listed under clinicaltrials.gov.

13 Study Finances

13.1 *Funding Source*

This study will be funded by Novartis Pharmaceuticals.

13.2 *Conflict of Interest*

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the regulatory sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

13.3 *Subject Stipends or Payments*

There is no subject stipend/payment for participation in this protocol.

13.4 *Study Discontinuation*

The study may be discontinued at any time by the IRB, CTSRMC and DSMC, the Sponsor, the Study Funder, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

14 Publication Plan

Publication of the results of this trial will be governed by University of Pennsylvania policies. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

15 References

Reference List

1. *Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62(1):10-29.*

2. *Smith A, Howell D, Patmore R, Jack A, Roman E. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer 2011;105(11):1684-1692.*

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

3. *Hernandez JA, Land KJ, McKenna RW. Leukemias, myeloma, and other lymphoreticular neoplasms. Cancer 1995;75(1 Suppl):381-394.*

4. *Kantar Health. Treatment Evolution: United States Leukemia, Chronic Lymphocytic. 2011. Ref Type: Online Source*

5. *Freedman AS, Boyd AW, Bieber FR et al. Normal cellular counterparts of B cell chronic lymphocytic leukemia. Blood 1987;70(2):418-427.*

6. *Uckun FM, Ledbetter JA. Immunobiologic differences between normal and leukemic human B-cell precursors. Proc Natl Acad Sci U S A 1988;85(22):8603-8607.*

7. *Fearon DT, Carroll MC. Regulation of B lymphocyte responses to foreign and self-antigens by the CD19/CD21 complex. Annu Rev Immunol 2000;18:393-422.:393-422.*

8. *Stamenkovic I, Seed B. CD19, the earliest differentiation antigen of the B cell lineage, bears three extracellular immunoglobulin-like domains and an Epstein-Barr virus-related cytoplasmic tail. J Exp Med 1988;168(3):1205-1210.*

9. *Ledbetter JA, Rabinovitch PS, June CH, Song CW, Clark EA, Uckun FM. Antigen-independent regulation of cytoplasmic calcium in B cells with a 12-kDa B-cell growth factor and anti-CD19. Proc Natl Acad Sci U S A 1988;85:1897-1901.*

10. *Tedder TF, Isaacs CM. Isolation of cDNAs encoding the CD19 antigen of human and mouse B lymphocytes. A new member of the immunoglobulin superfamily. J Immunol 1989;143(2):712-717.*

11. *Uckun FM, Jaszcz W, Ambrus JL et al. Detailed studies on expression and function of CD19 surface determinant by using B43 monoclonal antibody and the clinical potential of anti-CD19 immunotoxins. Blood 1988;71(1):13-29.*

12. *Gunther R, Chelstrom LM, Tuel-Ahlgren L, Simon J, Myers DE, Uckun FM. Biotherapy for xenografted human central nervous system leukemia in mice with severe combined immunodeficiency using B43 (anti-CD19)-pokeweed antiviral protein immunotoxin. Blood 1995;85(9):2537-2545.*

13. *Messinger Y, Yanishevski Y, Avramis VI et al. Treatment of human B-cell precursor leukemia in SCID mice using a combination of the investigational biotherapeutic agent B43-PAP with cytosine arabinoside. Clin Cancer Res 1996;2(9):1533-1542.*

14. *Li Q, Hudson W, Wang D, Berven E, Uckun FM, Kersey JH. Pharmacokinetics and biodistribution of radioimmunoconjugates of anti-CD19 antibody and single-chain Fv for treatment of human B-cell malignancy. Cancer Immunol Immunother 1998;47(3):121-130.*

15. *Ek O, Reaman GH, Crankshaw DL, Chelstrom LM, Myers DE, Uckun FM. Combined therapeutic efficacy of the thymidylate synthase inhibitor ZD1694 (Tomudex) and the immunotoxin B43(anti-CD19)-PAP in a SCID mouse model of human B-lineage acute lymphoblastic leukemia. Leuk Lymphoma 1998;28(5-6):509-514.*

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

16. *Ek O, Gaynon P, Zeren T, Chelstrom LM, Myers DE, Uckun FM. Treatment of human B-cell precursor leukemia in SCID mice by using a combination of the anti-CD19 immunotoxin B43-PAP with the standard chemotherapeutic drugs vincristine, methylprednisolone, and L-asparaginase. Leuk Lymphoma 1998;31(1-2):143-149.*

17. *Messinger Y, Yanishevski Y, Ek O et al. In vivo toxicity and pharmacokinetic features of B43 (anti-CD19)-genistein immunoconjugate in nonhuman primates. Clin Cancer Res 1998;4(1):165-170.*

18. *Uckun FM, Yanishevski Y, Tumer N et al. Pharmacokinetic features, immunogenicity, and toxicity of B43(anti-CD19)-pokeweed antiviral protein immunotoxin in cynomolgus monkeys. Clin Cancer Res 1997;3(3):325-337.*

19. *Chen CL, Levine A, Rao A et al. Clinical pharmacokinetics of the CD19 receptor-directed tyrosine kinase inhibitor B43-Genistein in patients with B-lineage lymphoid malignancies. J Clin Pharmacol 1999;39(12):1248-1255.*

20. *Bejcek BE, Wang D, Berven E et al. Development and characterization of three recombinant single chain antibody fragments (scFvs) directed against the CD19 antigen. Cancer Res 1995;55(11):2346-2351.*

21. *Nicholson IC, Lenton KA, Little DJ et al. Construction and characterisation of a functional CD19 specific single chain Fv fragment for immunotherapy of B lineage leukaemia and lymphoma. Mol Immunol 1997;34(16-17):1157-1165.*

22. *Wang D, Li Q, Hudson W, Berven E, Uckun F, Kersey JH. Generation and characterization of an anti-CD19 single-chain Fv immunotoxin composed of C-terminal disulfide-linked dgRTA. Bioconjug Chem 1997;8(6):878-884.*

23. *Kipriyanov SM, Moldenhauer G, Strauss G, Little M. Bispecific CD3 x CD19 diabody for T cell-mediated lysis of malignant human B cells. Int J Cancer 1998;77(5):763-772.*

24. *Le Gall F, Kipriyanov SM, Moldenhauer G, Little M. Di-, tri- and tetrameric single chain Fv antibody fragments against human CD19: effect of valency on cell binding. FEBS Lett 1999;453(1-2):164-168.*

25. *Brentjens RJ, Latouche JB, Santos E et al. Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. Nat Med 2003;9(3):279-286.*

26. *Cooper LJ, Topp MS, Serrano LM et al. T-cell clones can be rendered specific for CD19: toward the selective augmentation of the graft-versus-B-lineage leukemia effect. Blood 2003;101(4):1637-1644.*

27. *Kipriyanov SM, Moldenhauer G, Braunagel M et al. Effect of domain order on the activity of bacterially produced bispecific single-chain Fv antibodies. J Mol Biol 2003;330(1):99-111.*

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

28. *Pinthus JH, Waks T, Kaufman-Francis K et al. Immuno-Gene Therapy of Established Prostate Tumors Using Chimeric Receptor-redirected Human Lymphocytes. Cancer Res 2003;63(10):2470-2476.*

29. *Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci U S A 1989;86(24):10024-10028.*

30. *Brocker T, Karjalainen K. Adoptive tumor immunity mediated by lymphocytes bearing modified antigen-specific receptors. Advances in immunology 1998;68:257-269.*

31. *Sadelain M, Riviere I, Brentjens R. Targeting tumours with genetically enhanced T lymphocytes. Nat Rev Cancer 2003;3(1):35-45.*

32. *Mullaney BP, Pallavicini MG. Protein-protein interactions in hematology and phage display. Exp Hematol 2001;29(10):1136-1146.*

33. *Kohn DB, Dotti G, Brentjens R et al. CARS on Track in the Clinic: Report of a Meeting Organized by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Sub-Committee on Cell and Gene Therapy. Washington D.C., May 18, 2010. 2011;in press.*

34. *June CH, Blazar BR, Riley JL. Lymphocyte Subset Engineering: tools, trials and tribulations. Nature Reviews Immunology 2009;9:704-716.*

35. *June CH. Adoptive T cell therapy for cancer in the clinic. J Clin Invest 2007;117(6):1466-1476.*

36. *Milone MC, Fish JD, Carpenito C et al. Chimeric Receptors Containing CD137 Signal Transduction Domains Mediate Enhanced Survival of T Cells and Increased Antileukemic Efficacy In Vivo. Mol Ther 2009;17(8):1453-1464.*

37. *Imai C, Mihara K, Andreansky M et al. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. Leukemia 2004;18(4):676-684.*

38. *Yee C, Thompson JA, Byrd D et al. Adoptive T cell therapy using antigen-specific CD8+ T cell clones for the treatment of patients with metastatic melanoma: in vivo persistence, migration, and antitumor effect of transferred T cells. Proc Natl Acad Sci U S A 2002;99(25):16168-16173.*

39. *Dudley ME, Wunderlich JR, Robbins PF et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science 2002;298(5594):850-854.*

40. *Mitsuyasu RT, Anton PA, Deeks SG et al. Prolonged survival and tissue trafficking following adoptive transfer of CD4zeta gene-modified autologous CD4(+) and CD8(+) T cells in human immunodeficiency virus-infected subjects. Blood 2000;96(3):785-793.*

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

41. *Walker RE, Bechtel CM, Natarajan V et al. Long-term in vivo survival of receptor-modified syngeneic T cells in patients with human immunodeficiency virus infection. Blood 2000;96(2):467-474.*

42. *Riddell SR, Elliott M, Lewinsohn DA et al. T-cell mediated rejection of gene-modified HIV-specific cytotoxic T lymphocytes in HIV-infected patients. Nat Med 1996;2(2):216-223.*

43. *Lamers CH, Sleijfer S, Vulto AG et al. Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase IX: first clinical experience. J Clin Oncol 2006;24(13):e20-e22.*

44. *Riley JL, June CH. The CD28 family: a T-cell rheostat for therapeutic control of T-cell activation. Blood 2005;105(1):13-21.*

45. *Brocker T. Chimeric Fv-xi or Fv-epsilon receptors are not sufficient to induce activation or cytokine production in peripheral T cells. Blood 2000;96:1999-2001.*

46. *Rossig C, Bollard CM, Nuchtern JG, Merchant DA, Brenner MK. Targeting of G(D2)-positive tumor cells by human T lymphocytes engineered to express chimeric T-cell receptor genes. International Journal of Cancer 2001 2001;94:228-236.*

47. *Watts TH, DeBenedette MA. T cell co-stimulatory molecules other than CD28. Curr Opin Immunol 1999;11(3):286-293.*

48. *Maus MV, Thomas AK, Leonard D et al. Ex vivo expansion of polyclonal and antigen-specific cytotoxic T lymphocytes by artificial APCs expressing ligands for the T cell receptor, CD28 and 4-1BB. Nat Biotechnol 2002;20(2):143-148.*

49. *Levine BL, Bernstein W, Craighead N, Lindsten T, Thompson CB, June CH. Effects of CD28 Costimulation on Long Term Proliferation of CD4+ T cells in the Absence of Exogenous Feeder Cells. J Immunol 1997;159(12):5921-5930.*

50. *Eshhar Z, Waks T, Bendavid A, Schindler DG. Functional expression of chimeric receptor genes in human T cells. Journal of Immunological Methods 2001;248:67-76.*

51. *Finney HM, Akbar AN, Lawson AD. Activation of resting human primary T cells with chimeric receptors: costimulation from CD28, inducible costimulator, CD134, and CD137 in series with signals from the TCR zeta chain. J Immunol 2004;172(1):104-113.*

52. *Clay TM, Morse M, Lyerly HK. Redirecting cytotoxic T lymphocyte responses with T-cell receptor transgenes. Expert Opinion on Biological Therapy 2002 2002;353-360.*

53. *Hombach A, Heuser C, Abken H. The recombinant T cell receptor strategy: insights into structure and function of recombinant immunoreceptors on the way towards an optimal receptor design for cellular immunotherapy. Curr Gene Ther 2002;2(2):211-226.*

54. *Calogero A, De Leij YFMH, Mulder NH, Hospers GAP. Recombinant T-cell receptors: An immunologic link to cancer therapy. Journal of Immunotherapy 2000;393-400.*

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

55. *Pule M, Finney H, Lawson A. Artificial T-cell receptors. Cytotherapy 2003;5:211-226.*

56. *Roessig C, Scherer SP, Baer A et al. Targeting CD19 with genetically modified EBV-specific human T lymphocytes. Ann Hematol 2002;81 Suppl 2:S42-3.:S42-S43.*

57. *Serrano LM, Pfeiffer T, Olivares S et al. Differentiation of naive cord-blood T cells into CD19-specific cytolytic effectors for posttransplantation adoptive immunotherapy. Blood 2006;107(7):2643-2652.*

58. *Willemsen RA, Weijtens ME, Ronteltap C et al. Grafting primary human T lymphocytes with cancer-specific chimeric single chain and two chain TCR. Gene Ther 2000;7(16):1369-1377.*

59. *Finney HM, Lawson ADG, Bebbington CR, Weir ANC. Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product. Journal of Immunology 1998;161:2791-2797.*

60. *Krause A, Guo HF, Latouche JB, Tan C, Cheung NK, Sadelain M. Antigen-dependent CD28 signaling selectively enhances survival and proliferation in genetically modified activated human primary T lymphocytes. J Exp Med 1998;188(4):619-626.*

61. *Friedmann-Morvinski D, Bendavid A, Waks T, Schindler D, Eshhar Z. Redirected primary T cells harboring a chimeric receptor require costimulation for their antigen-specific activation. Blood 2005;105(8):3087-3093.*

62. *Maher J, Brentjens RJ, Gunset G, Riviere I, Sadelain M. Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCR zeta/CD28 receptor. Nature Biotechnology 2002;20(1):70-75.*

63. *Finney HM, Akbar AN, Lawson ADG. Activation of resting human primary T cells with chimeric receptors: Costimulation from CD28, inducible costimulator, CD134, and CD137 in series with signals from the TCR zeta chain. Journal of Immunology 2004;172(1):104-113.*

64. *Carpenito C, Milone MC, Hassan R et al. Control of large established tumor xenografts with genetically re-targeted human T cells containing CD28 and CD137 domains. Proc Natl Acad Sci U S A 2009;106(9):3360-3365.*

65. *Kershaw MH, Westwood JA, Parker LL et al. A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer. Clin Cancer Res 2006;12(20 Pt 1):6106-6115.*

66. *Till BG, Jensen MC, Wang J et al. Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells. Blood 2008;112(6):2261-2271.*

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

67. *Park JR, DiGiusto DL, Slovak M et al. Adoptive transfer of chimeric antigen receptor re-directed cytolytic T lymphocyte clones in patients with neuroblastoma. Mol Ther 2007;15(4):825-833.*

68. *Pule MA, Savoldo B, Myers GD et al. Virus-specific T cells engineered to coexpress tumor-specific receptors: persistence and antitumor activity in individuals with neuroblastoma. Nat Med 2008;14(11):1264-1270.*

69. *Dummer W, Niethammer AG, Baccala R et al. T cell homeostatic proliferation elicits effective antitumor autoimmunity. J Clin Invest 2002;110(2):185-192.*

70. *Goldrath AW, Bevan MJ. Selecting and maintaining a diverse T-cell repertoire. Nature 1999;402(6759):255-262.*

71. *Surh CD, Sprent J. Homeostatic T cell proliferation: how far can T cells be activated to self-ligands? J Exp Med 2000;192(4):F9-F14.*

72. *Klebanoff CA, Khong HT, Antony PA, Palmer DC, Restifo NP. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. Trends Immunol 2005;26(2):111-117.*

73. *Laport GG, Levine BL, Stadtmauer EA et al. Adoptive transfer of costimulated T cells induces lymphocytosis in patients with relapsed/refractory non-Hodgkin lymphoma following CD34+-selected hematopoietic cell transplantation. Blood 2003;102(6):2004-2013.*

74. *Rapoport A, Stadtmauer EA, Aqui N et al. Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T-cell transfer. Nat Med 2005;11(11):1230-1237.*

75. *Rapoport AP, Levine BL, Badros A et al. Molecular remission of CML after autotransplantation followed by adoptive transfer of costimulated autologous T cells. Bone Marrow Transplant 2004;33(1):53-60.*

76. *Levine BL, Bernstein WB, Aronson NE et al. Adoptive Transfer of Costimulated CD4+ T cells Induces Expansion of Peripheral T Cells and Decreased CCR5 Expression in HIV Infection. Nat Med 2002;8(1):47-53.*

77. *Wang GP, Levine BL, Binder GK et al. Analysis of lentiviral vector integration in HIV+ study subjects receiving autologous infusions of gene modified CD4+ T cells. Mol Ther 2009;17(5):844-850.*

78. *Henter JI, Horne A, Arico M et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48(2):124-131.*

79. *Brentjens R, Yeh R, Bernal Y, Riviere I, Sadelain M. Treatment of chronic lymphocytic leukemia with genetically targeted autologous T cells: case report of an unforeseen adverse event in a phase I clinical trial. Mol Ther 2010;18(4):666-668.*

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

80. *Morgan RA, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol Ther 2010;18(4):843-851.*

81. *Press MF, Cordon-Cardo C, Slamon DJ. Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues. Oncogene 1990;5(7):953-962.*

82. *Dudley ME, Wunderlich JR, Yang JC et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-2357.*

83. *Porter DL, Levine BL, Bunin N et al. A phase 1 trial of donor lymphocyte infusions expanded and activated ex vivo via CD3/CD28 costimulation. Blood 2006;107(4):1325-1331.*

84. *Hallek M, Cheson BD, Catovsky D et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. 2008;111(12):5446-5456.*

85. *Gribben JG, Hosing C, Maloney DG. Stem cell transplantation for indolent lymphoma and chronic lymphocytic leukemia. 2011;2011/01/14(1 Suppl):S63-S70.*

86. *Uckun FM, Messinger Y, Chen CL et al. Treatment of therapy-refractory B-lineage acute lymphoblastic leukemia with an apoptosis-inducing CD19-directed tyrosine kinase inhibitor. Clin Cancer Res 1999;5(12):3906-3913.*

87. *Rapoport AP, Aqui NA, Stadtmauer EA et al. Combination immunotherapy using adoptive T-cell transfer and tumor antigen vaccination on the basis of hTERT and survivin after ASCT for myeloma. Blood 2011;117(3):788-797.*

88. *Cheson BD, Bennett JM, Grever M et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 1996;87(12):4990-4997.*

89. *Chronic lymphocytic leukemia: recommendations for diagnosis, staging, and response criteria. International Workshop on Chronic Lymphocytic Leukemia. Ann Intern Med 1989;110(3):236-238.*

90. *Cruz CR, Hanley PJ, Liu H et al. Adverse events following infusion of T cells for adoptive immunotherapy: a 10-year experience. 2010;2010/05/01(6):743-749.*

91. *Zitvogel L, Apetoh L, Ghiringhelli F, Kroemer G. Immunological aspects of cancer chemotherapy. Nature Reviews Immunology 2008;8(1):59-73.*

92. *Ramakrishnan R, Assudani D, Nagaraj S et al. Chemotherapy enhances tumor cell susceptibility to CTL-mediated killing during cancer immunotherapy in mice. 2010;120(4):1111-1124.*

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

93. *Russell JA, Walley KR, Singer J et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358(9):877-887.*

94. *Hacein-Bey-Abina S, Garrigue A, Wang GP et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest 2008;118(9):3132-3142.*

95. *Cavazzana-Calvo M, Payen E, Negre O et al. Transfusion independence and HMGA2 activation after gene therapy of human beta-thalassaemia. Nature 2010;467(7313):318-322.*

96. *Montini E, Cesana D, Schmidt M et al. The genotoxic potential of retroviral vectors is strongly modulated by vector design and integration site selection in a mouse model of HSC gene therapy. Journal of Clinical Investigation 2009;119(4):964-975.*

97. *Cartron G, Watier H, Golay J, Solal-Celigny P. From the bench to the bedside: ways to improve rituximab efficacy. Blood 2004;104(9):2635-2642.*

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Appendix 1 - Schedule of Study Procedures

Week/Day of treatment period	**(-) 8 to 12[x]**	**~ Wk (-) 6 to 8[x]**	**~ Wk (-) 4[x] (+/- 1 wk)**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[s] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[t] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[bb]**
	Pre-entry evaluation	**Enrollment**	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion #1**	**Infusion #2**	**Infusion #3**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening Week -8 to -12**	**Baseline Week -6 to -8**	**Apheresis Week -4**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion #1 Day 1§**	**Infusion #2 Day 2 §[aa]**	**Infusion #3 Day 3 §[aa]**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	1	2	3	4	5	6	201	202	7	8	9	10,11	777	501, 502, 503, 504, 505	506	778	601
Clinical Assessments																	
Consent	**X**																
Demography	**X**																
Inclusion/Exclusion Criteria	**X**	**X**															
Eligibility Form/ Randomization		**X**															
Quality of Life Questionnaires (EORTC QLQ-C30 and CLL-16)		**X**		**X**									**X**	**X[v]**	**X**	**X**	
Relevant Medical History/Current Medical Conditions		**X**	**X**	**X**	**X**	**X[a]**	**X[a]**	**X[a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**(-) 8 to 12[x]**	**~ Wk (-) 6 to 8[x]**	**~ Wk (-) 4[x] (+/- 1 wk)**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[s] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[t] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[bb]**
	Pre-entry evaluation	**Enrollment**	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion #1**	**Infusion #2**	**Infusion #3**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening Week -8 to -12**	**Baseline Week -6 to -8**	**Apheresis Week -4**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion #1 Day 1§**	**Infusion #2 Day 2 §[aa]**	**Infusion #3 Day 3 §[aa]**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	1	2	3	4	5	6	201	202	7	8	9	10,11	777	501, 502, 503, 504, 505	506	778	601
Physical exam[b]		X			X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Performance Status Assessment		X			X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Concomitant Meds	X	X	X	X	X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Adverse Events[c]	X	X	X	X	X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
HIV test (1 ml SST)	X																
p53 Mutation		X															
Leukapheresis screening		X															
CT scan of chest, abdomen, pelvis[d]		X											X	X[v]	X	X	
Bone marrow biopsy/aspirate[o]		X											X	X[v]	X	X	
Lymph Node biopsy		X[e]											X[e]	X[v,e]	X[e]	X[e]	
ECHO/MUGA[f]		X															
Respiratory Virus Panel (RVP)				X[y]													

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**(-) 8 to 12[x]**	**~ Wk (-) 6 to 8[x]**	**~ Wk (-) 4[x] (+/- 1 wk)**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[s] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[t] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[bb]**
	Pre-entry evaluation	**Enrollment**	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion #1**	**Infusion #2**	**Infusion #3**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening Week -8 to -12**	**Baseline Week -6 to -8**	**Apheresis Week -4**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion #1 Day 1§**	**Infusion #2 Day 2 §[aaa]**	**Infusion #3 Day 3 §[aaa]**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	1	2	3	4	5	6	201	202	7	8	9	10,11	777	501, 502, 503, 504, 505	506	778	601
Blood Draws																	
Hematology (CBC, differential, platelet count) (5 ml lavender top, EDTA)[a]		X			X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Chemistry (3 ml SST)		X			X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Serum pregnancy test[g] (1 ml SST)		X															
Urine pregnancy test[g]					X												
CD3, CD4, CD8 Mon (4 ml lavender top, EDTA)						X	X	X					X	X[h]		X	
Autoimmune Screen[i] (ANA, ESR) (4 ml SST ; 3ml lavender top EDTA)		X															
Viral Serology[j] (CMV, EBV, Hepatitis B/C) (5ml red top, serum)		X															

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**(-) 8 to 12[x]**	**~ Wk (-) 6 to 8[x]**	**~ Wk (-) 4[x] (+/- 1 wk)**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[s] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[t] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[bb]**
	Pre-entry evaluation	**Enrollment**	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion #1**	**Infusion #2**	**Infusion #3**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening Week -8 to -12**	**Baseline Week -6 to -8**	**Apheresis Week -4**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion #1 Day 1§**	**Infusion #2 Day 2 §[aaa]**	**Infusion #3 Day 3 §[aaa]**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	1	2	3	4	5	6	201	202	7	8	9	10,11	777	501, 502, 503, 504, 505	506	778	601
β2 Microglobulin (1ml SST)		**X**															
Coagulation factors (PT, PTT, INR, fibrinogen, D-dimer) (4.5 ml blue top citrate)					**X**							**X[r]**					
HLH/MAS, (triglycerides, haptoglobin) (4 ml SST; 2.5 ml lavender top, EDTA)					**X**								**X**				
Serum immunoglobulin levels (1ml SST)[k]		**X**											**X**	**X[k]**	**X[k]**	**X[k]**	
Immunoglobulin Heavy Chain (4ml lavender; 0.5-1ml BM)		**X**															

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**(-) 8 to 12[x]**	**~ Wk (-) 6 to 8[x]**	**~ Wk (-) 4[x] (+/- 1 wk)**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§§**	**Day 3 (+1 day)§§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[s] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[t] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[bb]**
	Pre-entry evaluation	**Enrollment**	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion #1**	**Infusion #2**	**Infusion #3**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening Week -8 to -12**	**Baseline Week -6 to -8**	**Apheresis Week -4**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion #1 Day 1§**	**Infusion #2 Day 2 §§[aa]**	**Infusion #3 Day 3 §§[aa]**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	1	2	3	4	5	6	201	202	7	8	9	10,11	777	501, 502, 503, 504, 505	506	778	601
Relapse and Survival Follow-up																	**X[z]**
Intervention																	
Chemotherapy[l, e]				**X**													
CART-19 cell infusion						**X**	**X**	**X**									
Leukapheresis			**X[m]**														
Research Labs[o]																	
Research blood to CVPF for expansion screen (Two 10 ml green tops, Heparin)[p]	**X**																
Large Volume Peripheral Blood Draw (100mL)													**X[n]**				
Serum 5ml (Red top)		**X**	**X**		**X**	**X[q]**	**X[q]**	**X[q]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Immunogenicity (HAMA/HACA)		**X**													X	X	

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**(-) 8 to 12[x]**	**~ Wk (-) 6 to 8 [x]**	**~ Wk (-) 4 [x] (+/- 1 wk)**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[s] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[t] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[bb]**
	Pre-entry evaluation	**Enrollment**	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion #1**	**Infusion #2**	**Infusion #3**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening Week -8 to -12**	**Baseline Week -6 to -8**	**Apheresis Week -4**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion #1 Day 1§**	**Infusion #2 Day 2 §[aa]**	**Infusion #3 Day 3 §[aa]**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	1	2	3	4	5	6	201	202	7	8	9	10,11	777	501, 502, 503, 504, 505	506	778	601
Multiplex cytokine		**x**	**x**		X	X[q]	X[q]	X[q]	X	X	X	X	X	X	X	x	
PBMC 25ml (Lavender, EDTA)		**X**			**X**	**X[q]**	**X[q]**	**X[q]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
p53 Mutation Analysis		**x**															
DNA (Q-PCR persistence)		**x**			X	X[q]	X[q]	X[q]	X	X	X	X	X	X	X	X	
DNA RCL (VSV-G Q-PCR)		**x**			X									X[v]		X	
PBMC (functional assays, immunophenotyping, CART-19 and B cell enumeration[w])		**x**			X	X[q]	X[q]	X[q]	X[q]	X	X	X	X	X	X	X	
Bone marrow / LN aspirate (5 ml lavender top, EDTA)		**X**											**X[u]**	**X[u]**	**X[u]**	**X[u]**	
DNA (Q-PCR homing)		**X**											**X**	**X[u]**	**X**	**X**	
MMC (CART19 and B cell enumeration, immunophenotyping)		**X**											**X**	**X[u]**	**X**	**X**	
Marrow Serum (2 ml red top)		**X**											**X[u]**	**X[u]**	**X[u]**	**X[u]**	
Multiplex cytokine		**X**											**X**	**X[u]**	**X**	**X**	

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**(-) 8 to 12[x]**	**~ Wk (-) 6 to 8 [x]**	**~ Wk (-) 4 [x] (+/- 1 wk)**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[s] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[t] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[bb]**
	Pre-entry evaluation	**Enrollment**	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion #1**	**Infusion #2**	**Infusion #3**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening Week -8 to -12**	**Baseline Week -6 to -8**	**Apheresis Week -4**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion #1 Day 1§**	**Infusion #2 Day 2 §[aa]**	**Infusion #3 Day 3 §[aa]**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	1	2	3	4	5	6	201	202	7	8	9	10,11	777	501, 502, 503, 504, 505	506	778	601
Total research blood needs	20 ml	32 ml	5 ml	0 ml	30 ml	36 ml	36 ml	36 ml	30 ml	30 ml	30 ml	30 ml	130 ml	30 ml	30 ml	30 ml	N/A
TOTAL BLOOD DRAW	21 ml	60 ml	5 ml	0 ml	49-56 ml	45-56 ml	45-56 ml	45-56 ml	38-50 ml	38-50 ml	38-50 ml	49-61 ml	143-161 ml	42-61 ml	38-57 ml	42-61 ml	N/A

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

§ Lab tests specified on the infusion day will be drawn prior to infusion. A blood draw for potassium will be drawn 2 hours post infusion. The Investigator will review all pre-infusion lab (day -1) results to determine that it is appropriate to proceed with the infusion. Any abnormal Cr, Ca, K, Phos or uric acid result that is a change from the prior value should be reviewed by the PI prior to the infusion. Any new lab abnormalities that are also a change from the prior value will be reviewed by investigators. Additional Research Sample Collection: In the event something unexpected occurs the protocol, the research team may request an additional sample collection be performed to collect additional blood or marrow/LN samples for research analysis. This is being done with the intention of evaluating the likely effects from the investigational products received. The total amount of extra blood that will be collected will be 3 tablespoons of blood twice in one week. The total amount of extra bone marrow or lymph node biopsies collected from you will be up to 1 extra procedure per month.

a. Medical history, physical exam, documentation of adverse events and concomitant medications are to be done prior to infusion. Hematology and chemistry results are to be obtained prior to each infusion. Hematology includes CBC, differential, and platelet count. Chemistry will include Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid. A separate sample for serum K+ is taken approximately 2 hours post-infusion.
b. Physical exam includes vital signs. Height, weight, body surface area at enrollment and as clinically indicated.
c. Adverse events must be reported from the time the patient's informed consent has been obtained to end of the study.
d. CT scans should be performed within 42 days of study entry for disease evaluation and as clinically indicated for disease monitoring.
e. As clinically needed.
f. Should be performed within 6 weeks of the first CART-19 infusion, but does not need to be performed on the same day as apheresis.
g. Pregnancy test (quantitative) for female only.
h. Blood for CD3, CD4, CD8 Lymphocytes taken at months 3 and 6 only.
i. Autoimmune screen (ANA, ESR)
j. Viral Serology includes CMV, EBV, and Hepatitis B and C
k. Serum immunoglobulins will be collected at months 3, 6, 9 and 12 and as clinically indicated.
l. Chemotherapy as appropriate for disease type. See section 6.5
m. 12-15 liter apheresis to go to CVPF. 1 x 10^8 cells to be delivered to TCSL.
n. 100 mL peripheral blood draw (Lavender EDTA 10mL tubes) to be delivered to TCSL.
o. TCSL has requested labs samples for research be sent to TCSL as soon as collected. If required to keep research labs after hours, please keep red tops upright, lavender tubes should be room temperature on rotating platforms. In the event that something unexpected occurs, additional research sample collection may be done as necessary. Blood collects are not to exceed 3 tablespoons of blood twice in one week time window. Marrow/LN collections would not exceed more than one procedure per month. This would be at PI discretion.
p. Two 10 ml green tops to CVPF
q. The research blood collection is split on infusion days: 20 mL EDTA (lavender) and 2 mL serum (red) are collected pre-infusion for cytokines, qPCR and cellular assessments; 5 mL EDTA (lavender) and 2 mL serum (red) are collected 20-120min post-infusion for cytokines and qPCR only (cellular assessments only done pre-infusion).
r. Required on Day 14 and as clinically needed on Day 21.
s. Post infusion assessments will be performed monthly from month 2 to month 6.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

t. After year 1, patients will be enrolled into a destination protocol (IRB# 815699/UPCC 10908) for follow-up by phone or mail for up to 15 years post first T cell infusion, to monitor for delayed adverse events associated with the lentiviral vector genetic modification.
u. Concomitant with clinical draw, and also at months 1, 3, 6, 9 and 12 post-infusion. 5 ml in lavender top (DNA) and 2 ml in red top (serum) to be delivered to TCSL.
v. At months 3 and 6 only.
w. CART19 , tumor, and B cells enumerated by flow cytometry following pre-gating using CD3+/CAR19+, CD5,CD19/kappa or lambda and CD19+ expression respectively.
x. These windows are approximate and intended to be used as a guide. The intent of these windows is to ensure subjects are infused within 12 weeks after the subject has had a successful test expansion. If the subject completes these visits (pre-entry evaluation, enrollment, apheresis and infusion) within a shorter timeframe than 12 weeks, this will not be considered a protocol violation/deviation (e.g., for subjects with active disease, the shorter time frame is actually preferred). For subjects with a successful test expansion on another protocol, the HIV test may be performed during the enrollment visit. For subjects with a previous apheresis on another study, the enrollment window will not apply, but subjects must be officially enrolled in the study prior to the chemotherapy visit.
y. All patients must undergo a Respiratory Virus Panel (RVP) to test for influenza within 10 days prior to the first planned CART-19 infusion. The Respiratory Virus Panel includes: Influenza A, Influenza B, Respiratory Syncytial Virus A, Respiratory Syncytial Virus B, Parainfluenza Virus Type 1, Parainfluenza Virus Type 2, Parainfluenza Virus Type 3, Adenovirus. If the patient is positive for influenza, oseltamivir phosphate (Tamiflu®) or equivalent should be administered for 10 days as preventative treatment (see Tamiflu® package insert for dosing information). The patient must complete this course of preventative treatment prior to receiving the CART-19 infusion. If the patient is positive for influenza and is also experiencing flu-like symptoms, all clinical symptoms must also be resolved prior to the first CART-19 infusion. If the patient is positive for another virus on the RVP, the CART-19 infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the infusion will be delayed until resolution of these symptoms.
z. For subjects who complete or prematurely discontinue from study follow-up while in remission, follow-up attempts will be made to assess the subject's relapse and survival status every 3 months post CART-19 infusion until the end of the study (Last Patient/Last Visit). Once subjects' relapse or they begin a new cancer therapy, additional follow-up for relapse will not be required, and subjects will be followed for survival only.
aa. Day 2 and 3 infusions will take place in Stage 2 only.
bb. Secondary follow-up will take place in Stage 2 only.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Appendix 2 - Schedule of Study Procedures/Retreatment Cohort- Single Dose

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)**
	Screening/ Baseline	**Apheresis #1**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis #1 Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Post infusion Day 2**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
Clinical Assessments														
Retreatment Consent	**X**													
Retreatment Inclusion/Exclusion Criteria	**X**													
Quality of Life Questionnaires (EORTC QLQ-C30 and CLL-16)	**X**		**X**							**X**	**X[u]**	**X**	**X**	
Interim Treatment History	**X**													
Current Medical Conditions	**X**	**X**	**X**	**X**	**X[a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Physical exam[b]	**X**			**X**	**X[a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Performance Status Assessment	**X**			**X**	**X[a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Concomitant Meds	**X**	**X**	**X**	**X**	**X[a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Adverse Events[c]	**X**	**X**	**X**	**X**	**X[a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
HIV test (1 ml SST)	**X**													
p53 Mutation	**X**													

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)**
	Screening/ Baseline	**Apheresis #1**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis #1 Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Post infusion Day 2**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
Leukapheresis screening	**X[m]**													
CT scan of chest, abdomen, pelvis[d]	**X**									**X**	**X[u]**	**X**	**X**	
Bone marrow biopsy/aspirate[o]	**X**									**X**	**X[u]**	**X**	**X**	
Lymph Node biopsy	**X[e]**									**X[e]**	**X[u,e]**	**X[e]**	**X[e]**	
ECHO/MUGA[f]	**X**													
Respiratory Virus Panel (RVP)			**X[w]**											
Blood Draws														
Hematology (CBC, differential, platelet count) (5 ml lavender top, EDTA)[a]	**X**			**X**	**X[a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Chemistry (3 ml SST)	**X**			**X**	**X[a]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Serum pregnancy test[g] (1 ml SST)	**X**													
Urine pregnancy test[g]				**X**										
CD3, CD4, CD8 Mon (4 ml lavender top, EDTA)					**X**					**X**	**X[h]**		**X**	

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)**
	Screening/ Baseline	**Apheresis #1**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis #1 Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Post infusion Day 2**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
Autoimmune Screen[i] (ANA, ESR) (4 ml SST ; 3ml lavender top EDTA)	**X**													
Viral Serology[j] (CMV, EBV, Hepatitis B/C) (5ml red top, serum)	**X**													
β2 Microglobulin (1ml SST)	**X**													
Coagulation factors (PT, PTT, INR, fibrinogen, D-dimer) (4.5 ml blue top citrate)				**X**					**X[q]**					
HLH/MAS (triglycerides, haptoglobin (4 ml SST; 2.5 ml lavender top, EDTA)				**X**						**X**				
Serum immunoglobulin levels (1ml SST)[k]	**X**									**X**	**X[k]**	**X[k]**	**X[k]**	

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)**
	Screening/ Baseline	**Apheresis #1**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis #1 Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Post infusion Day 2**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
Immunoglobulin Heavy Chain (4ml lavender; 0.5-1ml BM)	**X**													
Relapse and Survival Follow-up														**X[x]**
Intervention														
Chemotherapy[l, e]			**X**											
CART-19 cell infusion					**X**									
Leukapheresis		**X[m]**												
Research Labs[o]														
Large Volume Peripheral Blood Draw (100mL)										**X[n]**				
Serum 5ml (Red top)	**X**	**X**		**X**	**X[p]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
HAMA	X											X	X	
HACA	X											X	X	
Multiplex cytokine	X	X		X	X[p]	X	X	X	X	X	X	X	x	
PBMC 25ml (Lavender, EDTA)	**X**			**X**	**X[p]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)**
	Screening/ Baseline	**Apheresis #1**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis #1 Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Post infusion Day 2**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
p53 Mutation Analysis	X													
DNA (Q-PCR persistence)	X			X	X[p]	X	X	X	X	X	X	X	X	
DNA RCL (VSV-G Q-PCR)	X			X							X[u]		X	
PBMC (functional assays, immunophenotyping, CART-19 and B cell enumeration[v])	X			X	X[p]	X[q]	X	X	X	X	X	X	X	
Bone marrow / LN aspirate (5 ml lavender top, EDTA)	**X**									**X[t]**	**X[t]**	**X[t]**	**X[t]**	
DNA (Q-PCR homing)	X									X	X[t]	X	X	
MMC (CART19 and B cell enumeration, immunophenotyping)	X									X	X[t]	X	X	
Marrow Serum (2 ml red top)	**X**									**X[t]**	**X[t]**	**X[t]**	**X[t]**	
Multiplex cytokine	X									X	X[t]	X	X	
Total research blood needs	32 ml	5 ml	0 ml	30 ml	36 ml	30 ml	30 ml	30 ml	30 ml	130 ml	30 ml	30 ml	30 ml	N/A

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)**
	Screening/ Baseline	**Apheresis #1**	**Chemo-therapy[i]**	**Pre – Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis #1 Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Post infusion Day 2**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14 Post infusion Day 21**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
TOTAL BLOOD DRAW	60 ml	5 ml	0 ml	49-56 ml	45-56 ml	38-50 ml	38-50 ml	38-50 ml	49-61 ml	143-161 ml	42-61 ml	38-57 ml	42-61 ml	N/A

§ Lab tests specified on the infusion day will be drawn prior to infusion. A blood draw for potassium will be drawn 2 hours post infusion. The Investigator will review all pre-infusion lab (day -1) results to determine that it is appropriate to proceed with the infusion. Any abnormal Cr, Ca, K, Phos or uric acid result that is a change from the prior value should be reviewed by the PI prior to the infusion. Any new lab abnormalities that are also a change from the prior value will be reviewed by investigators. Additional Research Sample Collection: In the event something unexpected occurs the protocol, the research team may request an additional sample collection be performed to collect additional blood or marrow/LN samples for research analysis. This is being done with the intention of evaluating the likely effects from the investigational products received. The total amount of extra blood that will be collected will be 3 tablespoons of blood twice in one week. The total amount of extra bone marrow or lymph node biopsies collected from you will be up to 1 extra procedure per month.

a. Medical history, physical exam, documentation of adverse events and concomitant medications are to be done prior to infusion. Hematology and chemistry results are to be obtained prior to infusion for day 1. Hematology includes CBC, differential, and platelet

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

count. Chemistry will include Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid. A separate sample for serum K+ is taken approximately 2 hours post-infusion.

b. Physical exam includes vital signs. Height, weight, body surface area at enrollment and as clinically indicated.
c. Adverse events must be reported from the time the patient signs the retreatment consent until the end of the study.
d. CT scans should be performed within 42 days of study entry for disease evaluation and as clinically indicated for disease monitoring.
e. As clinically needed at baseline and throughout the study.
f. Should be performed within 6 weeks of infusion, but does not need to be performed on the same day as apheresis.
g. Pregnancy test (quantitative) for female only.
h. Blood for CD3, CD4, CD8 Lymphocytes taken at months 3 and 6 only.
i. Autoimmune screen (ANA, ESR)
j. Viral Serology includes CMV, EBV, and Hepatitis B and C
k. Serum immunoglobulins will be collected at months 3, 6, 9 and 12, and as clinically indicated.
l. Chemotherapy as appropriate for disease type. See section 6.5
m. If there is an existing sufficient CART19 dose, leukapheresis screening to assess venous access will not be performed. However, if there is either an insufficient manufactured dose or starting material available in the CVPF, the subject will be asked to undergo apheresis to collect additional cells to manufacturer a sufficient dose for retreatment, and CART19 T cells will be administered via split dosing based on the Retreatment Cohort Schedule of Events for Split Dosing Administration below.
n. 100mL peripheral blood draw (lavender EDTA 10mL tubes) to be delivered to the TCSL.
o. TCSL has requested labs samples for research be sent to TCSL as soon as collected. If required to keep research labs after hours, please keep red tops upright, lavender tubes should be room temperature on rotating platforms. In the event that something unexpected occurs, additional research sample collection may be done as necessary. Blood collects are not to exceed 3 tablespoons of blood twice in one week time window. Marrow/LN collections would not exceed more than one procedure per month. This would be at PI discretion.
p. The research blood collection is split on infusion day: 20 mL EDTA (lavender) and 2 mL serum (red) are collected pre-infusion for cytokines, qPCR and cellular assessments; 5 mL EDTA (lavender) and 2 mL serum (red) are collected 20-120min post-infusion for cytokines and qPCR only (cellular assessments only done pre-infusion).
q. Required on Day 14 and as clinically needed on Day 21.
r. Post infusion assessments will be performed monthly from month 2 to month 6.
s. After year 1, patients will be enrolled into a destination protocol (IRB# 815699/UPCC 10908) for follow-up by phone or mail for up to 15 years post first T cell infusion, to monitor for delayed adverse events associated with the lentiviral vector genetic modification.
t. Concomitant with clinical draw, and also at months 1, 3, 6, 9 and 12 post-infusion. 5 ml in lavender top (DNA) and 2 ml in red top (serum) to be delivered to TCSL.
u. At months 3 and 6 only.
v. CART19 , tumor, and B cells enumerated by flow cytometry following pre-gating using CD3+/CAR19+, CD5,CD19/kappa or lambda and CD19+ expression respectively.
w. All patients must undergo a Respiratory Virus Panel (RVP) to test for influenza within 10 days prior to the planned CART-19 infusion. The Respiratory Virus Panel includes: Influenza A, Influenza B, Respiratory Syncytial Virus A, Respiratory Syncytial Virus B,

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Parainfluenza Virus Type 1, Parainfluenza Virus Type 2, Parainfluenza Virus Type 3, Adenovirus. If the patient is positive for influenza, oseltamivir phosphate (Tamiflu®) or equivalent should be administered for 10 days as preventative treatment (see Tamiflu® package insert for dosing information). The patient must complete this course of preventative treatment prior to receiving the CART-19 infusion. If the patient is positive for influenza and is also experiencing flu-like symptoms, all clinical symptoms must also be resolved prior to the CART-19 infusion. If the patient is positive for another virus on the RVP, the CART-19 infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the infusion will be delayed until resolution of these symptoms.

x. For subjects who complete or prematurely discontinue from study follow-up while in remission, follow-up attempts will be made to assess subject's relapse and survival status every 3 months post CART-19 infusion until the end of the study (Last Patient/Last Visit). Once subjects' relapse or they begin a new cancer therapy, additional follow-up for relapse will not be required, and subjects will be followed for survival only.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Schedule of Study Procedures/Retreatment Cohort- Split Dosing Administration

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[y]**
	Screening/ Baseline	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Infusion #2 Day 2 §**	**Infusion #3 Day 3 §**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	203	204	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
Clinical Assessments																
Retreatment Consent	X															
Retreatment Inclusion/Exclusion Criteria	X															
Quality of Life Questionnaires (EORTC QLQ-C30 and CLL-16)	X		X									X	X[u]	X	X	
Interim Treatment History	X															
Current Medical Conditions	X	X	X	X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Physical exam[b]	X			X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Performance Status Assessment	X			X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Concomitant Meds	X	X	X	X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
Adverse Events[c]	X	X	X	X	X[a]	X[a]	X[a]	X	X	X	X	X	X	X	X	
HIV test (1 ml SST)	X															

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[y]**
	Screening/ Baseline	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Infusion #2 Day 2 §**	**Infusion #3 Day 3 §**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	203	204	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
p53 Mutation	**X**															
Leukapheresis screening	**X[m]**															
CT scan of chest, abdomen, pelvis[d]	**X**											**X**	**X[u]**	**X**	**X**	
Bone marrow biopsy/aspirate[o]	**X**											**X**	**X[u]**	**X**	**X**	
Lymph Node biopsy	**X[e]**											**X[e]**	**X[u,e]**	**X[e]**	**X[e]**	
ECHO/MUGA[f]	**X**															
Respiratory Virus Panel (RVP)			**X[w]**													
Blood Draws																
Hematology (CBC, differential, platelet count) (5 ml lavender top, EDTA)[a]	**X**			**X**	**X[a]**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Chemistry (3 ml SST)	**X**			**X**	**X[a]**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Serum pregnancy test[g] (1 ml SST)	**X**															

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[y]**
	Screening/ Baseline	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Infusion #2 Day 2 §**	**Infusion #3 Day 3 §**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	203	204	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
Urine pregnancy test[g]				**X**												
CD3, CD4, CD8 Mon (4 ml lavender top, EDTA)					**X**							**X**	**X[h]**		**X**	
Autoimmune Screen[i] (ANA, ESR) (4 ml SST ; 3ml lavender top EDTA)	**X**															
Viral Serology[j] (CMV, EBV, Hepatitis B/C) (5ml red top, serum)	**X**															
β2 Microglobulin (1ml SST)	**X**															
Coagulation factors (PT, PTT, INR, fibrinogen, D-dimer) (4.5 ml blue top citrate)				**X**							**X[q]**					

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[y]**
	Screening/ Baseline	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Infusion #2 Day 2 §**	**Infusion #3 Day 3 §**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	203	204	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
HLH/MAS (triglycerides, haptoglobin (4 ml SST; 2.5 ml lavender top, EDTA)				**X**								**X**				
Serum immunoglobulin levels (1ml SST)[k]	**X**											**X**	**X[k]**	**X[k]**	**X[k]**	
Immunoglobulin Heavy Chain (4ml lavender; 0.5-1ml BM)	**X**															
Relapse and Survival Follow-up																**X[x]**
Intervention																
Chemotherapy[l, e]			**X**													
CART-19 cell infusion					**X**											
Leukapheresis		**X[m]**														
Research Labs[o]																

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[y]**
	Screening/ Baseline	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Infusion #2 Day 2 §**	**Infusion #3 Day 3 §**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	203	204	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
Large Volume Peripheral Blood Draw (100mL)												**X[n]**				
Serum 5ml (Red top)	**X**	**X**		**X**	**X[p]**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	
HAMA	X													X	X	
HACA	X													X	X	
Multiplex cytokine	X	X		X	X[p]	X[p]	X[p]	X	X	X	X	X	X	X	x	
PBMC 25ml (Lavender, EDTA)	**X**			**X**	**X[p]**	**X[p]**	**X[p]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
p53 Mutation Analysis	X															
DNA (Q-PCR persistence)	X			X	X[p]	X[p]	X[p]	X	X	X	X	X	X	X	X	
DNA RCL (VSV-G Q-PCR)	X			X									X[u]		X	
PBMC (functional assays, immunophenotyping, CART-19 and B cell enumeration[v])	X			X	X[p]	X[p]	X[p]	X[q]	X	X	X	X	X	X	X	
Bone marrow / LN aspirate (5 ml lavender top, EDTA)	**X**											**X[t]**	**X[t]**	**X[t]**	**X[t]**	

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Week/Day of treatment period	**~ Wk (-) 1 to 6**	**~ Wk (-) 4 to 6 (+/- 1 wk)[m]**	**~ Wk (-) 1 (+2 days)**	**~ Day (-) 1§**	**Day 1§**	**Day 2 (+1 day)§**	**Day 3 (+1 day)§**	**Day 4 (+1 day)**	**Day 7 (+/- 1 day)**	**Day 10 (+/- 1 day)**	**Day 14, 21 (+/- 1 day)**	**Day 28 (+/- 3 days)**	**Month 2 to 6[r] (+/- 7 days)**	**Month 9 (+/- 7 days)**	**Month 12[s] (+/- 7 days)**	**Every 3 Months (+/- 1 month)[y]**
	Screening/ Baseline	**Apheresis**	**Chemo-therapy[j]**	**Pre – Infusion**	**Infusion**	**Infusion**	**Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**Post Infusion**	**End of Treatment**	**Post Infusion**	**Post Infusion**	**End of study**	**Secondary Follow-up**
Visit Name	**Screening/Baseline Week -1 to -6**	**Apheresis Week -4 to -6[m]**	**Chemotherapy Week (-1)**	**Pre-infusion Day -1§**	**Infusion Day 1§**	**Infusion #2 Day 2 §**	**Infusion #3 Day 3 §**	**Post infusion Day 4**	**Post infusion Day 7**	**Post infusion Day 10**	**Post infusion Day 14**	**End of Treatment**	**Safety follow-up 1 to 5**	**Safety follow-up 6**	**End of study**	**Secondary Follow-up**
Visit number	101	102	103	104	105	203	204	106	107	108	109, 110	779	551, 552, 553, 554, 555	556	780	602
DNA (Q-PCR homing)	X											X	X[t]	X	X	
MMC (CART19 and B cell enumeration, immunophenotyping)	X											X	X[t]	X	X	
Marrow Serum (2 ml red top)	**X**											**X[t]**	**X[t]**	**X[t]**	**X[t]**	
Multiplex cytokine	X											X	X[t]	X	X	
Total research blood needs	32 ml	5 ml	0 ml	30 ml	36 ml	36 ml	36 ml	30 ml	30 ml	30 ml	30 ml	130 ml	30 ml	30 ml	30 ml	N/A
TOTAL BLOOD DRAW	60 ml	5 ml	0 ml	49-56 ml	45-56 ml	45-56 ml	45-56 ml	38-50 ml	38-50 ml	38-50 ml	49-61 ml	143-161 ml	42-61 ml	38-57 ml	42-61 ml	N/A

§ Lab tests specified on the infusion day will be drawn prior to infusion. A blood draw for potassium will be drawn 2 hours post infusion. The Investigator will review all pre-infusion lab (day -1) results to determine that it is appropriate to proceed with the infusion. Any abnormal Cr, Ca, K, Phos or uric acid result that is a change from the prior value should be reviewed by the PI prior to the infusion. Any new lab abnormalities that are also a change from the prior value will be reviewed by investigators. Additional Research Sample Collection: In the event something unexpected occurs

This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

the protocol, the research team may request an additional sample collection be performed to collect additional blood or marrow/LN samples for research analysis. This is being done with the intention of evaluating the likely effects from the investigational products received. The total amount of extra blood that will be collected will be 3 tablespoons of blood twice in one week. The total amount of extra bone marrow or lymph node biopsies collected from you will be up to 1 extra procedure per month.

a. Medical history, physical exam, documentation of adverse events and concomitant medications are to be done prior to each infusion. Hematology and chemistry results are to be obtained prior to infusion. Hematology includes CBC, differential, and platelet count. Chemistry will include Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Ferritin, CRP and Uric Acid. A separate sample for serum K+ is taken approximately 2 hours post-infusion.
b. Physical exam includes vital signs. Height, weight, body surface area at enrollment and as clinically indicated.
c. Adverse events must be reported from the time the patient signs the retreatment consent until the end of the study.
d. CT scans should be performed within 42 days of study entry for disease evaluation and as clinically indicated for disease monitoring.
e. As clinically needed at baseline and throughout the study.
f. Should be performed within 6 weeks of the first CART19 infusion, but does not need to be performed on the same day as apheresis.
g. Pregnancy test (quantitative) for female only.
h. Blood for CD3, CD4, CD8 Lymphocytes taken at months 3 and 6 only.
i. Autoimmune screen (ANA, ESR)
j. Viral Serology includes CMV, EBV, and Hepatitis B and C
k. Serum immunoglobulins will be collected at months 3, 6, 9 and 12, and as clinically indicated.
l. Chemotherapy as appropriate for disease type. See section 6.5
m. If there is an existing sufficient CART19 dose, leukapheresis screening to assess venous access will not be performed. However, if there is either an insufficient manufactured dose or starting material available in the CVPF, the subject will be asked to undergo apheresis to collect additional cells to manufacturer a sufficient dose for retreatment. If apheresis is required: 12-15 liter apheresis to go to CVPF. 1 x 10^8 cells to be delivered to TCSL.
n. 100 mL peripheral blood draw (Lavender EDTA 10mL tubes) to be delivered to the TCSL.
o. TCSL has requested labs samples for research be sent to TCSL as soon as collected. If required to keep research labs after hours, please keep red tops upright, lavender tubes should be room temperature on rotating platforms. In the event that something unexpected occurs, additional research sample collection may be done as necessary. Blood collects are not to exceed 3 tablespoons of blood twice in one week time window. Marrow/LN collections would not exceed more than one procedure per month. This would be at PI discretion.
p. The research blood collection is split on infusion day: 20 mL EDTA (lavender) and 2 mL serum (red) are collected pre-infusion for cytokines, qPCR and cellular assessments; 5 mL EDTA (lavender) and 2 mL serum (red) are collected 20-120min post-infusion for cytokines and qPCR only (cellular assessments only done pre-infusion).
q. Required on Day 14 and as clinically needed on Day 21.
r. Post infusion assessments will be performed monthly from month 2 to month 6.
s. After year 1, patients will be enrolled into a destination protocol (IRB# 815699/UPCC 10908) for follow-up by phone or mail for up to 15 years post first T cell infusion, to monitor for delayed adverse events associated with the lentiviral vector genetic modification.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

t. Concomitant with clinical draw, and also at months 1, 3, 6, 9 and 12 post-infusion. 5 ml in lavender top (DNA) and 2 ml in red top (serum) to be delivered to TCSL.
u. At months 3 and 6 only.
v. CART19 , tumor, and B cells enumerated by flow cytometry following pre-gating using CD3+/CAR19+, CD5,CD19/kappa or lambda and CD19+ expression respectively.
w. All patients must undergo a Respiratory Virus Panel (RVP) to test for influenza within 10 days prior to the first planned CART-19 infusion. The Respiratory Virus Panel includes: Influenza A, Influenza B, Respiratory Syncytial Virus A, Respiratory Syncytial Virus B, Parainfluenza Virus Type 1, Parainfluenza Virus Type 2, Parainfluenza Virus Type 3, Adenovirus. If the patient is positive for influenza, oseltamivir phosphate (Tamiflu®) or equivalent should be administered for 10 days as preventative treatment (see Tamiflu® package insert for dosing information). The patient must complete this course of preventative treatment prior to receiving the first CART-19 infusion. If the patient is positive for influenza and is also experiencing flu-like symptoms, all clinical symptoms must also be resolved prior to the first CART-19 infusion. If the patient is positive for another virus on the RVP, the CART-19 infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the infusion will be delayed until resolution of these symptoms.
x. For subjects who complete or prematurely discontinue from study follow-up while in remission, follow-up attempts will be made to assess subject's relapse and survival status every 3 months post CART-19 infusion until the end of the study (Last Patient/Last Visit). Once subjects' relapse or they begin a new cancer therapy, additional follow-up for relapse will not be required, and subjects will be followed for survival only.
y. Secondary follow-up will take place in Stage 2 only.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.

Appendix 3. New York Heart Association (NYHA) Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

CONFIDENTIAL
This material is the property of the University of Pennsylvania. Do not disclose or use except as authorized in writing by the study sponsor.