University of Pennsylvania

PHASE IIA STUDY OF REDIRECTED AUTOLOGOUS T CELLS ENGINEERED TO CONTAIN ANTI-CD19 ATTACHED TO TCRζ AND 4-1BB SIGNALING DOMAINS IN PATIENTS WITH CHEMOTHERAPY RELAPSED OR REFRACTORY CD19+ LYMPHOMAS

Principal Investigator	*Stephen Schuster, MD* *University of Pennsylvania*
Regulatory Sponsor:	*University of Pennsylvania*
Sponsor Medical Director:	[redacted]
Sponsor Scientific Advisor:	[redacted]
Clinical Protocol Advisor:	[redacted]
Funding Organization:	*Novartis Pharmaceuticals*
Study Product:	*CD19 redirected autologous T cells (CART-19; or CTL019/CTL119 cells)*
Protocol Number:	*UPCC#13413; IRB# 818607*
IND Number:	[redacted]
Sponsor Cell Manufacturing – University of Pennsylvania:	[redacted]
Laboratory Team:	[redacted]
Biostatistician:	[redacted]
Medical Monitor:	[redacted]

Date Amended:
07-26-2013
08-22-2013
11-20-2013
07-18-2014
03-05-2015
06-08-2015
10-17-2016
08-07-2017

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

APC	antigen presenting cell
aAPC	artificial APC
AE	adverse event
CAR	chimeric antigen receptor
CART-19 cells	CD19 redirected autologous T cells
CIR	chimeric immune receptor, interchangeable with CAR
CFR	code of federal regulations
CMV	Cytomegalovirus
CRF	case report form
CTC	common toxicity criteria
CTRC	clinical and translational research center
CTL	cytotoxic T lymphocyte
CVPF	clinical cell and vaccine production facility
CTL	cytotoxic T lymphocyte
CD137	4-1BB costimulatory molecule
DFS	disease free survival
DSMB	data safety and monitoring board
FDA	food and drug administration
GCP	good clinical practices
GMP	good manufacturing practices
GVHD	graft versus host disease
IBC	Institutional Biosafety Committee
IRB	Institutional Review Board
MRD	minimal residual disease
PBMC	peripheral blood mononuclear cells
RAC	NIH Office of Biotechnology Recombinant DNA Advisory Committee
RCR/L	replication competent lentivirus
RVP	respiratory virus panel
scFv	single chain Fv fragment
SPD	the sum of the product of the longest perpendicular dimensions of all dominant tumor masses
TCR	T cell receptor
TCR-ζ	signaling domain found in the intracellular region of the TCR zeta, gamma and epsilon chains
UPenn	University of Pennsylvania
Vβ	a rearranged T cell specific gene that can be used to determine clonality of a T cell population
VSV-G	Vesicular Stomatitis Virus, Glycoprotein

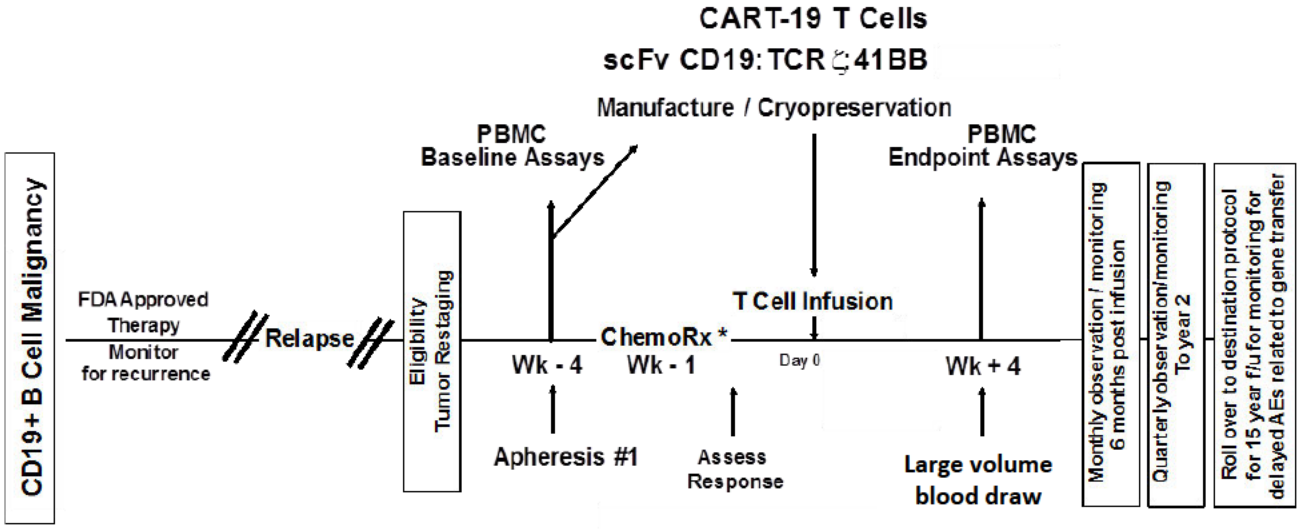
STUDY SUMMARY AND STUDY SCHEMA

Title	PHASE IIA STUDY OF REDIRECTED AUTOLOGOUS T CELLS ENGINEERED TO CONTAIN ANTI-CD19 ATTACHED TO TCRζ AND 4-1BB SIGNALING DOMAINS IN PATIENTS WITH CHEMOTHERAPY RELAPSED OR REFRACTORY CD19+ LYMPHOMAS
Short Title	CD19 redirected autologous T cells
Protocol Numbers	IRB #818607, UPCC #13413, INDs #[redacted]
Phase	Phase 2a
Methodology	Phase IIa study to estimate the efficacy of a single infusion of autologous T cells expressing CD19 chimeric antigen receptors expressing tandem TCRζ and 4-1BB (TCRζ /4-1BB) costimulatory domains (referred to as "CART-19" or "CTL019" cells) in non-Hodgkin's Lymphoma (NHL) patients.
Study Duration	The duration of active protocol intervention is approximately 24 months from screening visit. The protocol will require approximately 48 months to complete.
Study Center(s)	Single-center
Objectives	The primary objective is to estimate the efficacy of CART-19 cells in NHL patients by measuring the overall response rate (ORR) in evaluable patients at 3 months. 1. We will treat a total of 60 patients with either DLBCL, FL or MCL. (Cohort A, N=39 NHL treated with murine CART19; Cohort B, N=7 T cell/histiocyte-rich DLBCL treated with murine CART19; Cohort C, N=14 DLBCL treated with humanized CART19). Since there is no a priori suggestion that CART-19 cells would be more or less effective or safe for any histology, all patients in Cohort A will be analyzed together. A subset analysis according to histology will also be performed as a secondary objective. Cohorts B and C will be analyzed individually to focus on ORR for patients with T cell/histiocyte-rich DLBCL and DLBCL subjects treated with huCART19, respectively. Secondary objectives are to: 1. Determine persistence, trafficking and function of CART-19 cells 2. Determine the effects of CART-19 infusion on B cells and CD19 expression *in vivo.* 3. Evaluate impact of CART-19 treatment on systemic soluble immune factors in patients 4. Determine if cellular or humoral host immunity develops *against* CART-19 cells. 5. Characterize the relative subsets of CART-19 T cells (Tcm, Tem, and Treg). 6. Evaluate MRD using molecular technologies 7. Describe survival and response rates.

	a. Describe overall response rate (ORR) for each individual histology with either murine CART19 or humanized CART19, as well as CR, CRu and PR rates. b. Describe overall survival (OS) and progression-free survival (PFS) for all patients c. Describe duration of response (DOR) for responding patients 8. Assess the safety and tolerability of CART-19 in NHL subjects by recording the frequency and severity of adverse events reporting, including but not limited to, estimating the frequency of CRS and MAS. 9. Determine the dose manufacturing feasibility. 10. Follow subjects infused with less than protocol-specified target dose.
Numb*er of Subjects*	A total of 60 evaluable subjects with Follicular Lymphoma (FL), Diffuse Large B Cell Lymphoma (DLBCL) and Mantle Cell Lymphoma (MCL) will be enrolled on this study in one of three Cohorts. **Cohort A:** Will include a total of 39 evaluable subjects; with a minimum of 20 DLBCL subjects and a minimum of 16 total subjects with either FL or MCL histologies (enrolled on a first-come, first-serve basis). All subjects in Cohort A will receive murine CART19. **Cohort B:** Will include 7 evaluable DLBCL subjects with T-cell rich disease. All subjects in Cohort B will receive murine CART19. **Cohort C:** Will include 14 evaluable DLBCL subjects, without restriction on T-cell or non-T-cell rich disease. All subjects in Cohort C will receive humanized CART19.
Diagnosis a*nd Main* Inclusion Criteria	Inclusion criteria include adult patients age ≥18 with CD19+ B cell lymphomas with no available potentially curative treatment options (such as autologous or allogeneic stem cell transplantation) who have a limited prognosis (several months to ≤2 year expected survival) with currently available therapies.
Study Product, Dose, Route, Regimen	Single infusion of CART-19 cells administered by i.v. injection (total dose of $1 – 5 \times 10^8$ CART-19 cells). The dose will be the same for Cohorts A, B and C and for subjects receiving either murine or humanized CART19 cells.
Duration of administration	Based on the total volume to be infused and the recommended infusion rate of 10-20mL per minute
Reference therapy	None. Enrollment in this protocol will be offered to subjects with unmet medical needs for which there are no effective therapies known at this time.
Statistical Methodology	A total of 60 evaluable subjects will be planned for analysis of the primary endpoints. Analyses will be done principally by cohort. For cohort A, if 18 out of 39 evaluable subjects have partial or complete response at 3 months, we will have strong evidence (i.e., 95% confidence) that the true ORR following CART-19 infusion is at least above an ORR of 30%. For cohort B (N=7), if 0/7 respond, we would be 90% confident that the ORR was less than 35%. For cohort C, both the safety and the efficacy are primary interests. For Cohort C, with n=14 and treatment limiting toxicity (TLT) defined as unexpected ≥grade 3 non-hematologic toxicity probably related to the CART-

	19 infusion, the probability of observing no (i.e., 0), 1, 2 or 3 treatment limiting toxicities (i.e., a TLT rate of 0%, 7%, 14%, and 21%) is 0.7%, 4.1%, 11.3% and 22.9%, respectively, assuming a maximum acceptable toxicity rate of 30%.If 7/14 subjects respond, the 95% CI is (0.23, 0.77). Descriptive statistics will be computed for all study variables for the evaluable populations as whole and within cohorts and histologic subgroups. The primary endpoint of overall response will be summarized as overall response rate (ORR) and the 95% exact confidence interval will be calculated based on binomial distribution. For secondary objectives, all adverse events will be described and exact 95% confidence intervals will be produced for adverse event rates, both overall and within major categories. Overall survival, progression-free survival, and duration of response will be analyzed using Kaplan-Meier curves and median survival time will be computed. To evaluate the persistence of CART-19 (or its subsets), the within-subject change in the ratio of CART-19 cells (or subsets) between two pre-specified time points will be compared using a Wilcoxon signed-rank test, or to simultaneously analyze multiple times, linear mixed effects model methodology will be used. All other secondary endpoints are measured as continuous variable and the effects of CART-19 infusion can be evaluated by analyzed the change of various immunity measures from its baseline values using the nonparametric Wilcoxon signed-rank test. All the analyses will be two-sided and cut-off for statistical significance will be a P-value <0.05. The number of patients enrolled versus the number of patients infused and proportion of subjects with manufacturing failure will be computed as a measure of feasibility.

Study Schema (Figure 1)



1 INTRODUCTION

1.1 Background

CD19 positive hematologic malignancies. B cell malignancies comprise a heterogeneous group of neoplasms including multiple non-Hodgkin's lymphomas (NHL), acute lymphoblastic leukemias (ALL) and chronic lymphocytic leukemias (CLL). An estimated 87,000 new cases of leukemia and NHL are diagnosed in the US annually[1]. This protocol will evaluate potential of CART-19 cells to treat NHL, specifically diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle cell lymphoma (MCL), which account for 31%, 22% and 6%, respectively, of the total NHL cases. As mentioned below, current treatments for these B cell malignancies include chemotherapy, radiation therapy, or autologous and allogeneic blood and bone marrow transplantation. Despite these treatment modalities, many patients remain incurable. Taken together, these data demonstrate that there is still a need to develop therapies for NHL that is relapsed or refractory to available therapies.

Diffuse Large B Cell Lymphoma: DLBCL has at least several subtypes, including but not limited to germinal center B cell (GCB) type, activated B-cell type (ABC) and primary mediastinal DLBCL[2]. The 3-year overall survival (OS) for GCB and ABC subsets of CLBCL in treated subjects is 84% and 56%, respectively[3]. Most DLBCL subjects are cured with conventional immunochemotherapy. However, for patients who relapse, while at least 60% of subjects remain sensitive to conventional treatment, < 10% have prolonged disease-free survival with second-line treatment conventional dose immunochemotherapy regimens[4]. Patients with relapsed or refractory (r/r) DLBCL are treated with chemotherapy (±rituximab) with the goal of subsequent high-dose chemotherapy and bone marrow or stem cell transplantation (HSCT), for the subset of subjects with chemotherapy-sensitive disease. Approximately 20-50% of responders to a second chemotherapy regimen followed by HSCT maintain their response at 2 years[5]. Patients with relapses within 12 months of rituximab-containing first-line therapy have a particularly poor prognosis even with transplantation[4]. For non-transplant candidates who fail second line therapy or who relapse post-transplant, therapy is palliative. Without transplant, chemotherapy provides short-term disease control in r/r DLBCL. Primary refractory subjects are unlikely to achieve CR with a second chemotherapy regimen and following relapse, second remissions are usually not durable[6].

Follicular Lymphoma (FL): FL is the second most common non-Hodgkin lymphoma (NHL) and comprises approximately 22% of all NHL cases[7]. The overall incidence of B-cell lymphoid neoplasms in the United States (US) is estimated at 26.13/100,000 person years[8], with FL accounting for 3.18 new cases per 100,000 persons each year in the US. Follicular lymphoma is subdivided into 3 grades[9], with Grade 3 is often further subdivided into 3a or 3b, with 3b considered more aggressive[10]. Treatment depends on the stage of the disease, symptoms, patient age, and comorbidities. When treatment is provided, initial therapy may include rituximab as a single agent or rituximab combined with one or more cytotoxic drugs. Alkylating agents such as cyclophosphamide or bendamustine, in combination with rituximab, constitute the mainstay of combination therapy. The most commonly used alkylating agent-based regimens include BR (bendamustine and rituximab), R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone), or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone)[11].

Response rates in excess of 85% are observed with many different combinations in the first-line setting[12-15]. In addition, when rituximab is used as maintenance treatment, both response rate and disease-free survival increase[16-18]. Despite availability of multiple active agents, high response rates, and long progression-free survival (PFS) with first line therapy, FL remains an incurable disease. Most patients treated will eventually relapse, and subsequent responses and durations of responses become increasingly shorter. Patients who become resistant to chemoimmunotherapy, clinically defined as relapsed or progressive within 12 months, have no good treatment options[19,20]. In these patients, toxicity commonly outweighs the benefit of treatment with chemotherapy[20,21]. Investigational agents (e.g., ofatumumab, lenalidomide, bortezomib) have been used with response rates of 10% to 27% and a median PFS of 4 to 6 months[22-24]. For a select group of eligible patients, radioimmunotherapy achieves a long-term remission in <20%[25]. The Bruton tyrosine kinase inhibitor, ibrutinib, and the PI3 kinase δ isoform inhibitor, idelalisib, are promising new agents under investigation in this setting and clinical trials are ongoing.

Mantle Cell Lymphoma (MCL): MCL is a less common, incurable subtype of non-Hodgkin lymphoma (NHL). It accounts for about 6% of all NHL cases in the Western world. At the molecular level, MCL is uniquely characterized by overexpression of the cell cycle regulatory protein cyclin D1. This is due to the chromosomal translocation t(11;14)(q13;q32), which puts the cyclin D1 gene, also called the B-cell leukemia/lymphoma 1 (bcl-1) gene, under the control of the immunoglobulin heavy chain enhancer with subsequent overexpression of cyclin D1[26-28]. In association with overexpression of cyclin D1, cell surface markers such as CD20 and CD5 are also evident in MCL. Current initial therapy for the treatment of MCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with rituximab (R-CHOP or R-Hyper CVAD); however, many other chemotherapeutic regimens have been evaluated. Younger patients with good performance status are frequently considered for more intensive induction therapy with combinations such as R-Hyper CVAD or alternating R-CHOP and rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) followed by consolidation therapy with autologous stem cell transplant (SCT); however, this degree of intensive therapy is not an option for most patients with MCL because of their age and comorbidities[29,30]. Once MCL has relapsed after or failed to respond to initial treatment, the prognosis is poor. Following relapse, the median survival is around 1 to 2 years[29-31]. The Bruton tyrosine kinase inhibitor, ibrutinib, is a promising new agent under investigation in this setting and clinical trials are ongoing

CD19 as target for NHL adoptive immunotherapy. CD19 is a highly attractive target for NHL immunotherapy. CD19 is expressed by most B cell lymphomas, mantle cell lymphoma, ALL, CLL, hairy cell leukemia, and a subset of acute myelogenous leukemias[32-34]. CD19 is a 95kDa glycoprotein present on the B cell surface from early development until differentiation into plasma cells[34-36]. 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[36-38]. CD19 expression is restricted to B lineage cells and is not expressed by pluripotent blood stem cells or on most other normal tissues[39]. 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[40-44] and human and non-human primates[45-55].

Because of this limited tissue expression profile, targeting CD19 is also favorable due to a reduced on-target, off-organ activity toxicity profile.

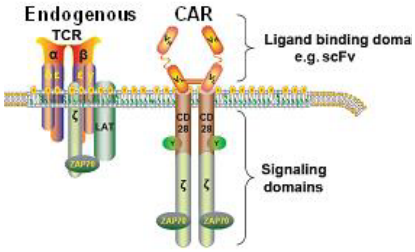


Fig. 2. CAR design. Bispecific T cells are created by the introduction of genes encoding CAR proteins that recognize target surface antigens in

Engineered T cells with redirected specificity: chimeric antigen receptors (CARs). 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[56,57]. 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 signaling domain that mediates T cell activation (reviewed in[58,59]). 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[60]. First generation CARs contain a minimal TCR signaling domain consisting of TCRζ. Second generation CARs contain double costimulatory signaling domains both CD28 and TCRζ or 4-1BB and TCRζ. The third generation CARs contain further advancements such as triple costimulatory modules comprised of CD28, 41-BB, and TCRζ. See reviews of CARs for details[61-63]. There are several potential limitations to the CAR T cells: 1) the tumor must express the target antigen on the cell surface; 2) large amounts of shed or soluble antigen could inhibit the CAR T cells; 3) the chimeric receptor may be immunogenic, resulting in the elimination of the redirected T cells by the host immune system.

1.2 Investigational Agent

The investigational agent in this protocol is CART-19 cells (also known as CTL019 cells). 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 by the City of Hope Center for Applied Technology Development, the Indiana University Vector Production Facility, The Children's Hospital Of Philadelphia, or equivalent lentiviral vector production facility. The extracellular single chain antibody (scFv) with specificity for CD19 was previously reported[64]. The scFv used will either be derived from a mouse monoclonal antibody using hybridoma cell line FMC63 described in Nicholson et al. or a humanized version of that sequence developed by Novartis Biomedical Institutes of Research. The signaling domains are entirely of the native human sequences[65,66].

The CART-19 cells will be manufactured in the Clinical Cell and Vaccine Production Facility at the University of Pennsylvania. At the end of cell cultures, the cells are cryopreserved in

infusible cryomedia. A single dose of CART-19 transduced T cells will consist of the infusion of 1-5 x 10^8 CART-19 cells. 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, 7.5% DMSO, 1% dextran 40, 5% human serum albumin.

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, ontak. 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[67]; importantly, this immune mediated elimination was not accompanied by adverse effects and required 6 to 8 weeks to occur. It is important to note that it is possible the CART-19 T cells may be rejected in our patients.

Rationale for lymphodepletion. Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation[68], 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[69,70]. 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[71]. This hypothesis has been tested clinically in patients with metastatic melanoma refractory of conventional treatments[72]. The patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide (60mg/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, NHL, and CLL with infusions of ex-vivo co-stimulated and expanded autologous T cells after lymphodepleting chemotherapy, and observed improved engraftment[73-76]. In this protocol we propose to transfer CART-19 cells into subjects that 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.

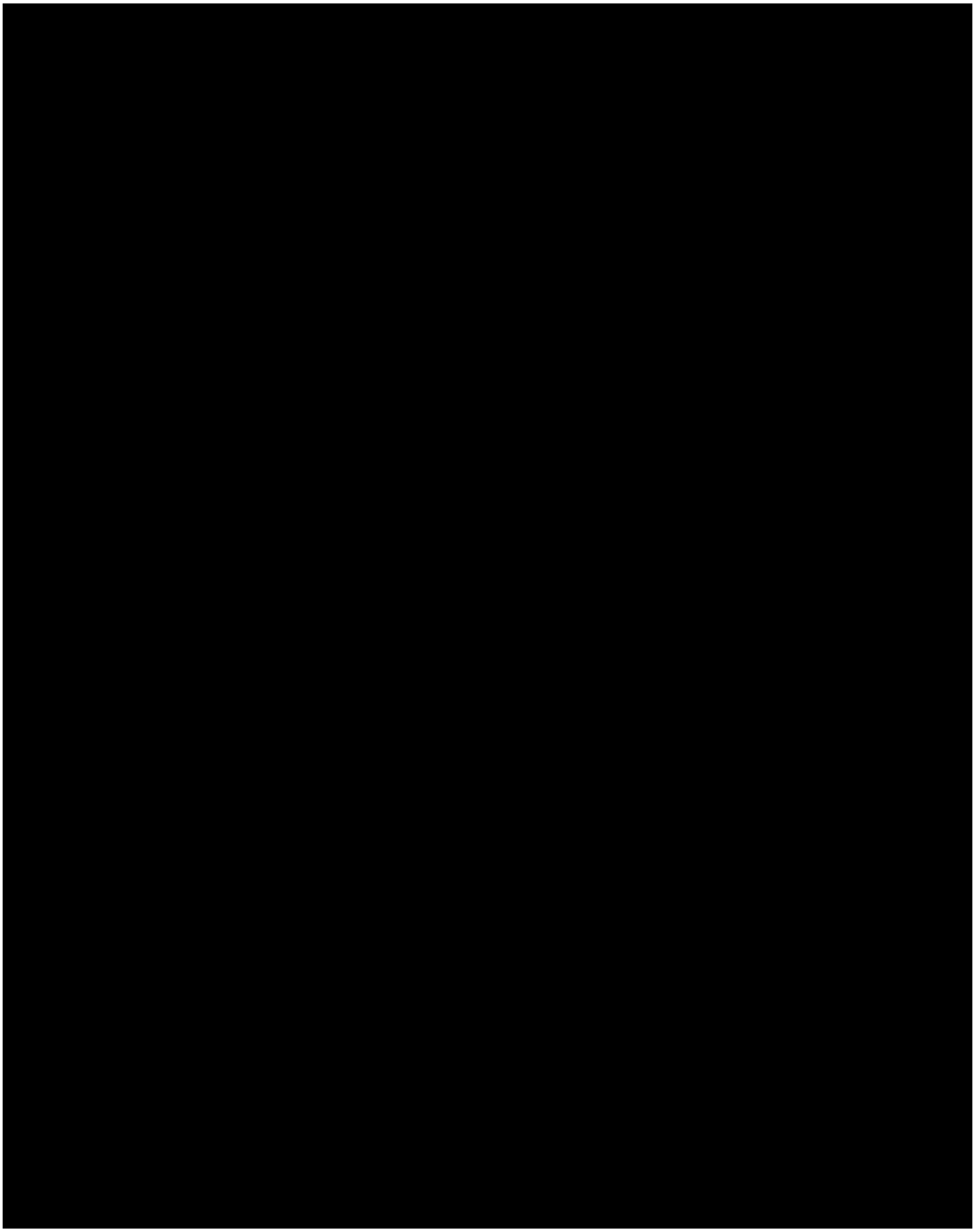
1.3 Preclinical Data

An extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models, reviewed[77-81]. 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[48,82-85]. 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[65,86-91]. The pre-clinical data supporting CART-19 has been previously published[92,93].

1.4 Previous Clinical Data with CART-19 cells

[redacted]



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 at 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 three cases of refractory CRS that resulted in death on UPCC21413. 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.

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.

1.5 Dose Rationale and Risk/Benefits

We have chosen to use flat dosing via the intravenous route of administration for this protocol. The dose that we have selected for administration is 1-5x10^8 CART-19 cells. This is the "high dose" from our randomized CART-19 dose-finding protocol (UPCC03712) as described in Section 1.5.1 (Dose Rationale).

1.5.1 Dose Rationale

After treatment of 42 CLL and ALL patients in our ongoing trial UPCC04409 and CHP959, respectively, we have observed durable clinical responses at doses ranging from 1.4x10^7 to 1.1x10^9 CART-19 cells. Efficacy across this two-log-fold difference does not support an obvious dose relationship. Unlike standard drugs that are metabolized, 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. Thus, the administered dose may underestimate the *in vivo* amount of CART-19 T cells. Based on our recent clinical experience we have chosen to use a cell dose, 1-5x10^8 CART-19 cells, which has been identified as safe and effective in patients with CLL in UPCC04409 and ALL patients in CHP959.

We are currently performing a randomized dose finding study for patients with CLL (UPCC03712) comparing responses with 1-5 x 10^7 and 1-5 x 10^8 CART-19 cells. If new information regarding an optimal dose level and corresponding clinical response were to become available, then this trial will be appropriately modified.

Manufacturing of this target dose is deemed achievable for the majority of patients based on our published data for manufactured CD3+/CD28+ costimulated and expanded T cells from patients with non-Hodgkin's lymphoma. Fifteen of the sixteen patients for which T cell products were manufactured had DLBCL[94]. In the event that manufacturing feasibility is not met for a particular patient, we will request approval from the FDA to proceed with infusion. These patients will be included in the safety evaluable population only. We will continue to accumulate data in this regard regarding the relationship of cell dose to toxicity and response.

1.5.2 Risk/Benefits

Potential Risks:
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 or in any CART-19 treated patients thus far. In this case, corticosteroids and chemotherapy would be given to eradicate the CAR cells; this has worked in previous cases[95].

Immunogenicity. Another risk is that the cells may be immunogenic, and that the patients will have an immune response directed against the scFv or novel sequences generated by the fusion protein; this has not had clinical consequences in previous trials studying lentivirus transduced T cells. If an immune response to the cells occurs, it is possible that the cells will be rejected. Three of 3 patients in an anti-carbonic anhydrase IX (CAIX) CAR trial developed Human Anti-Murine Antibody (HAMA) and loss of T cell engraftment[96]. This has generally not been an issue in patients treated with CARs directed towards B cells as temporary or persistent B cell aplasia results in reduced antibody formation.

Hypogammaglobulinemia. Persistent B cell aplasia leads to hypogammaglobulinemia and may increase the risk of infection. This can be managed with IVIG repletion. In the UPenn and CHOP CART19 trials, hypogammaglobulinemic CLL and ALL patients have received IVIG. No significant unusual infection patterns have been identified in patients receiving IVIG repletion at regular intervals.

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 gammaretroviral modified T cells treated on multiple protocols at many academic centers[97], and in the 21 HIV patients treated with lentiviral modified T cells treated at Penn[98] or any of the 200 patients treated to date with CART19.

General Safety. 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[73,94,99-101].

Infusion reactions. Immediately following T cell infusions, reactions could occur and may include transient fever, chills, and/or nausea. Patients must be pre-medicated with acetaminophen and anti-histamine prior to the infusion of CART19. A review of infusion-related adverse events of 381 T cell products administered to 180 recipients, enrolled on 18 studies, over a 10 year period was conducted by Cruz et al.[94] and found no grade 3-4 infusion reactions during initial monitoring or 24-hour follow-up. Grade 1-2 adverse events were observed in 21 patients during or shortly after infusion and included nausea, vomiting, fever, and/or chills. A mild infusion reaction was recorded in one of more than 20 CLL patients with CART19 infusion.

Intracranial Hemorrhage. As of February 2016, there have been two events of intracranial hemorrhage on CART19 trials under IND#[redacted]. One event occurred on UPCC#21413 (adult ALL) in the setting of thrombocytopenia (related to prior lymphodepleting chemotherapy and underlying leukemia), was determined to be possibly related to the CART19 cell infusion, occurred with concurrent Grade 4 CRS, and resulted in death. Another event occurred on the CNS3 cohort on CHP959 (pediatric ALL) in the setting of active circulating leukemia, CRS, sepsis/bacteremia, and acute renal failure requiring dialysis. The subject died, and intracranial hemorrhage (suspected clinically, unconfirmed radiologically) was felt to be the immediate cause of death in this critically ill patient. A third event occurred on 16CT022 (pediatric ALL study) in February 2017. A 3-year-old subject with refractory ALL and CNS2 disease experienced severe CRS complicated by DIC and multi-organ failure. While on extracorporeal membrane oxygenation, the subject experienced an intracranial hemorrhage, with associated cerebral edema as a terminal event.

Cytokine Release Syndrome.

Overview and Clinical Manifestations: 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), altered mental status including delirium and confusion (in several patients), word finding difficulties, evidence of disseminated intravascular coagulation, as well as macrophage activation syndrome (MAS). Additional symptoms of CRS may also include rigors, sweating, dyspnea, and seizures. 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 (MAS) 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.

Diagnosis is based on the fulfillment of criteria established in 2004[102] 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. 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 severe enough CRS (i.e. there were no instances of more than transient oxygen requirements, or hypotension requiring pressor support) to require treatment with steroids or cytokine blockade.

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 CRS that occurs after CART19 infusion. 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 8-1 in Section 8.1).

Replication-competent lentivirus (RCL). RCL may be generated during the CART19 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 patient. Nevertheless, generation of an RCL following infusion of the vector product remains a theoretical possibility. The consequences of such recombination events in patients without a known lentiviral infection are unknown, and therefore patients with coexistent HIV infection are excluded from participation in this study in order to minimize this possibility.

Clonality and insertional oncogenesis. The occurrence of adverse events caused by insertional mutagenesis in five patients in a gene therapy trial for X-linked SCID following stem cell therapy emphasizes the potential for problems in translating this approach to the clinic[95-98]. The T cell leukemias were attributable to clonal expansion conferred by gammaretroviral vector integration sites in the CD34+ bone marrow stem cell modification[98]. 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 ß-thalassaemia without malignancy[99]. The lentiviral vector used for CART19 manufacturing is part of a vector class that may have a lower risk for integration in or near oncogenic regions than oncoretroviral vectors[100].

Uncontrolled T cell proliferation. CART19 cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies, CART19 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[51,101].

Graft versus host disease (GVHD). The chance of GVHD occurring is low, but it is a potential risk with CART19 therapy if administered after prior allogeneic transplantation. A prior UPenn/CHOP study of activated DLI (*ex vivo* activated cells collected from the donor and grown in the same fashion as CART19 but without CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with Grade 4)[102].

Patients with active, acute or chronic GVHD requiring systemic therapy are excluded from enrolling in this study. However, due to the possibility of some degree of residual donor engraftment, which will include T cells of donor origin, patients that received a previous HSCT at the Hospital of the University of Pennsylvania will be assessed for donor chimerism at screening and will be monitored closely throughout the study for signs of GVHD. To date, no patient that had a prior allogeneic HSCT developed GVHD after autologous CART19 infusion[61,87,88] even when "autologous" cell included cells of donor origin[94].

B cell aplasia. B cell aplasia has been seen in CART19-treated subjects as well as B cell recovery in some subjects who had lost CART19[88103103103102][102][102](Maude et al., 2014). Persistent B cell aplasia leads to hypogammaglobulinemia and may increase the risk of infection. This is common with anti-CD20 directed therapies[103]. This can be managed with IVIG repletion by established clinical dosing guidelines to support IgG levels. In previous CART19 trials, responding CLL and ALL patients who are hypogammaglobulinemic have received IVIG. No significant unusual infection patterns have been identified.

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 sub-acute 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[104].

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[105], the CAR ERBB2 T cells bound to native low level expression pulmonary epithelial cell ERBB2 proteins[106], leading to CAR activation and pulmonary microvascular injury.

Other fatal SAEs using CD19-targeting T cells have been reported, including five fatal events at the University of Pennsylvania and two events in April 2014 at the Memorial Sloan Kettering Cancer Center. At the University of Pennsylvania, three of the first six adult ALL subjects infused on UPCC21413 died as a result of refractory Cytokine Release Syndrome (CRS) in the setting of intercurrent infections. Thereafter, the single dose administered in UPCC21413 was reduced to 1-5x10^7 CART19 cells. In the next six adult ALL subjects treated at the de-escalated dose, two died from an intracranial bleed and sepsis, respectively.

Risk of tumor lysis syndrome (TLS) related to cytoreductive chemotherapy or CAR T cells. The risk of tumor lysis syndrome (TLS) is dependent on the disease and burden of disease. Several of the patients treated with CART19 on this protocol have in fact developed tumor lysis syndrome. Therefore, all patients will be closely monitored both before and after chemotherapy and CART-19 infusions including blood tests for potassium and uric acid. All patient-subjects will receive allopurinol prophylactically. TLS resulting in renal insufficiency, or rapidly rising uric acid, or evidence of organ dysfunction will be managed with intravenous fluids and rasburicase as needed and determined by the treating physicians. Appropriate clinical therapy will be administered should any significant tumor lysis occur.

Unknowns: At this time there are still several unknowns regarding the observed CRS after CART19 infusion. It is unknown which patient factors (including type of disease; disease burden; prior therapies; genetic predisposition) correlate with severity of CRS. It is also unknown if cell dose correlates with severity of clinical CRS and if the duration and intensity of the CRS correlates with disease response. It is evident that responding patients have had CRS, it

remains unknown if abrogating the CRS with anti-cytokine directed therapy abrogates anti-tumor responses.

Potential benefits:
Based on inclusion criteria and published literature[107,108], eligible patients will have a median anticipated survival of <2 years without allogeneic SCT. The risks associated with allogeneic are high and include a minimum 20% treatment-related mortality (TRM); in many cases TRM would be even higher, and many of these patients would not be eligible for allogeneic SCT. 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[108,109]. Patients not eligible or appropriate for allogeneic SCT will have limited treatment options. It is possible that the CART-19 T cells will exert an anti-tumor effect; as demonstrated in our preliminary data for patients with advanced CLL, including 8/17 ongoing CRs or very significant PRs. In the two patients with longest follow up, CR has persisted beyond 2 ½ years. Therefore, we believe the risk:benefit ratio for this study is quite favorable.

2 STUDY OBJECTIVES

Primary objective:

1. To estimate the efficacy of a single target dose of 1-5 x10^8 CART-19 cells for patients with advanced B cell non-Hodgkin's lymphoma.
    a. Describe overall response rate for patients with NHL. We will treat a total of 60 patients with either DLBCL, FL or MCL. (Cohort A, N=39 NHL treated with murine CART19; Cohort B, N=7 T cell/histiocyte-rich DLBCL treated with murine CART19; Cohort C, N=14 DLBCL treated with humanized CART19). Since there is no a priori suggestion that CART-19 cells would be more or less effective or safe for any histology, all patients in Cohort A will be analyzed together. A subset analysis according to histology will also be performed as a secondary objective. Cohorts B and C will be analyzed individually to focus on ORR for patients with T cell/histiocyte-rich DLBCL and DLBCL subjects treated with huCART19, respectively.

Secondary objectives:

1. Determine persistence, trafficking and function of CART-19 cells
2. Determine the effects of CART-19 infusion on B cells and CD19 expression *in vivo.*
3. Evaluate impact of CART-19 treatment on systemic soluble immune factors in patients
4. Determine if cellular or humoral host immunity develops *against* CART-19 cells.
5. Characterize the relative subsets of CART-19 T cells *(Tcm, Tem,* and Treg).
6. Evaluate MRD using molecular technologies
7. Describe survival and response rates.
    a. Describe overall response rate (ORR) for each individual histology with either murine CART19 or humanized CART19, as well as CR, CRu and PR rates.
    b. Describe overall survival (OS) and progression-free survival (PFS) for all patients
    c. Describe duration of response (DOR) for responding patients

8. Assess the safety and tolerability of CART-19 in NHL subjects by recording the frequency and severity of adverse events reporting, including but not limited to, estimating the frequency of CRS and MAS.
9. Determine the dose manufacturing feasibility.
10. Follow subjects infused with less than protocol-specified target dose.

3 STUDY DESIGN

3.1 General Design

This is phase IIa trial to test the **central hypothesis** that CART-19 cell infusions will result in anti-tumor responses for patients with advanced B cell NHL. The primary objective of the study is to estimate the ORR at 3 months in patients with NHL. We will also insure that patients with the most common NHL histologies (DLBCL, MCL, FL) are treated and describe activity according to histology. The initial study design included at least 8 subjects with one of three histologies to be treated with murine CART19. The remaining 6 subjects would be enrolled within any of the 3 NHL histologies on a first-come, first-serve basis. The DLBCL histology group in Cohort A has reached full enrollment as of this protocol version. The 8 subject limit for MCL and FL is now removed to allow a total of 16 subjects with MCL or FL to be treated on a first-come, first-serve basis. These 30 NHL subjects will all receive murine CART19 and will be known as Cohort A (V5.03-05-15).

As of protocol Version 5.03-05-15, two additional cohorts are also added: (1) Cohort B; N=7 T-cell/histiocyte rich DLBCL treated with murine CART19; and, (2) Cohort C; N=14 DLBCL treated with humanized CART19. Cohort B will expand upon the two subjects with this particularly aggressive sub-type already treated per protocol prior to this amendment and included in Cohort A. Cohort C expands upon the treatment experience of the DLBCL subject 13413-09 with humanized CART19, included in Cohort A per prior protocol version.

As of protocol Version 7.10-17-2016, Cohort A was further expanded to allow for 6 additional DLBCL subjects to be enrolled. Therefore, a total of 57 evaluable subjects will be enrolled on this protocol across all three Cohorts.

As of protocol Version 8.08-07-2017, three additional enrollment slots were added to further expand Cohort A. A maximum of 60 evaluable subjects will now be enrolled across the three cohorts as follows:

- **Cohort A:** Will include a total of 39 evaluable subjects; with a minimum of 20 DLBCL subjects and a minimum of 16 total subjects with either FL or MCL histologies (enrolled on a first-come, first-serve basis). All subjects in Cohort A will receive murine CART19.
- **Cohort B:** Will include 7 evaluable DLBCL subjects with T-cell rich disease. All subjects in Cohort B will receive murine CART19.
- **Cohort C:** Will include 14 evaluable DLBCL subjects, without restriction on T-cell or non-T-cell rich disease. All subjects in Cohort C will receive humanized CART19.

We will monitor and describe safety, tolerability and engraftment potential of CART-19 T cells in all of these patient cohorts. This protocol is an open label study. The general protocol schema is shown above in **Figure 1**.

At entry, subjects will be staged and the suitability of their T cells for CART-19 manufacturing will be determined. Subjects who have adequate T cells will be leukapheresed to obtain large numbers of peripheral blood mononuclear cells (PBMC) for CART-19 manufacturing. The T cells will be purified from the PBMC, transduced with TCRζ/4-1BB lentiviral vector, expanded *in vitro* and then frozen for future administration after passing all release tests.

Unless contraindicated and medically not advisable based on previous chemotherapy, patients will be given conditioning chemotherapy prior CART-19 cell infusion. The chemotherapy will be planned so that it completes 1-4 days BEFORE the planned infusion of the first dose of CART19 cells. Each regimen is of different duration so the start day will vary.

We will enroll 57 evaluable patients for the primary efficacy endpoint analysis. Primary efficacy evaluable patients are those who have received CART-19 cells at the protocol-specified dose (1-5x10^8 CART-19 cells). These patients will be evaluable for primary efficacy endpoints.

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 (2x10^7 CART-19 cells) and all other manufacturing release criteria are met. The subjects that are infused with ≥2x10^7-≤1x10^8 CART-19 cells 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 ≥2x10^7 CART-19 will be assessed for clinical response according to the criteria discussed in Sections 6.11 and 6.12. Again, patients scored as manufacturing failures and receiving ≥2x10^7-<1x10^8 CART-19 cells (e.g. the primary efficacy non-evaluable patients) will not be included in primary efficacy endpoint analysis (see Section 7). **Table 3-1** summarizes nomenclature, endpoint analysis and clinical evaluations for all possible CART-19 dose manufacturing and infusion scenarios.

All subjects will have blood tests to assess safety, engraftment and persistence of the CART-19 cells at regular intervals as outlined in the Schedule of Study Procedures (Section 15.1). Trafficking of CART-19 cells will be assessed in bone marrow aspirates if performed. Response assessments will also be performed for primary endpoint analysis as described in Section 6.11. Patients will be followed weekly for 4 weeks, monthly for 6 months, then quarterly for two years with a medical history, physical examination, blood tests and CT scans as outlined. Following this evaluation, subjects will enter a long-term follow-up study for annual follow-up by phone

and questionnaire for up to an additional thirteen years to assess the diagnosis of long-term health problems, such as development of new malignancy, as per the FDA guidelines.

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

Manufactured CART-19 Dose	Released from CVPF*? (Y/N)	Can subject be infused**? (Y/N)	Included in endpoint analysis? (Y/N)				Primary Efficacy Evaluable Patient Set; Followed according to SOE (Y/N)?
			Primary Efficacy	Secondary Efficacy	Correlative and Safety	Manufacturing Feasibility	
$1\text{-}5x10^8$	Y	Y	Y	Y	Y	Y	Primary Efficacy Evaluable; Y
$\geq 2x10^7$- $<1x10^8$	Y	Y	N	Y	Y	Y	Primary Efficacy Non-Evaluable; Y
$<2x10^7$	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**

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 that will be released from CVPF for infusion is $2x10^7$; 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 7.4.

In Penn's UPCC04409 adult CART-19 trial, $1.4x10^7$– 15.5 x 10^8 CART-19 cells have been administered. Complete responses have been achieved at both the highest and lowest dose levels. Though numbers are small over this wide range of cell doses, there is no evidence for either a dose:response or dose:toxicity relationship. Therefore, there is scientific and clinical justification for giving subjects the manufactured cell dose, even if below the protocol-specified dose range. Moreover, the minimum CART-19 dose release criteria ($\geq 2x10^7$ CART-19 cells) is higher than the lowest CART-19 dose that has been administered to date that has resulted in a complete response in a patient.

3.3 Primary Study Endpoints

This phase IIa trial is designed to test the efficacy of autologous T cells transduced with the CD19 TCRζ/4-1BB in patients with relapsed, refractory and incurable non-Hodgkin's lymphomas by describing the overall response rate (ORR) at 3 months. Responders will include those patients achieving complete response (CR), complete response unconfirmed (CRu) and partial response (PR) according to the Tumor Response Assessment defined in Section 6.11.

3.4 Secondary Study Endpoints

Secondary endpoints include laboratory measures to evaluate:

1. Engraftment, persistence and trafficking to tumor sites: These analyses will be performed using Q-PCR assays. The 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 after infusion on day 1, 2, and 3 weekly x 4, monthly x 6, and every 3 months thereafter until any 2 sequential tests are negative documenting loss of CART-19 cells.

2. The effects of CART-19 infusion on peripheral B cell levels and levels of CD19 antigen expression, as well as in marrow and other biopsy tissues. These analyses will be performed using multi-parametric flow cytometry

3. The impact of CART-19 treatment on systemic soluble immune factors will be evaluated by measuring systemic changes in soluble immune factors in patients post CART-19 infusion. These analyses will be performed using Luminex assays.

4. Determine if host immunity develops against the murine anti-CD19 or other elements of the transgene or vector such as VSV-G, and assess correlation with loss of detectable CART-19 (loss of engraftment). These analyses will be performed using multiparametric flow cytometry.

5. Determine phenotypic and functional evolution of CART-19 T cells in vivo. These analyses will be performed using multiparametric flow cytometry.

6. Evaluate MRD using molecular technologies. These analyses will be performed on nucleic acid isolated from patient samples pre- and post-treatment using quantitative molecular approaches.

Secondary safety and feasibility endpoints include:

1. Occurrence of study related adverse events, defined as NCI CTC $\geq$ grade 3 signs/symptoms, laboratory toxicities and clinical events that are possible, likely or definitely related to study treatment at any time from the infusion until week 24. this will include infusional toxicity, and any toxicity possibly related to the CART-19 cells including but not limited to:
    a. Fevers
    b. Rash

c. Neutropenia, thrombocytopenia, anemia, marrow aplasia
d. Hepatic dysfunction
e. Pulmonary infiltrates or other pulmonary toxicity
f. Cytokine release syndrome (CRS)
g. Macrophage activation syndrome (MAS)

2. Feasibility to manufacture CART-19 cells from patient apheresis products. The number of manufactured products that do not meet release criteria for vector transduction efficiency, T cell purity, viability, sterility and tumor contamination will be determined.
3. New onset secondary malignancies.
4. Describe anti-tumor responses to CART-19 cell infusions and survival.
    a. Describe overall response rate (ORR) for each individual histology with either murine CART19 or humanized CART19, as well as CR, CRu and PR rates.
    b. Describe overall survival (OS) and progression-free survival (PFS) for all patients
    c. Describe duration of response (DOR) for responding patients
5. Exploratory analyses to inform on dose-response activity, inclusive of subjects infused with the less than protocol-specified dose.
    a. For subjects with active disease, consensus response criteria for partial response (PR), complete response unconfirmed (CRu), or complete response (CR) will be determined. Response determination will be only "descriptive" given the small number of subjects to be treated. Exploratory analyses of available CT, MRI, and/or PET imaging datasets may also be performed (e.g., to assess whether there are imaging biomarkers that are obtainable from pretreatment scans to predict response to therapy).
    b. Describe the overall survival and cause(s) of death
    c. Evaluate MRD by deep sequencing or PCR of patient samples post-treatment
    d. For treated subjects with MRD (identified by analysis of blood or marrow), determine elimination of MRD scored as yes/no.

4 SUBJECT SELECTION AND WITHDRAWAL

No exceptions to eligibility will be granted for this study

4.1 Inclusion Criteria

Male or female subjects with CD19+ B cell lymphomas with no available curative treatment options (such as autologous or allogeneic SCT) who have a limited prognosis (several months to <2 year survival) with currently available therapies will be enrolled. The study will enroll 57 evaluable subjects as follows:

1. CD19+ Lymphoma
   <u>Cohort A Subjects:</u>
    a. Follicular lymphoma, previously identified as CD19+
        i. At least 2 prior chemotherapy or immunochemotherapy regimens (not including single agent monoclonal antibody therapy)
        ii. Patients who progress within 2 years after second or higher line of therapy will be eligible. For instance, patients who have progression of lymphoma < 2 years after second or greater line therapy, but who have responded to their most recent treatment (3rd line or higher) will be eligible. Patients may

have progression, stable disease or responding disease at the time of enrollment.
iii. Patients with a history of large cell transformation are eligible.

b. Mantle cell lymphoma, previously identified as CD19+
i. Beyond 1st CR with relapsed disease, progressive disease during first line rituximab-chemotherapy combination, or persistent disease after first line rituximab-chemotherapy combination and not eligible or appropriate for conventional allogeneic or autologous SCT.
ii. Relapsed after prior autologous SCT.

c. Diffuse large B cell lymphoma, previously identified as CD19+
i. Residual disease after primary therapy and not eligible for autologous SCT
ii. Relapsed or persistent disease after prior autologous SCT
iii. Beyond 1st CR with relapsed or persistent disease and not eligible or appropriate for conventional allogeneic or autologous SCT
iv. Patients with an antecedent history of follicular lymphoma or CLL/SLL are eligible.

Cohort B Subjects:

a. Diffuse large B cell lymphoma, previously identified as CD19+
i. Residual disease after primary therapy and not eligible for autologous SCT
ii. Relapsed or persistent disease after prior autologous SCT
iii. Beyond 1st CR with relapsed or persistent disease and not eligible or appropriate for conventional allogeneic or autologous SCT
iv. Patients with an antecedent history of follicular lymphoma or CLL/SLL are eligible.
v. Patients with T cell/histiocyte-rich disease as confirmed by surgical pathology report

Cohort C Subjects:

a. Diffuse large B cell lymphoma, previously identified as CD19+
i. Residual disease after primary therapy and not eligible for autologous SCT
ii. Relapsed or persistent disease after prior autologous SCT
iii. Beyond 1st CR with relapsed or persistent disease and not eligible or appropriate for conventional allogeneic or autologous SCT
iv. Patients with an antecedent history of follicular lymphoma or CLL/SLL are eligible.

2. Age ≥18 years
3. Creatinine < 1.6 mg/dL
4. ALT/AST < 3x upper limit of normal
5. Bilirubin <2.0 mg/dL, unless subject has Gilbert's Syndrome (≤3.0 mg/dL)
6. Any relapse after prior autologous SCT will make patient eligible regardless of other prior therapy.
7. Patients with relapsed disease after prior allogeneic SCT (myeloablative or non-myeloablative) 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

8. Measurable or assessable disease according to the "Revised Response Criteria for Malignant Lymphoma" (Cheson et al., *J. Clin. Onc.*, 1999)[110]. Patients in complete remission with no evidence of disease are not eligible.
9. Performance status (ECOG) 0 or 1.
10. Left Ventricle Ejection Fraction (LVEF) ≥ 40% confirmed by ECHO/MUGA
11. Written informed consent is given.
12. Successful T cell test expansion (first 10 subjects, see Section 6.1).

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 pregnancy test at enrollment. A urine pregnancy test will be performed within 48 hours before infusion.
2. Uncontrolled active infection.
3. Active hepatitis B or hepatitis C infection.
4. Concurrent use of systemic steroids. Recent or current use of inhaled steroids is not exclusionary. For additional details regarding use of steroids, please see Section 5.5.
5. Any uncontrolled active medical disorder that would preclude participation as outlined.
6. Class III/IV cardiovascular disability according to the New York Heart Association Classification (see Appendix 1).
7. HIV infection.
8. Patients with active CNS involvement by malignancy. Patients with prior CNS disease that has been effectively treated will be eligible providing treatment was >4 weeks before enrollment
9. Patients in complete remission with no assessable disease.
10. Patients with a known history or prior diagnosis of optic neuritis or other immunologic or inflammatory disease affecting the central nervous system.

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.

To be eligible, the subjects must have an adequate number of T cells that can be successfully transduced and expanded with the anti-CD19 lentiviral vector, as determined from a sample of PBMCs obtained by phlebotomy at the first screening visit (~week -8) for the first 10 subjects only. 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.

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 pregnancy test performed at the time of screening and a urine pregnancy test within 48 hours of T cell infusion.

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 at least one reliable method of contraception during their participation in the study (from the time of screening/enrollment through the Month 24 follow-up visit).

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, salpingotomy, and/or bilateral oophorectomy or men who have documented azoospermia) do not require use of contraception. Acceptable documentation of sterilization, azoospermia, and menopause is specified next:
Written or oral documentation communicated by clinician or clinician's staff of 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
- Laboratory report of azoospermia
- Follicle stimulating hormone measurement elevated into the menopausal range

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

1. Subjects who enroll but do not receive CART-19 cells will be prematurely discontinued from the study, will not be followed, and will be replaced in the study. Reasons for premature discontinuation prior to receipt of CART-19 cells include, but are not limited to, the following: The subject is lost to follow-up.
2. The judgment of the principal investigator that the patient is too ill to continue if this occurs prior to the CART-19 T-cell infusion.
3. Pregnancy: Withdraw patient if pregnancy occurs prior to the CART-19 T-cell infusion.
4. 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.
5. 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.
6. A serious adverse event that requires the subject's being withdrawn from the trial if this occurs prior to the CART-19 T-cell infusion.

7. 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.
8. Termination of the study by the principal investigator, the sponsor, the study funder, the IRB, or the Food and Drug Administration.

Reasons for discontinuation of subjects after receipt of CART-19 cells include, but are not limited to, the following:

1. The subject is lost to follow-up.
2. Voluntary withdrawal: a subject may remove himself/herself from the study at any time.
3. Disease progression of targeted malignancy
4. Receipt of alternative treatment for their targeted disease
5. Termination of the study by the Principal Investigator, the Sponsor, the Funding Sponsor, the IRB, ACC CTSRMC, ACC DSMC, DSMB, or the Food and Drug Administration.

The reasons for discontinuation (for example, voluntary withdrawal, toxicity, death) must be recorded on the case report form (CRF). Final study evaluations will be completed at the time of discontinuation.

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 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 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; or until the patient withdraws consent for clinical data collection, enrolls into a 15 year long-term follow-up protocol, or the end of the study (Last Subject/Last Visit).

Subjects who complete the 2 year follow-up as part of this protocol, or discontinue participation early for any reason, will be encouraged to enroll into a 15 year long term follow-up protocol to further evaluate long term adverse events related to the study product. Once subjects are enrolled on the long-term follow-up protocol, all follow-up data collection under this protocol will be discontinued.

In the event that a subject cannot return to the study site for follow-up visits because of subject preference or geographical concerns, the subject's primary care physician and/or local oncologist will be asked to provide information from the subject's medical record to the study team at protocol defined time points (including the results of any routine care examinations and/or laboratory assessments), and assist in the collection of protocol required blood samples (if applicable) which will be sent to the University of Pennsylvania for protocol required analysis. The subject and local provider will also be contacted via telephone by a member of the study team to assess any potential toxicity.

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 should be maintained 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.

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 a single infusion. 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, and rigors. In order to minimize these events, patients will receive premedication as instructed below in Section 5.4. Toxicities that could potentially occur but are unprecedented are primarily related to the gene transfer and are described in Section 8.4.2. 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

1. All patients must undergo a Respiratory Virus Panel (RVP) within 10 days prior to the planned CART-19 infusion. If the patient is positive for influenza, Tamiflu® or equivalent, should administered per package insert. The patient must complete treatment **prior** to receiving CART-19. The test does not need to be repeated prior to 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.
2. Patient should not experience a significant change in performance or clinical status compared to initial eligibility criteria that would, in the opinion of the treating physician, would 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 will have their infusion schedule delayed until these toxicities have resolved. 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: Positive blood cultures for bacteria, fungus, or virus.

5.3 Treatment Regimen

A single dose of CART-19 transduced T cells will be administered by i.v. infusion consisting of 1-5 x 10^8 cells transduced with the CD19 TCRζ/4-1BB vector. The infusion will be scheduled to occur approximately 1 to 4 days following chemotherapy. Cohorts A and B will receive murine CART19 and Cohort C will receive humanized CART19.

5.4 Preparation and Administration of Study Drug

Cell manufacturing is done according to Figure 3 under INDs [redacted]. 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 taken to the bedside for administration.

Package and Labeling

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.

Each infusion bag will be affixed with a label containing information regarding the dose, the method of manipulation, the vector and the following statements "FOR AUTOLOGOUS USE ONLY" And "Caution: New Drug- Limited by Federal Law to Investigational Use". In addition the label will have at least two unique identifiers. 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.

Cell thawing

The frozen cells will be transported in dry ice to the subject's bedside at the CTRC or Rhoads (or elsewhere at the Hospital of the University of Pennsylvania). The cells will be thawed at the bedside 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 at the time of infusion. 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 as specified below.

Premedication

Side effects following T cell infusions include transient fever, chills, and/or nausea. It is recommended that the subject be pre-medicated with 650mg acetaminophen and 25-50mg diphenhydramine hydrochloride prior to the 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. It is recommended that patients 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 T 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 unlikely event that the subject 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.

Administration
The infusion will take place at the Hospital of the University of Pennsylvania by a licensed Registered Nurse using precautions for immunosuppressed patients. The transduced T cells will be administered by rapid intravenous infusion at a flow rate of approximately 10mL to 20 ml per minute through a latex free Y-type blood set. 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.

Emergency medical equipment (i.e., emergency trolley) will be available during the infusion in case the subject has an allergic response, or severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, respiration rate, pulse, blood pressure, and oxygen saturation by pulse oximetry) will be measured within 10 minutes prior to the infusion and within 15 minutes after the infusion. Thereafter, vital signs will be measured at 30 (+/- 5) minutes, 45 (+/- 5) minutes, and 60 (+/- 5) minutes after the infusion, and then every hour (+/- 10 minutes) for the next 2 hours until these signs are satisfactory and stable. If the subject's vital signs are not satisfactory and stable three hours post-CART-19 infusion, vital signs will continue 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.

Return or Destruction of Study Drug
CART-19 cells may need to be returned to the CVPF for a variety of reasons, including but not limited to: 1) Mislabeled product; 2) Condition of patient prohibits infusion/injection, and 3) Subject refuses infusion. Any unused product will be returned to CVPF by CVPF personnel as per CVPF SOP.

There is an ongoing reconciliation of drug shipped, drug consumed, and drug remaining performed by the CVPF. Final disposition of the investigational product will also be documented in the site Investigational Product Accountability logs appropriately.

5.5 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 first dose up to Week 24 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.
- 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 infusion (refer to Section 5.4) or following CART-19 infusion unless under life threatening circumstances or at the physicians' discretion to manage CRS.

6 STUDY PROCEDURES

Overview

The study consists of 1) a screening phase, 2) followed by an intervention/treatment phase consisting of apheresis, chemotherapy and infusions of CART-19 cells, 3) 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 Section 15.1.

6.1 Pre-Entry Evaluations

After informed consent is obtained, blood test for HIV will be performed and a blood sample is sent to the CVPF for test expansion to determine T cell manufacturing feasibility. In approximately 1 week, the CVPF will provide the test expansion result indication whether the subject's PBMC are likely to be adequate for large scale CART-19 T cell manufacturing process. The test expansions will be done for the first 10 subjects enrolled.

6.2 Enrollment and Baseline Assessment.

In accordance with section 15.1, eligible subjects who have signed an informed consent and have adequate pre-screening evaluation will undergo a routine lymphoma staging workup including:

a. History and Physical Examination (including vital signs, height, weight), past and current medications, leukapheresis screening
b. Radiologic imaging (diagnostic CT or MRI scans) of the Chest, Abdomen, and Pelvis done within 12 weeks of study entry and after the subjects' last chemotherapy treatment. CT or MRI imaging of neck will be performed if required for disease evaluation.
c. Complete Blood Count, Differential and Platelet Count.
d. Chemistry Panel (Glucose, Ca, Mg, Phos, Alk Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, BUN, uric acid, Cr, ALT, AST and Lactate Dehydrogenase Level)
e. PT/INR, PTT
f. β2 Microglobulin Level, autoantibody panel (ANA and ESR)
g. Serum immunoglobulin levels
h. Serum pregnancy test for females of child bearing potential. Follicle stimulating hormone (FSH) test may be performed to confirm menopausal status.
i. ECOG performance status assessment

j. 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.
k. Bone marrow evaluation within 42 days of infusion; *and lymph node biopsy (optional)*
l. Documentation of CD19 expression.
m. A baseline cardiac ECHO/MUGA should be performed within 8 weeks of the first infusion.

6.3 Enrollment.

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

Protocol Monitor and Sponsor Project Manager [redacted]

Documents required:

- Complete Enrollment Form
- Copy of signed patient consent and HIPAA form
- Source documentation to confirm enrollment/eligibility

Upon receipt of screening and eligibility documentation, the Sponsor 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.

6.4 Apheresis

A 12-15 liters or 4-6 blood volumes or a target of $5x10^9$ apheresis procedure will be performed at the apheresis center. PBMC are obtained for CART-19 during this procedure. From a single leukapheresis, the intention is to harvest at least 5×10^9 white blood cells to manufacture CART-19 T cells. If a single apheresis does not yield the adequate number of cells for manufacturing, then subjects can undergo an additional apheresis as needed. Baseline blood leukocytes for FDA look-back requirements and for research are also obtained and cryopreserved. The cell product is expected to be ready for release approximately 4 weeks later. Flow cytometry lymphocyte subset quantitation, including CD19 and CD20 B cell determination.

Recommended criteria for apheresis product acceptance to initiate processing for clinical manufacturing to meet the dosing requirements includes the following specifications: A CBC with automated differential on the apheresis product following completion of collection that reports absolute lymphocyte count (ALC) ≥ 500/uL. If the ALC <500/uL in the apheresis product, it is recommended that the CD3 cell count should be ≥ 150/uL for acceptance to begin processing for clinical manufacturing to achieve the target dose.

Historical Apheresis Sample

Cryopreserved historical apheresis products collected from the patient prior to study entry are usable for CART-19 manufacturing if collected at an appropriately certified apheresis center and

the product meets adequate mononuclear cell yields. The 12 week window for the apheresis collection does not apply to historical samples (e.g. if an approved apheresis sample has been collected outside of the 12 week timeframe, this will not be considered a protocol violation/deviation. If a historical apheresis sample is used, the patient would not have to repeat the baseline apheresis. If a historical apheresis product is not available, an apheresis procedure (as described above) will be performed for cell procurement after study eligibility has been confirmed.

6.5 Cytoreductive chemotherapy

It is anticipated that many patients will have been receiving chemotherapy for relapsed or resistant lymphoma. Patients referred with stable disease on no recent therapy will also be eligible. For inclusion, patients will have responding or stable disease to their most recent therapy. Prior to CART-19 cell infusion, an additional chemotherapy cycle is planned. Patients referred with stable disease on no recent therapy will be eligible. The regimen of chemotherapy will be at the discretion of the investigator and dependent on the patient's disease burden, histology and past therapies.

Chemotherapy may include cyclophosphamide, fludarabine, bendamustine or any other appropriate combination chemotherapy.

The chemotherapy will be planned so that it completes approximately 1-4 days BEFORE the planned infusion of the first dose of CART19 cells. Each regimen is of different duration so the start day of chemotherapy will vary. 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[85, 86]. 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 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 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.

If it has been greater than 42 days since the subjects' previous radiologic disease assessment (performed for enrollment), a repeat CT/MRI of the chest/abdomen/pelvis is required prior to receiving cytoreductive chemotherapy. If it has been less than 42 days since the subjects' enrollment radiologic disease assessment, but the subject has received additional treatment during this time, a repeat CT/MRI of the chest/abdomen/pelvis is also required prior to receiving cytoreductive chemotherapy.

6.6 Pre-Infusion Visit

Subjects will undergo the following work-up including:

a) Current medical conditions and physical examination (including vital signs and weight)
b) ECOG performance status assessment
c) Concomitant medications
d) Hematology (complete blood count, differential and platelet count)
e) Chemistry panel (Glucose, Ca, Mg, Phos, Alk Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, BUN, uric acid, Cr, ALT, AST and Lactate Dehydrogenase Level)
f) Urine pregnancy test (Females only)
g) Baseline screens for HLH/MAS: ferritin, triglycerides, haptoglobin and CRP
h) Baseline screen for coagulation factors: PT, PTT, INR, fibrinogen, D-dimer
i) Research labs: HAMA and HACA testing, molecular labs (including VSV-G), cytokine and cellular assessments

6.7 CART-19 Infusion

Infusion begins approximately 1 to 4 days after completion of chemotherapy.

On day 0 prior to the infusion, patients will have a physical exam, medical history, performance status evaluation, CBC with differential, and assessment of CD3, CD4 and CD8 counts since chemotherapy is given in part to induce lymphopenia. If clinically indicated, coagulation labs (PT, PTT, INR, fibrinogen, D-dimer) and HLH/MAS labs (including ferritin, triglycerides, haptoglobin, and CRP) will be drawn.

Subjects will premedicated and administered the CART-19 T cells as described in section 5.4. The CART-19 cell dose will be administered by i.v. infusion. The cells are thawed at the patient's bedside. The thawed cells will be given at an infusion rate of 10 to 20 mL per minute. In order to facilitate mixing, the cells will be administered simultaneously using a Y-adapter or equivalent. Subjects' vital signs will be assessed and pulse oximetry will be measured within 10 minutes prior to dosing and within 15 minutes after the infusion. Thereafter, vital signs will be measured at 30 (+/- 5) minutes, 45 (+/- 5) minutes, and 60 (+/- 5) minutes after the infusion, and then every hour (+/- 10 minutes) for the next 2 hours until these signs are satisfactory and stable. If the subject's vital signs are not satisfactory and stable three hours post-CART-19 infusion, vital signs will continue 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.

A blood sample for determination of a baseline CART-19 level is obtained any time prior to the infusion and 20 minutes to 2 hours post each infusion (and sent to TCSL).

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.

6.8 Post infusion laboratories to assess engraftment, persistence and bioactivity

For molecular 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 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. 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.

Translational and Correlative Studies Laboratory

In accordance with Section 15.1, subjects will return to the clinic at days 1, 2, 7, 10, 14 and 21 to have blood drawn for serum cytokine levels, and CART-19 Q-PCR in order to evaluate the presence of CART-19 cells. At these visits, subjects will also undergo the following: physical exam, documentation of adverse events and blood draws for hematology, chemistry, engraftment and persistence of CART-19 cells and research labs. Additional research draws and/or lumbar punctures may be performed after CART-19 T cell infusion at the clinician's discretion (i.e. during CRS or other clinically indicated event) to study samples at peaks of bioactivity and/or clinical event, according to the treating physician's discretion.

Additionally, if a subject undergoes a tissue, lymph node biopsy, or lumbar puncture for clinical reasons, then remaining material may be analyzed for research purposes including, but not limited to, CART-19 persistence, trafficking and research MRD analyses.

6.9 Day 28: Engraftment Endpoint

A 60cc blood draw will be performed. PBMCs are obtained from this blood draw for research and will be cryopreserved in the TCSL. Subjects will undergo tests and procedures in accordance with the Schedule of Study Procedures in Section 15.1.

6.10 Monthly evaluations 2 to 6 months post infusion

Subjects will return to the clinic on a monthly basis during month 2 to 6 post CART-19 cell infusion. At these study visits, subjects will undergo tests and procedures in accordance with the Schedule of Study Procedures in Section 15.1.

6.11 Quarterly evaluations after 6 months for up to 2 Years Post Infusion

After month 6, subjects will be evaluated on a quarterly basis until 2 years post infusion. At these study visits, subjects will undergo tests and procedures in accordance with the Schedule of Study Procedures in Section 15.1.

6.12 Secondary Follow-up Phase

Subjects who complete or prematurely discontinue from the Primary Follow-up Phase, who do not enroll in a separate 15 year long-term follow-up protocol, will continue to be followed in the Secondary Follow-up Phase of this study until the subject withdraws consent, the subject enrolls in a long-term follow-up protocol, or the end of the study (Last Patient/Last Visit), whichever occurs first.

Secondary follow-up assessments will be performed every 3 months and consist of the following:

- Progression-free survival (PFS) - in patients who discontinue from Primary Follow-up in remission. Subjects will continue to be followed for PFS until disease progression or they begin a new cancer therapy (with the exception of alloSCT).
- Survival Follow-up Status

Additional research blood may also be collected. The total amount of extra blood that may be collected will not exceed 3 tablespoons of blood twice in one week. In addition, portions of bone marrow aspirates that are performed during Secondary Follow-up for clinical disease monitoring may be provided to TCSL for correlative studies.

6.13 Long-term Follow-up Protocol

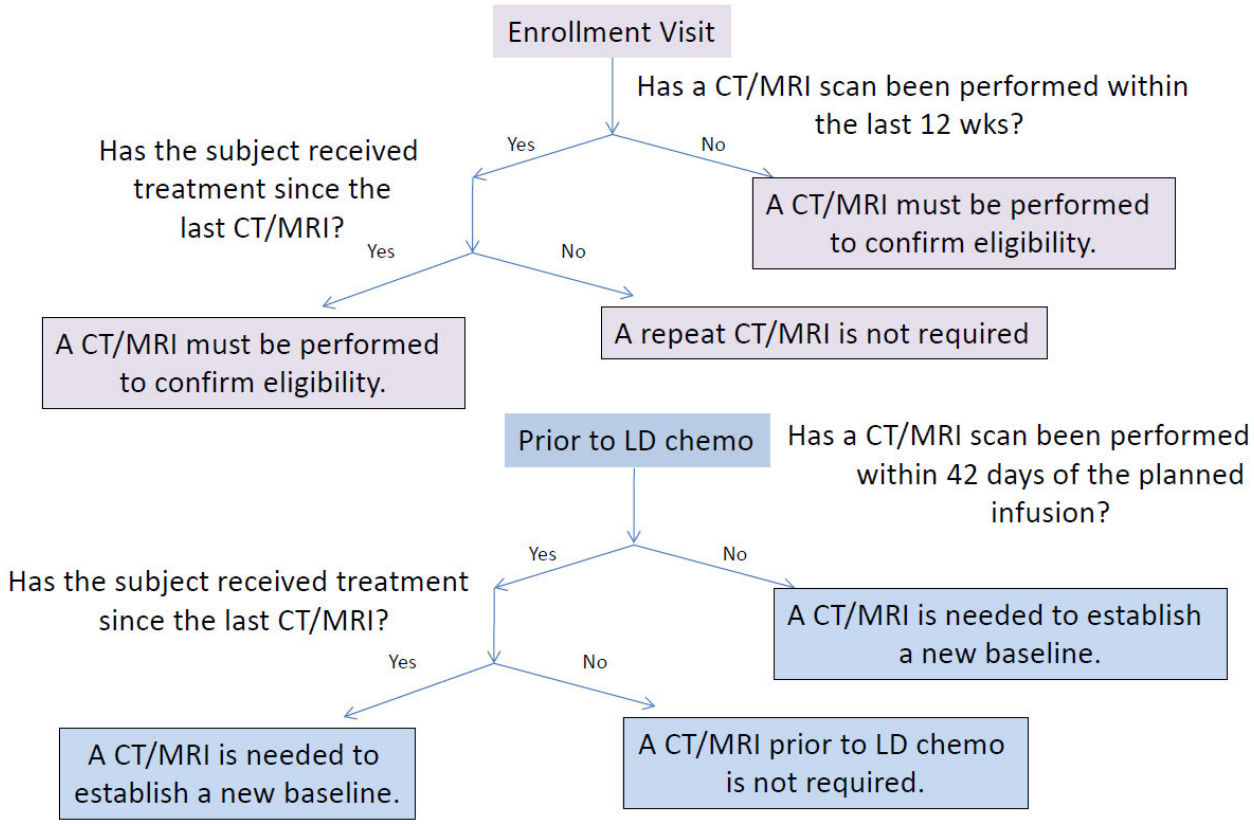
After subjects complete or prematurely discontinue participation in this study, subjects will be asked to participate in a separate 15 year long-term follow-up destination protocol to further evaluate long-term adverse events related to the study product. Once subjects are enrolled on the long-term follow-up protocol, all follow-up data collection under this protocol will be discontinued.

6.14 Tumor Assessments

Baseline and subsequent tumor assessments will be performed according to standard of care practice, using anatomic imaging to assess tumor volume by CT or MRI. Tumor measurements will be done at the University of Pennsylvania within 12 weeks prior to study entry. These enrollment scans must be performed after the subjects' last chemotherapy treatment. In addition, if it has been greater than 42 days since the subject's previous radiologic disease assessment (performed for enrollment), a repeat CT/MRI of the chest/abdomen/pelvis is required prior to receiving cytoreductive chemotherapy. If it has been less than 42 days since the

subjects' enrollment radiologic disease assessment, but the subject has received additional treatment during this time, a repeat CT/MRI of the chest/abdomen/pelvis is also required prior to receiving cytoreductive chemotherapy. Please see Figure 4 below for complete details.

Figure 4:



Patients will have imaging assessments for tumor response every 3 months post-infusion for the first year, every 6 months during the second year. Functional imaging (^{18}FDG-PET/CT) may be used at the discretion of the treating physician if in the opinion of the treating investigator it is more clinically appropriate (for example- to assess certain extranodal sites like bone marrow or to confirm complete response). Exploratory analyses of available CT, MRI, and/or PET imaging datasets may also be performed (e.g., to assess whether there are imaging biomarkers that are obtainable from pretreatment scans to predict response to therapy). Tumor response assessments will be done by a dedicated independent radiologist and the Principal Investigator. Tumor response assessments are based on the patient's underlying disease anatomy using the following response definitions. Measurable disease is defined per Cheson et al., 1999)[110]. Final response assessments will be based on Cheson 2007 criteria[111].

CHESON 2007 RESPONSE DEFINITIONS:

Complete Response (CR):

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Complete Response Unconfirmed (CRu):

The use of the above definition for CR and that below for PR eliminates the category of CRu.

Partial Response (PR):

The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and

they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
   When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD):

Stable disease (SD) is defined as the following:
1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD):

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 × ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Table 4- Tumor Response Assessment Criteria from Cheson et al., 2007

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of		

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
		disease and no new sites on CT or PET		
		(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
		Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy		

7 STATISTICAL PLAN

7.1 General Design Issues

This is an open label, Phase IIa study to provide exploratory data on the efficacy of CART-19, in patients with chemotherapy relapsed or refractory CD19+ lymphoma. Failure to complete the study due to the treatment limiting toxicity being invoked will be the main basis for determining safety and feasibility.

Upon enrollment, patients will undergo leukapheresis. Between leukapheresis and CART-19 infusion, patients may undergo an additional chemotherapy treatment at the treating physician's discretion. At dosing, patients will receive CART-19 cells, and will be monitored weekly for four weeks. Observation and monitoring of patients will continue on a monthly basis until week 24 post dosing. Quarterly evaluations will follow from this point up to two years. After two years, annual follow-up for lentiviral vector safety will be carried out under a separate destination protocol for 15 years post infusion in accordance with FDA guidelines for retroviral vectors.

Sixty evaluable subjects will be targeted for this study, with an expected rate of drop out of up to 20-30% due to disease progression between enrollment and the week twelve post-dosing response assessment (this will take about 22-24 weeks for screening-apheresis-dosing-to the final

12 week endpoint). Additionally, we anticipate an approximately 20% screen failure rate due to subjects not meeting eligibility criteria (e.g., unsuccessful cell expansion screen test) based on our current experience. Thus, approximately 94 subjects will be screened so that sufficient subjects will be enrolled to ensure at least 60 subjects evaluable at the week 12 post-dosing response assessment.

7.2 Sample Size

A total of 60 evaluable subjects will be planned for analysis of the primary endpoints, Subjects are enrolled in 3 cohorts. Sample sizes are determined by practical considerations and to obtain useful pilot data with which to estimate safety and efficacy in each of the disease and treatment sub-cohorts. Cohort A has 39 evaluable subjects: with a minimum of 20 with diffuse large B cell lymphoma (DLBCL) and a minimum of 16 who have either follicular lymphoma (FL) or mantle cell lymphoma (MCL) (enrolled on a first come first-served basis). Cohort B has 7 evaluable subjects with DLBCL and T cell/histiocyte-rich disease. Cohort C has 14 evaluable subjects with DLBCL treated with humanized CART19.

The primary endpoint of this study is overall response (i.e. either complete response or partial response) evaluated at three months post infusion. For cohort A, the following table displays the exact 95% confidence interval (CI) with various observed ORR.

Table 7.2-1 Potentially observed Overall response rate (ORR) and exact 95% Confidence interval for Cohort A

Cohort A: N=39 Evaluable Subjects	
Observed ORR	95% Exact Confidence Interval
0% (0/39)	(0%, 9.0%)*
12.8% (5/39)	(4.3%,27.45%)
25.6% (10/39)	(13.0%,42.1%)
38.5% (15/39)	(23.4%,55.4%)
46.2% (18/39)	(30.1%,62.8%)
51.3% (20/39)	(34.8%,67.7%)
64.1% (25/39)	(47.2%,78.8%)
76.9% (30/39)	(60.7%,88.9%)
89.7% (35/39)	(75.8%, 97.1%)
100% (39/39)	(91.0, 100%)*

*one-sided, 97.5% confidence interval

Based on **Table 7.2-1**, if 18 out of 39 evaluable subjects have partial or complete response at 3 month, we will have strong evidence (i.e., 95% confidence) that the true ORR following CART-19 infusion is at least above an ORR of 30%, which would be considered clinically significant in this patient population. In addition, overall response rate for each of the three histology types will be analyzed as a secondary objective in an exploratory analysis. There will be a minimum of 20 evaluable subjects with DLBCL and a minimum of 16 evaluable subjects with either FL or MCL. **Table 7.2-2** displays the exact 95% confidence interval (CI) with various observed ORR among 7, 14, and 20 evaluable subjects, from the different subgroups of interest. For example, if

71% (5/7) of individuals are observed to has an ORR in Cohort B (N=7), then the 95% Confidence interval is (29%,96%), then with 95% confidence we will be able to rule out an ORR of <29%.

Table 7.2-2 Potentially observed Overall response rate (ORR) and exact 95% Confidence interval for different subgroup sizes.

N=7 evaluable		N=14 evaluable		N=20 evaluable	
Observed ORR	95% Exact CI	Observed ORR	95% Exact CI	Observed ORR	95% Exact CI
29% (2/7)	(4%, 71%)	29% (4/14)	(8%, 58%)	25% (5/20)	(9%, 49%)
43% (3/7)	(10%, 82%)	36% (5/14)	(13%, 65%)	30% (6/20)	(12%, 54%)
57% (4/7)	(18%, 90%)	43% (6/14)	(18%, 71%)	35% (7/20)	(15%, 59%)
71% (5/7)	(29%, 96%)	50% (7/14)	(23%, 77%)	40% (8/20)	(19%, 64%)
86% (6/7)	(42%, 100%)	57% (8/14)	(29%, 82%)	50% (10/20)	(27%, 73%)
100% (7/7)	(59%, 100%)	71% (10/14)	(42%, 92%)	60% (12/20)	(36%, 81%)
		86% (12/14)	(57%, 86%)	75% (15/20)	(51%,91%)
		100% (14/14)	(77%,100%)	85% (17/20)	(62%,97%)
				100% (20/20)	(83%,100%)

The safety endpoint of grade 3-4 toxicity (toxicity possibly attributed to CART-19 T cells) that is unmanageable, unexpected and unrelated to chemotherapy and attributable to protocol therapy will be also be analyzed. Evaluable subjects for safety points will be analyzed by CART19 treatment group, murine (cohorts A and B) and humanized (cohort C), because we do not expect the CART-19 related toxicity may differ in different histology types. The 95% confidence intervals will be similar to those presented in Tables 7.2-1 and 7.2-2. Given at least 46 evaluable subjects in cohorts A and B and a maximum acceptable toxicity rate of 30%, the probability to observe no (i.e., 0), 4, 8, and 12 treatment limiting toxicities (i.e., a TLT rate of 0%, 9%, 17%, and 26%) will be <0.0001%, 0.04%, 2.2%, and 11.2%, respectively. If the true underlying toxicity rate decreases to 10%, then the above probabilities become 0.78%, 19.5%, 4.8%, and 0.11%, respectively. For Cohort C, with n=14, and a maximum acceptable toxicity rate of 30%, the probability to observe no (i.e., 0), 1, 2 and 3 treatment limiting toxicities (i.e., a TLT rate of 0%, 7%, 14%, and 21%) will be 0.7%, 4.1%, 11.3% and 22.9%, respectively. If the true underlying toxicity rate decreases to 10%, then the above probabilities become 22.9%, 35.6%, 25.7%, and 3.5 %.

7.3 Accrual

Accrual is anticipated to take approximately 36-48 months.

7.4 Subject Population(s) for Analysis

- The **Enrolled Set** comprises all patients who sign an informed consent form and are enrolled in the study, excluding screen failure patients.
- The **Efficacy Evaluable Set** comprises all patients who receive the CART-19

cells at the intended dose range 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. These are the primary efficacy evaluable patients as defined below. The Efficacy Evaluable Set will be used for the primary efficacy endpoint analysis.

- The **Full Analysis Set (FAS)** comprises all patients who received the CART-19 cells. This set includes both primary efficacy evaluable and non-evaluable patients as defined below. The Full Analysis Set will be used for the secondary efficacy, safety and correlative endpoints or other exploratory analyses.

Definitions relevant to the Analysis Sets:

1) **Screening failure -** Any patient who fails to meet the inclusion/exclusion criteria specified by the protocol.
2) **Manufacturing failure** – Any patient who has manufactured CART-19 cells that do not meet the manufacturing release criteria or the minimum protocol-specified dose ($1x10^8$ CART-19 cells).
3) **Primary efficacy evaluable patient** – Any patient who is infused with the CART-19 cells at the protocol-specified dose ($1\text{-}5x10^8$) 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.
4) **Primary efficacy non-evaluable patient** – Any patient who is infused with the CART-19 cells at less than the protocol-specified dose. These patients are also counted as manufacturing failures.

7.5 Statistical Analysis

Descriptive statistics will be computed for all study variables for the evaluable populations as whole and within cohort and histology subgroups. Primary endpoint of overall response will be summarized as overall response rate (ORR) and 95% exact confidence interval will be calculated based on binomial distribution. All adverse events will be described and exact 95% confidence intervals will be produced for adverse event rates, both overall and within major categories. Overall survival, progression-free survival, and duration of response will be analyzed using Kaplan-Meier curves. Median survival time and survival probability at selected time points (e.g., 3 month) will be computed with associated confidence interval. To evaluate the persistence of CART-19 (or its subsets), the within-subject change in the ratio of CART-19 cells (or other subsets) between two pre-specified time points will be compared using a Wilcoxon signed-rank test, or to simultaneously analyze multiple times, linear mixed effects model methodology will be used. The use of the nonparametric test is very efficient (>95%) compared to the t-test if the underlying data are normally distributed. Other secondary endpoints in this trial are all measured as continuous variable and can be analyzed in a similar fashion using nonparametric Wilcoxon signed-rank test. All the analyses will be two-sided and cut-off for statistical significance will be 5%.

The number of patients enrolled versus the number of patients infused will be described and is a measure of the feasibility of this therapy. Proportion of subjects with manufacturing failure will be computed.

8 SAFETY AND ADVERSE EVENTS

8.1 Definitions

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. Intercurrent illnesses or injuries should be regarded as adverse events.

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
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Note that hospitalizations that meet the following criteria should not be reported as serious adverse events:

- 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
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse 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 prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in 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***.

Unexpected adverse events
An adverse event is considered unexpected (or unanticipated) if the event severity and/or frequency is not described in the investigator brochure and/or protocol (in the absence of an Investigator Brochure). Please refer to the investigator brochure for additional detail related to severity and/or frequency of a particular event.

Related adverse events
An adverse event is considered related to participation in the research if there is a reasonable possibility that an event was caused by an investigational product, intervention or research-required procedures. For the purposes of this study, "reasonable possibility" means there is evidence to suggest a causal relationship.

Treatment Limiting Toxicity (TLT)
Treatment limiting toxicity is defined as an unexpected grade 3 or 4 non-hematologic toxicity probably related to the CART-19 infusion (for instance grade 4 neutropenia or thrombocytopenia related to pre-infusion chemotherapy would not be related to study drug and would not be considered as TLT).

Adverse Event Reporting Period
For this study, collection of adverse events will begin on Day 0 (from the start of the CART-19 infusion) and continue until the subject is off study or until the year 2 end of study visit. 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.

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. Any SAEs experienced after this 30 day period should be reported to the sponsor if the investigator suspects a causal relationship to the study treatment.

Preexisting Condition/General Physical Examination Findings
A preexisting condition is one that is present at the start of the study. At screening, any clinically significant abnormality should be recorded as a preexisting condition on the medical history eCRF. During the course 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. Preexisting conditions that improve should also be recorded appropriately.

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
- 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 above and/or as per investigator's discretion. Whenever possible, a diagnosis, rather than a symptom should be provided (i.e. anemia instead of low hemoglobin).

8.2 Recording of Adverse Events

Safety will be assessed by monitoring and recording potential adverse effects of the treatment using the Common Toxicity Criteria version 4.03 at each study visit. Subjects 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, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject, the investigator must seek information on adverse events by specific 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 in the source documentation. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be 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 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 8.1 above) must be recorded.

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

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (start and end dates)
3. Its relationship to the study treatment - [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment- [Unexpected- if the event severity and/or frequency is not described in the investigator brochure and protocol (in the absence of an investigator brochure)].
5. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

6. Whether medication or therapy taken (i.e. no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether it is serious; as defined in Section 8.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded. 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.
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. Progression of malignancy resulting in death should be reported as a serious adverse event.

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.

Grading System for Cytokine Release Syndrome (CRS)
A protocol specific grading system (**Table 8-1**) has been developed to capture cytokine release syndrome (CRS) in CAR T-cell protocols. Please refer to section 1.5.2 for additional detail on CRS in CAR T-cell therapy.

For the purposes of reporting and grading on clinical trials using CART-19 cells, we will use the following grading for CRS Toxicity. 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. For the purposes of defining the CRS start date, a fever is defined as a temperature of 100.4°F/38°C.

Table 8-1 - CRS Toxicity Grading				
1	2	3	4	5
Mild reaction: Treated with supportive care such as anti-pyretics, anti-emetics	Moderate reaction requiring IV fluids or parenteral nutrition; some 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.	More severe reaction: Hospitalization required for management of symptoms related to 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.	Life-threatening complications such as hypotension requiring high-dose pressors (see Table 8-2) or hypoxia requiring mechanical ventilation.	Death

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

Table 8-2 High Dose Vasopressor Use

Definition of "High-Dose" Vasopressors	
Vasopressor	Dose for ≥ 3 hours
Norepinephrine monotherapy	≥ 0.2 mcg/kg/min or ≥ 20 mcg/min (if institutional practice is to use flat dosing)
Dopamine monotherapy	≥ 10 mcg/kg/min or ≥ 1000 mcg/min (if institutional practice is to use flat dosing)
Phenylephrine monotherapy	≥ 2 mcg/kg/min or ≥ 200 mcg/min (if institutional practice is to use flat dosing)
Epinephrine monotherapy	≥ 0.1 mcg/kg/min or ≥ 10 mcg/min (if institutional practice is to use flat dosing)
If on vasopressin	High-dose if vaso + Norepinephrine Equivalent (NE) of > 0.1 mcg/kg/min (or >10 mcg/min) (using Vasopressin and Septic Shock Trial (VASST) formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 0.2 mcg/kg/min (or ≥ 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[113].

8.3 Reporting of Serious Adverse Events

Every SAE, **regardless of suspected causality**, occurring during the adverse event reporting period defined in Section 8.1 above must be reported to the sponsor within 24 hours of learning of its occurrence. The original SAE notification may take place by email to meet the 24 hour reporting window. However within 3 business days of knowledge of the event, the investigator must submit a complete SAE form to the Sponsor along with 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.

Follow-up information on SAEs should be reported when updates are available, as a follow-up to the initial SAE form, and should include both the follow-up number and report date. New information on ongoing serious adverse events should be provided promptly to the sponsor. The follow-up information should describe whether the event has resolved or continues, if there are any changes in assessment, if and how it was treated, and whether the patient continued or withdrew from study participation.

Report serious adverse events by email to:

Attention: Sponsor Clinical Safety Manager or designee

[redacted]

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
- Expectedness relative to investigational product(s)

8.3.1 Investigator reporting: notifying the Penn 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

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.
- 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.

8.3.2 Reporting obligations to the DSMC of the ACC

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:

- Unless covered by exclusions below, grade 3 or higher events must be reported within 10 days of knowledge of the adverse event.
  Exceptions:
  - 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.
  - All grade 3 or 4 events that are judged by a study investigator to be clearly unrelated to protocol therapy.
  - Grade 3 or 4 events that are probably or definitely related to progression of disease as judged by the study investigator.
  - Grade 3 or 4 events that are probably or definitely related to an FDA approved agent.
- All unexpected deaths within one business day of knowledge
- All others deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

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.

8.3.3 IBC Notification by Investigator

Notify the Institutional Biosafety Committee of serious adverse events according to institutional requirements.

8.3.4 FDA Notification by Sponsor

The study 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 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 an 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 8-1
- 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.

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 Sponsor will report the SAE in the IND Annual Report.

8.3.5 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the regulatory sponsor within 24 hours of learning of its occurrence. The pregnancy must 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 Study Pregnancy Form and reported by the investigator to the regulatory sponsor. Pregnancy follow-up should be recorded on the same form and must include an assessment of the possible relationship to the study treatment of 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.

8.4 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 probably related to the CART-19 cells would define a stopping rule.

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, determination that there are problems in the cell product generation, as a result of safety concerns, or at the discretion of the Sponsor or study investigators. Additionally, recruitment may be stopped for reasons of particularly low recruitment, protocol violations, or inadequate data recording.

8.4.1 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 independent review board or regulatory body decides for any reason that subject safety may be compromised by continuing the study.
- 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 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 CART-19 infusion.
    - Life-threatening (grade 4) toxicity attributable to protocol therapy that is unmanageable, unexpected and unrelated to chemotherapy and attributable to CART-19 infusion. We expect high fevers, hypotension, possible ICU admission and even mechanical ventilation. 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 and any proposed

modifications, then the pause will be lifted.

The protocol manufacturing will be paused to review the manufacturing process should there be ≥33% primary efficacy non-evaluable patients (i.e. the manufacturing process fails to meet the protocol-specified dose range of 1-5x10^8 CART-19 cells).

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.

8.4.2 General 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 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 DNA assay for detection of the lentivirus (for example: HIV gag DNA or VSV-G DNA). If a positive RCL DNA assay result is obtained, the PI will be informed and the subject 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 subjects 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 RCL testing for detection and/or characterization of the RCL.

- **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[112]. 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[113]. The lentiviral vector used for CART19 manufacturing is part of a vector class that may have a lower risk for integration in or near oncogenic regions than oncoretroviral vectors[114]. As of March 2014, none of the patients treated with CART19 have developed a new malignancy, T cell or otherwise, related to lentiviral vector integration. Subjects will be monitored for evidence of unexpected CART19 expansion by CART19 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 CART19 expansion is observed (i.e. CART19 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 CART19 expansion and/or a new malignancy arises. Subjects will 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 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. T body associated toxicity has been reported to respond to systemic corticosteroids[95]. If uncontrolled T cell proliferation occurs (grade 3 or 4 toxicity related to CART-19 cells), subjects may 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 an expected "on target" effect of the CART-19 cells. B cell depletion is common with anti-CD20 directed therapies[115]. B cell depletion has been observed in CLL and ALL patients treated with CART-19 cells. 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.

  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. This resulted in rapid reversal of the high persistent fevers 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

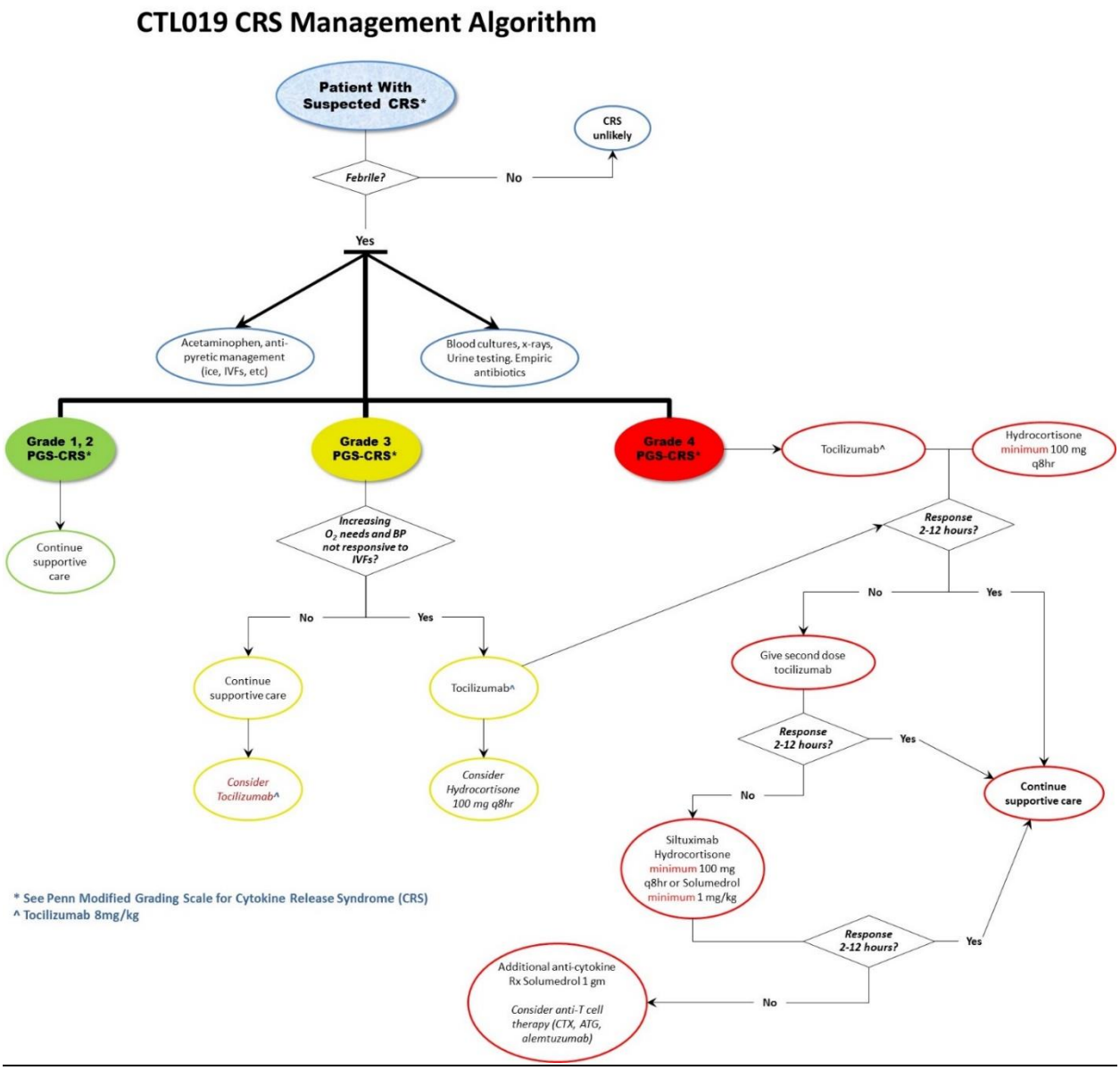
The recommended dosing for tocilizumab is 8 mg/kg i.v. single dose. Not all Grade 4 CRS reactions following CART-19 have been immediately treated with tocilizumab and decisions are, in part, based upon the rapidity of the syndrome onset and underlying patient reserve.

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*. **Refer to Figure 8-1 below for a CRS Management Algorithm.**

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 8.1 and **Table 8-1** for modified definitions of grading of CART-19 delayed CRS events.

Figure 8-1 CRS Management Algorithm



- **Tumor lysis syndrome.** Patients will receive allopurinol for 28 days to prevent complications from TLS. For patients with an allergy to allopurinol, febuxostat may be used at the discretion of the treating physician. TLS resulting in renal insufficiency, or rapidly rising uric acid level, or evidence of organ dysfunction will be managed with fluids and rasburicase as needed and as determined by the treating physicians.
- **GVHD.** The chance of GVHD occurring is low, but it is a potential risk with CART-19 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)[116]. ALL patients treated to date with autologous CART19 therapy who had prior allogeneic hematopoietic SCT with residual donor chimerism have developed GVHD after autologous CART19 infusion[117]. Patients treated with CART-19 post allogeneic SCT will be monitored for GVHD.

8.4.3 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.

8.5 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 approval from the Regulatory Sponsor, IRB, ACC DSMC and other local regulatory review committees per institutional guidelines is required. Approval from the Regulatory Sponsor must be received prior to submission to the IRB, ACC DSMC and local regulatory review committees for approval.

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.

No exceptions to eligibility will be granted for this study.

Deviation
A one time, **unintentional** action or process that departs from the 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 Regulatory Sponsor and ACC DSMC within 5 business days and the IRB within 10 business days of PI knowledge.

Any departure from the protocol that meets the following criteria is a protocol deviation and 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

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
[redacted]

The Sponsor Project Manager will submit the exception request or deviation notification 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.

Other deviations should be explained in a memo to file (such as a subject missing a visit- unless a critical/important treatment or procedure was missed and must have been done at that specific time).

8.6 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 10 Study Monitoring, Auditing 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 event 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 the study team's awareness.
- Deviations reported to the regulatory sponsor, ACC DSMC and IRB as they occur
- Exceptions prior to submission to the IRB and ACC DSMC
- 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.

8.6.1 Independent Data and Safety Monitoring Board

An Independent Data and Safety Monitoring Board (DSMB) comprised of a minimum of four individuals including physicians with experience in oncology and/or gene transfer therapy and a statistician will be assembled, and will work under a charter specifically developed for safety oversight of this study. The DSMB will provide guidance/advice to the Sponsor. The DSMB will evaluate patient-subject safety as specified in the DSMB Charter.

The DSMB will meet approximately every 4 months. 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 a DSMB outcome letter to the PI via email within 10 business days of receipt of the approved minutes, for submission to local regulatory review committees as required per institutional policy.

9 DATA HANDLING AND RECORDKEEPING

9.1 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.

9.2 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.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All entries will be entered into an electronic data capture system (EDC). 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.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

This study will be monitored according to the Sponsor Data and Safety Monitoring Plan.

Interim Monitoring Visits will be conducted during the course of the study. The 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 subject 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. 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.

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 (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 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.

Please notify the Sponsor in real-time if an audit/inspection notification is received.

11 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA 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 sponsor before commencement of this study.

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.

The protocol is listed under clinicaltrials.gov.

12 STUDY FINANCES

12.1 Funding Source

This study will be funded by Novartis Pharmaceuticals.

12.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

12.3 Subject Stipends or Payments

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

12.4 Study Discontinuation

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

13 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 study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

14 REFERENCES

Reference List

1. *Surveillance, Epidemiology, and End Results (SEER) Program of the NCI. 2006.*
Ref Type: Internet Communication

2. *Gisselbrecht C, Mounier N. Novel Agents for Diffuse Large B-cell Lymphoma. 321. 2011. ASCO Education Book.*
Ref Type: Report

3. *Lenz G, Wright GW, Emre NC, Kohlhammer H, Dave SS, Davis RE et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc. Natl. Acad. Sci. U. S. A 2008; 105: 13520-13525.*

4. *Gisselbrecht C, Glass B, Mounier N, Singh GD, Linch DC, Trneny M et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J. Clin. Oncol. 2010; 28: 4184-4190.*

5. *Cortelazzo S, Rambaldi A, Rossi A, Oldani E, Ghielmini M, Benedetti F et al. Intensification of salvage treatment with high-dose sequential chemotherapy improves the outcome of patients with refractory or relapsed aggressive non-Hodgkin's lymphoma. Br. J. Haematol. 2001; 114: 333-341.*

6. *Singer CR, Goldstone AH. Clinical studies of ABMT in non-Hodgkin's lymphoma. Clin. Haematol. 1986; 15: 105-150.*

7. *Marcus R, Hagenbeek A. The therapeutic use of rituximab in non-Hodgkin's lymphoma. Eur. J. Haematol. Suppl 2007: 5-14.*

8. *Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006; 107: 265-276.*

9. *. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997; 89: 3909-3918.*

10. *Hans CP, Weisenburger DD, Vose JM, Hock LM, Lynch JC, Aoun P et al. A significant diffuse component predicts for inferior survival in grade 3 follicular lymphoma, but cytologic subtypes do not predict survival. Blood 2003; 101: 2363-2367.*

11. *Lymphoma Research Foundation. National comprehensive clinical network clinical practice guidelines in oncology (NCCN guidelines) Non-Hodgkin's Lymphoma. 2011.*
Ref Type: Online Source

12. *Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J. Clin. Oncol. 2005; 23: 3383-3389.*

13. *Peterson BA, Petroni GR, Frizzera G, Barcos M, Bloomfield CD, Nissen NI et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J. Clin. Oncol. 2003; 21: 5-15.*

14. *Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005; 106: 3725-3732.*

15. *Czuczman MS, Koryzna A, Mohr A, Stewart C, Donohue K, Blumenson L et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. J. Clin. Oncol. 2005; 23: 694-704.*

16. *Colombat P, Salles G, Brousse N, Eftekhari P, Soubeyran P, Delwail V et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood 2001; 97: 101-106.*

17. *Hainsworth JD. First-line and maintenance treatment with rituximab for patients with indolent non-Hodgkin's lymphoma. Semin. Oncol. 2003; 30: 9-15.*

18. *Salles G, Seymour JF, Offner F, Lopez-Guillermo A, Belada D, Xerri L et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011; 377: 42-51.*

19. *Sehn LH, Fenske TS, Laport GG. Follicular lymphoma: prognostic factors, conventional therapies, and hematopoietic cell transplantation. Biol. Blood Marrow Transplant. 2012; 18: S82-S91.*

20. *Fisher RI, DeVita VT, Hubbard SP, Simon R, Young RC. Prolonged disease-free survival in Hodgkin's disease with MOPP reinduction after first relapse. Ann. Intern. Med. 1979; 90: 761-763.*

21. *Tinmouth A, Zanke B, Imrie KR. Fludarabine in alkylator-resistant follicular non-Hodgkin's lymphoma. Leuk. Lymphoma 2001; 41: 137-145.*

22. *Witzig TE, Wiernik PH, Moore T, Reeder C, Cole C, Justice G et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J. Clin. Oncol. 2009; 27: 5404-5409.*

23. *Di BN, Taetle R, Kolibaba K, Boyd T, Raju R, Barrera D et al. Results of a phase 2 study of bortezomib in patients with relapsed or refractory indolent lymphoma. Blood 2010; 115: 475-480.*

24. *Czuczman MS, Fayad L, Delwail V, Cartron G, Jacobsen E, Kuliczkowski K et al. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. Blood 2012; 119: 3698-3704.*

25. *Fisher RI, Kaminski MS, Wahl RL, Knox SJ, Zelenetz AD, Vose JM et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J. Clin. Oncol. 2005; 23: 7565-7573.*

26. *Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84: 1361-1392.*

27. *Van Den Berghe H, Parloir C, David G, Michaux JL, Sokal G. A new characteristic karyotypic anomaly in lymphoproliferative disorders. Cancer 1979; 44: 188-195.*

28. *Williams ME, Swerdlow SH, Rosenberg CL, Arnold A. Characterization of chromosome 11 translocation breakpoints at the bcl-1 and PRAD1 loci in centrocytic lymphoma. Cancer Res. 1992; 52: 5541s-5544s.*

29. *Dreyling M, Hiddemann W. Current treatment standards and emerging strategies in mantle cell lymphoma. Hematology. Am. Soc. Hematol. Educ. Program. 2009: 542-551.*

30. *O'Connor OA, Vose JM. Getting the Facts: Mantle Cell Lymphoma. 2008. Lymphoma Research Foundation.*

Ref Type: Online Source

31. *Armitage JO. Management of mantle cell lymphoma. Oncology (Williston. Park) 1998; 12: 49-55.*

32. *Schwonzen M, Pohl C, Steinmetz T, Seckler W, Vetten B, Thiele J et al. Immunophenotyping of low-grade B-cell lymphoma in blood and bone marrow: poor correlation between immunophenotype and cytological/histological classification. Br. J. Haematol. 1993; 83: 232-239.*

33. *Scheuermann RH, Racila E. CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. Leuk. Lymphoma. 1995; 18: 385-397.*

34. *Freedman AS, Boyd AW, Bieber FR, Daley J, Rosen K, Horowitz JC et al. Normal cellular counterparts of B cell chronic lymphocytic leukemia. Blood 1987; 70: 418-427.*

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

36. *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.*

37. *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.*

38. *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: 1205-1210.*

39. *Uckun FM, Jaszcz W, Ambrus JL, Fauci AS, Gajl-Peczalska K, Song CW 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: 13-29.*

40. *Messinger Y, Yanishevski Y, Avramis VI, Ek O, Chelstrom LM, Gunther R 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: 1533-1542.*

41. *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: 121-130.*

42. *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: 2537-2545.*

43. *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: 509-514.*

44. *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: 143-149.*

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

46. *Brentjens RJ, Latouche JB, Santos E, Marti F, Gong MC, Lyddane C 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: 279-286.*

47. *Chen CL, Levine A, Rao A, O'Neill K, Messinger Y, Myers DE 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: 1248-1255.*

48. *Cooper LJ, Topp MS, Serrano LM, Gonzalez S, Chang WC, Naranjo A 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: 1637-1644.*

49. *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: 763-772.*

50. *Kipriyanov SM, Moldenhauer G, Braunagel M, Reusch U, Cochlovius B, Le Gall F et al. Effect of domain order on the activity of bacterially produced bispecific single-chain Fv antibodies. J Mol. Biol. 2003; 330: 99-111.*

51. *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: 164-168.*

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

53. *Nicholson IC, Lenton KA, Little DJ, Decorso T, Lee FT, Scott AM 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: 1157-1165.*

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

55. *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: 878-884.*

56. *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: 10024-10028.*

57. *Pinthus JH, Waks T, Kaufman-Francis K, Schindler DG, Harmelin A, Kanety H et al. Immuno-Gene Therapy of Established Prostate Tumors Using Chimeric Receptor-redirected Human Lymphocytes. Cancer Res 2003; 63: 2470-2476.*

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

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

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

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

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

63. *Kohn DB, Dotti G, Brentjens R, Savoldo B, Jensen MC, Cooper LJ 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.*

64. *Nicholson IC, Lenton KA, Little DJ, Decorso T, Lee FT, Scott AM 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: 1157-1165.*

65. *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.*

66. *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.*

67. *Riddell SR, Elliott M, Lewinsohn DA, Gilbert MJ, Wilson L, Manley SA et al. T-cell mediated rejection of gene-modified HIV-specific cytotoxic T lymphocytes in HIV-infected patients. Nat. Med. 1996; 2: 216-223.*

68. *Dummer W, Niethammer AG, Baccala R, Lawson BR, Wagner N, Reisfeld RA et al. T cell homeostatic proliferation elicits effective antitumor autoimmunity. J. Clin Invest 2002; 110: 185-192.*

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

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

71. *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: 111-117.*

72. *Dudley ME, Wunderlich JR, Robbins PF, Yang JC, Hwu P, Schwartzentruber DJ et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science 2002; 298: 850-854.*

73. *Rapoport A, Stadtmauer EA, Aqui N, Badros A, Cotte J, Chrisley L et al. Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T-cell transfer. Nat Med 2005; 11: 1230-1237.*

74. *Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N. Engl. J. Med. 2011; 365: 725-733.*

75. *Laport GG, Levine BL, Stadtmauer EA, Schuster SJ, Luger SM, Grupp S 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: 2004-2013.*

76. *Kalos M, Levine BL, Porter DL, Katz S, Grupp SA, Bagg A et al. T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia. Sci. Transl. Med. 2011; 3: 95ra73.*

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

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

79. *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: 211-226.*

80. *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.*

81. *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.*

82. *Brentjens RJ, Latouche JB, Santos E, Marti F, Gong MC, Lyddane C 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: 279-286.*

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

84. *Serrano LM, Pfeiffer T, Olivares S, Numbenjapon T, Bennitt J, Kim D et al. Differentiation of naive cord-blood T cells into CD19-specific cytolytic effectors for posttransplantation adoptive immunotherapy. Blood. 2006; 107: 2643-2652.*

85. *Willemsen RA, Weijtens ME, Ronteltap C, Eshhar Z, Gratama JW, Chames P et al. Grafting primary human T lymphocytes with cancer-specific chimeric single chain and two chain TCR. Gene Ther. 2000; 7: 1369-1377.*

86. *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: 70-75.*

87. *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: 619-626.*

88. *Imai C, Mihara K, Andreansky M, Nicholson IC, Pui CH, Geiger TL et al. Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia. Leukemia 2004; 18: 676-684.*

89. *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: 3087-3093.*

90. *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: 104-113.*

91. *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: 104-113.*

92. *Milone MC, Fish JD, Carpenito C, Carroll RG, Binder GK, Teachey D 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: 1453-1464.*

93. *Carpenito C, Milone MC, Hassan R, Simonet JC, Lakhal M, Suhoski MM 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: 3360-3365.*

94. *Laport GG, Levine BL, Stadtmauer EA, Schuster SJ, Luger SM, Grupp S 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: 2004-2013.*

95. *Lamers CH, Sleijfer S, Vulto AG, Kruit WH, Kliffen M, Debets R 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: e20-e22.*

96. *Lamers CH, Sleijfer S, Vulto AG, Kruit WH, Kliffen M, Debets R 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: e20-e22.*

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

98. *Wang GP, Levine BL, Binder GK, Berry CC, Malani N, McGarrity G et al. Analysis of lentiviral vector integration in HIV+ study subjects receiving autologous infusions of gene modified CD4+ T cells. Mol Ther. 2009; 17: 844-850.*

99. *Rapoport AP, Levine BL, Badros A, Meisenberg B, Ruehle K, Nandi A et al. Molecular remission of CML after autotransplantation followed by adoptive transfer of costimulated autologous T cells. Bone Marrow Transplant. 2004; 33: 53-60.*

100. *Rapoport AP, Stadtmauer EA, Aqui N, Vogl D, Chew A, Fang HB et al. Rapid immune recovery and graft-versus-host disease-like engraftment syndrome following adoptive transfer of Costimulated autologous T cells. Clin. Cancer Res. 2009; 15: 4499-4507.*

101. *Levine BL, Bernstein WB, Aronson NE, Schlienger K, Cotte J, Perfetto S 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: 47-53.*

102. *Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr. Blood Cancer 2007; 48: 124-131.*

103. *Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N. Engl. J. Med. 2014; 371: 1507-1517.*

104. *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: 666-668.*

105. *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: 843-851.*

106. *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: 953-962.*

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

108. *Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H 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: 5446-5456.

109. *Cruz CR, Hanley PJ, Liu H, Torrano V, Lin YF, Arce JA et al. Adverse events following infusion of T cells for adoptive immunotherapy: a 10-year experience. 2010; 2010/05/01: 743-749.*

110. *Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J. Clin. Oncol. 1999; 17: 1244.*

111. *Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ et al. Revised response criteria for malignant lymphoma. J. Clin. Oncol. 2007; 25: 579-586.*

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

113. *Cavazzana-Calvo M, Payen E, Negre O, Wang G, Hehir K, Fusil F et al. Transfusion independence and HMGA2 activation after gene therapy of human beta-thalassaemia. Nature 2010; 467: 318-322.*

114. *Montini E, Cesana D, Schmidt M, Sanvito F, Bartholomae CC, Ranzani 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: 964-975.*

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

116. *Porter DL, Levine BL, Bunin N, Stadtmauer EA, Luger SM, Goldstein S et al. A phase 1 trial of donor lymphocyte infusions expanded and activated ex vivo via CD3/CD28 costimulation. Blood 2006; 107: 1325-1331.*

117. *Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N. Engl. J. Med. 2014; 371: 1507-1517.*

15 SCHEDULE OF STUDY PROCEDURES

	~Wk (-) 8 [24]	~ Wk (-) 6 to 8 [24, 25]	~ Wk (-) 4 [24]	~ Wk (-) 1	~ Day (-) 1§	D 0§	D+1§	D+2 (+1d)	D+7 (+/-1d)	D+10 (+/-1)	D+14 (+/-3d)	D+21 (+/- 3d)	D+28 (+/-3d)	Monthly to 6 mo. (+/-2 wk)	Quarterly to Yr2 [8] (+/- 1 mo)	Secondary Follow-up
	Pre-entry eval	Enrollment	Apheresis	Chemo-therapy[1]	Pre – Infusion	*Infusion*	Post Infusion	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Engraftment Endpoint	Response Endpoint at 3 months and Follow - up		Secondary Follow-up
Clinical Assessments																
Consent	X	X														
Recent Med. History and PE, PS		X			X	X[15]	X	X	X	X	X	X	X	X	X	
Concomitant Meds.		X			X	X[15]	X	X	X	X	X	X	X	X	X	
Adverse Events						X[15]	X	X	X	X	X	X	X	X	X	
HIV test (1 ml SST)	X															
Leukapheresis screening		X														
Disease monitoring[4]		X[4]		X[25]										X[4]	X[4]	
Bone marrow / LN aspirate[5]		X[23]												X[12]	X[12]	
Tumor response assessments[7]		X		X[25]										X	X	
Documented CD19 expression		X														
ECHO/MUGA		X[17]														
CBC, differential (5 ml EDTA)		X			X	X[15]	X	X	X	X	X	X	X	X	X	
Chemistry (3 ml SST)[16]		X			X	X[15]	X	X	X	X	X	X	X	X	X	
Serum pregnancy test[2] (1 ml SST)		X														
Urine pregnancy test[2]					X											
CD4 Mon (4ml lav)						X							X	X[9]		
Autoantibody Panel[3] (4 ml SST; 3ml EDTA)		X														
CMV, EBV, Hepatitis B/C (5ml)		X														

	~Wk (-) 8 [24]	~ Wk (-) 6 to 8 [24, 25]	~ Wk (-) 4 [24]	~ Wk (-) 1	~ Day (-) 1§	D 0§	D+1§	D+2 (+1d)	D+7 (+/-1d)	D+10 (+/-1)	D+14 (+/-3d)	D+21 (+/- 3d)	D+28 (+/-3d)	Monthly to 6 mo. (+/-2 wk)	Quarterly to Yr2 [8] (+/- 1 mo)	Secondary Follow-up
	Pre-entry eval	Enrollment	Apheresis	Chemo-therapy[1]	Pre – Infusion	*Infusion*	Post Infusion	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Engraftment Endpoint	Response Endpoint at 3 months and Follow - up		Secondary Follow-up
β2 Microglobulin (1x 1ml SST)		X														
Serum immunoglobulin (1x 1ml SST)		X					X[21]	X[21]	X[21]	X[21]	X[21]	X[22]	X	X[21]	X[21]	
Coagulation Factors (PT, PTT, INR, fibrinogen, D-dimer)		X			X	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	
HLH/MAS (serum ferritin, triglycerides, haptoglobin) (4ml SST; 3ml EDTA)					X	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	
CRP					X	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	
Respiratory Virus Panel (RVP)				X[26]												
Relapse and Survival Follow-up																X[27]
Intervention																
Chemotherapy[1]				X												
CART-19 cell infusion						X										
Leukapheresis			X[11]													
Research draws[14, 22]																
Research blood to CVPF for expansion screen (20mL green)[13]	X															
Additional large volume research blood draw (60 mL)													X			
Marrow mononuclear cells 5 cc (Lavender)		X													X	
DNA (Q-PCR persistence)		X													X	
DNA (MRD)		X												X	X	
MMC (functional assays,		X												X	X	

	~Wk (-) 8 [24]	~ Wk (-) 6 to 8[24, 25]	~ Wk (-) 4[24]	~ Wk (-) 1	~ Day (-) 1§	D 0§	D+1§	D+2 (+1d)	D+7 (+/-1d)	D+10 (+/-1)	D+14 (+/-3d)	D+21 (+/- 3d)	D+28 (+/-3d)	Monthly to 6 mo. (+/-2 wk)	Quarterly to Yr2 [8] (+/- 1 mo)	Secondary Follow-up
	Pre-entry eval	Enrollment	Apheresis	Chemo-therapy[1]	Pre – Infusion	*Infusion*	Post Infusion	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Engraftment Endpoint	Response Endpoint at 3 months and Follow - up		Secondary Follow-up
immunophenotyping, CART-19 and B cell enumeration)																
Marrow 2cc (Red)		X													X	
HACA																
Multiplex cytokines		X													X	
Total research marrow needs		**7 ml**												**7 ml**	**7 ml**	
Lavender top		**5 ml**												**5 ml**	**5 ml**	
Red top		**2 ml**												**2 ml**	**2 ml**	
Peripheral blood mononuclear cells 25 cc (Lavender)					X	X[20]	X	X	X	X	X	X	X	X	X	
DNA (Q-PCR persistence)					X	X	X	X	X	X	X	X	X	X	X	
DNA RCL (Q-PCR)[6]					X									X	X	
DNA (MRD)					X								X	X	X	
PBMC (functional assays, immunophenotyping, CART-19 and B cell enumeration[19])					X[19]		X	X	X	X	X	X	X	X	X	
Peripheral blood Serum 5 cc (Red)					X	X[5, 10]	X	X	X	X	X	X	X	X	X	
HAMA					X								X			
HACA					X									X	X	
Multiplex cytokines					X	X	X	X	X	X	X	X	X	X	X	
Total research blood needs	**20**				**30 ml**	**29 ml**	**30 ml**	**30 ml**	**30 ml**	**30 ml**	**30 ml**	**30 ml**	**90 ml**	**30 ml**	**30 ml**	
Lavender top					25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	25 ml	
Red top	-				5 ml	4 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	
TOTAL BLOOD DRAW (ml)	**21**	**30**			**45**	**48**	**46**	**46**	**46**	**46**	**46**	**46**	**106**	**46**	**46**	

§ The Investigator will review all pre- and post-infusion lab results to determine that it is appropriate to proceed with the infusion. Any abnormal Cr, Ca, K, Phos, uric acid, AND 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 Blood Collection: In the event that something unexpected occurs, the research team may request an additional blood draw be performed to collect additional blood samples for research analysis. Samples will be delivered to TCSL. 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. Additionally, if clinically indicated, CSF from lumbar punctures can be analyzed for CART-19.

1. Chemotherapy appropriate for disease type.
2. Pregnancy test-Females of child bearing potential only. Follicle stimulating hormone may be performed to confirm menopausal status.
3. Autoimmune screen (ANA, ESR)
4. Disease monitoring: Anatomic imaging (CT or MRI) for response assessment will be performed within 12 weeks of study entry and after the subjects' last chemotherapy treatment; at month 3 (to assess the primary study endpoint); and at months 6, 9, 12, 18 and 24 (to monitor disease). Functional imaging (^{18}FDG-PET/CT) may be used at the discretion of the treating physician if in the opinion of the treating investigator it is more clinically appropriate (for example- to assess certain extranodal sites like bone marrow or to confirm complete response).
5. Bone marrow aspirate for tumor and T body PCR. Lymph node aspirate or biopsy to be performed if tumor accessible and clinically appropriate.
6. The RCL DNA test performed at months 3 and 6 and annually. If all RCL DNA tests during the first year (including the first annual visit) are negative, then samples for future annual tests may be archived. VSV-G or other suitable Q-PCR assay for RCL detection will be used.
7. Baseline imaging for tumor response assessments will be done within 12 weeks of study entry and after the subjects' last chemotherapy. Imaging for tumor response assessments post-CART-19 infusion will be done every 3 months for first year and every 6 months for the second year after infusion. Tumor response assessment criteria are described in Section 6.12. For subjects who achieve a CR or CRu, a confirmatory FDG-PET/CT scan will be performed within 4 weeks of the initial CT/MRI scan.
8. Subjects who complete follow-up as part of this study or discontinue participation early for any reason will be encouraged to enroll into a separate long-term follow-up protocol to further evaluate the safety of CART-19for up to 15 years post T cell infusion and to monitor for delayed adverse events associated with the lentiviral vector genetic modification.
9. Blood for CD3, CD4, CD8 Monocytes taken at months 3 and 6 only.
10. Research blood (5 cc red top) taken prior to infusion and between 20-120 minutes post-infusion.
11. 12-15 liter apheresis to go to CVPF, 1 x 10^9 cells to be delivered to TCSL
12. To be performed as clinically indicated at months 3, 6, 9, 12, 18, and 24. Lymph node aspirate or biopsy to be performed if tumor accessible and clinically appropriate.

13. 20mL green top to CVPF. This will be performed for the first 10 subjects.
14. TCSL has requested labs be delivered to TCSL as soon as drawn. 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, research sample collection may be done as necessary, not to exceed 3 tablespoons of blood twice in one week time window. This would be done at the PI's discretion.
15. Medical history, physical exam, and concomitant medications are to be collected prior to infusion on Day 0. Hematology and chemistry results are to be obtained prior to infusion on Day 0. Adverse events will be collected from the start of the CART19 infusion.
16. Chemistry – Glucose, BUN, Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Uric Acid, Cl
17. Should be performed within 8 weeks of infusion.
19. CART-19 and B cells enumerated by flow cytometry using CD3+/CAR19+ and CD19+ expression respectively
20. 25 cc lavender top collected prior to infusion and between 20-120 minutes post-infusion.
21. As clinically appropriate
22. Additional Blood Collection: In the event that something unexpected occurs, the research team may request an additional blood draw be performed to collect additional blood samples for research analysis. Samples will be delivered to TCSL. 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.
23. To be performed within 42 days of CART-19 infusion.
24. The intent of these windows is to ensure subjects are infused within 8 weeks of enrollment. If the subject completes these visits within a shorter timeframe than 8 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 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.
25. If it has been greater than 42 days since the subjects' previous radiologic disease assessment, a repeat CT/MRI of the chest/abdomen/pelvis is required prior to receiving cytoreductive chemotherapy. If it has been less than 42 days since the subjects' enrollment radiologic disease assessment, but the subject has received additional treatment during this time, a repeat CT/MRI of the chest/abdomen/pelvis is also required prior to receiving cytoreductive chemotherapy.
26. 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, 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 per package insert. The patient must complete this course of 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.

27. Subjects who complete or prematurely discontinue from the Primary Follow-up Phase, who do not enroll in a separate 15 year long-term follow-up protocol will continue to be followed in the Secondary Follow-up Phase of this study until the subject withdraws consent, the subject enrolls in a long-term follow-up protocol, or the end of the study (Last Patient/Last Visit), whichever occurs first. See Section 6.12 for complete details.

Appendix 1. 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.