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DEPARTMENT OF HEMATOLOGY/ HEMATOPOEITIC CELL TRANSPLANTATION

TITLE: PHASE I/II STUDY OF CELLULAR IMMUNOTHERAPY USING CENTRAL MEMORY-ENRICHED $CD8^+$ T CELLS LENTIVIRALLY TRANSDUCED TO EXPRESS A CD19-SPECIFIC CHIMERIC IMMUNORECEPTOR FOLLOWING PERIPHERAL BLOOD STEM CELL TRANSPLANTATION FOR PATIENTS WITH HIGH-RISK INTERMEDIATE GRADE B-LINEAGE NON-HODGKIN LYMPHOMA

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SPONSOR/IND NUMBER: **City of Hope/IND 14645**

DISEASE SITE: Lymph Nodes and/or Bone Marrow

STAGE (if applicable): Not applicable

MODALITY: Cellular Immunotherapy Using CD19-Specific Chimeric Immunoreceptor Expressing T_{CM}-Enriched $CD8^+$ T Cells

PHASE/TYPE: Phase I/II

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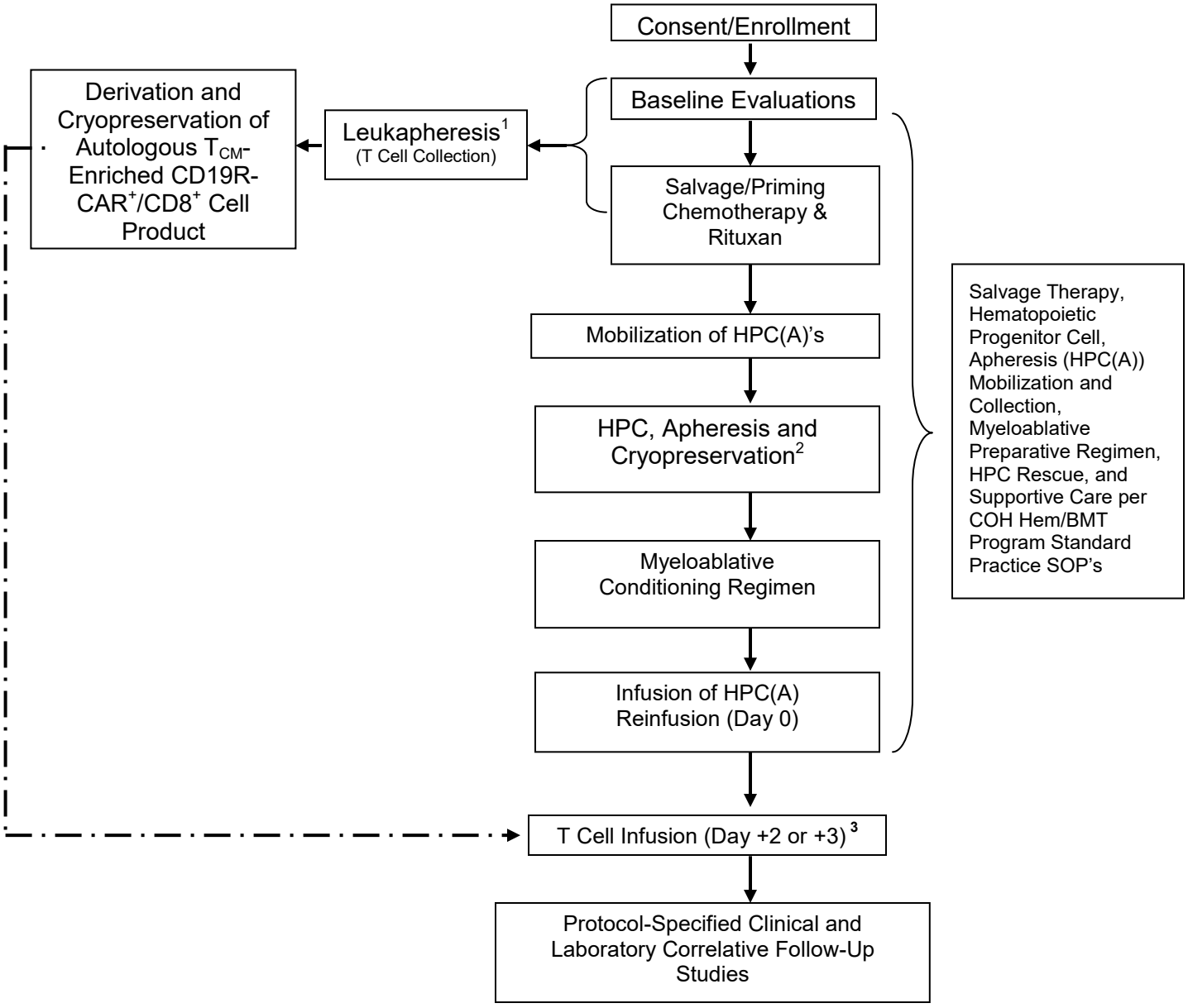
Experimental Design Schema



[1]Leukapheresis for T cell manufacturing may be drawn prior to or after cycles of Salvage Chemotherapy

[2]Phase I portion includes HPC back-up product, reference **Section 7.5.2**

[3] Research participants will enter the protocol in cohorts of 3 and receive T cell infusion on approximately day +2 or +3 post HSCT. The starting dose will be 50M CAR+ cells (where M = 10^6). Dose escalation will take whole steps (in black) until a DLT is seen. Once a DLT is seen the study will move in half steps (in grey) as described in **Section 12, Table 5**.

Table of Contents

1.0 Goals and Objectives (Scientific Aims)

1.1 Phase I

1.1.1 Primary Objectives

- To assess the safety of cellular immunotherapy utilizing *ex vivo* expanded autologous T_{CM}-enriched $CD8^+$ T cells genetically-modified to express a CD19-specific chimeric antigen receptor (CAR) in conjunction with a standard myeloablative autologous HSCT (aHSCT) for research participants with high-risk intermediate grade B-lineage non-Hodgkin lymphomas (NHL) who have relapsed after primary therapy, or who did not achieve complete remission with primary therapy.
- To determine the maximum tolerated dose (MTD) on dose limiting toxicities (DLTs) and to describe the full toxicity profile

1.2 Phase II

1.2.1 Primary Objectives

To determine the rate of research participants receiving T_{CM}-enriched $CD8^+$ T cells genetically-modified to express a CD19-specific CAR for which the transferred cells are detected in the circulation 28 days (+/- 3 days) by WPRE Q-PCR

1.2.2 Secondary Objectives

- To determine the tempo, magnitude, and duration of engraftment of the transferred T cell product as it relates to the number of cells infused.
- To study the impact of this therapeutic intervention on the development of $CD19^+$ B-cell precursors in the bone marrow as a surrogate for the *in vivo* effector function of transferred CD19-specific T cells
- To describe the progression-free and overall survival of treated research participants on this protocol

2.0 Background and Rationale

This Phase I/II, open-label, nonrandomized study proposes to enroll adult research participants with high-risk intermediate grade B-cell lymphomas who are candidates for an autologous myeloablative stem cell transplant to examine the safety and feasibility of administering autologous *ex vivo* expanded central memory (T_{CM})-enriched $CD8^+$ T cell that are genetically modified using a SIN lentiviral vector to express a CD19-specific CAR to research participants in this population.

The trial consists of dose escalation by cohort (pilot portion), followed by expanded enrollment at the tolerable dose (phase II portion) for a potential total enrollment of fifty-seven research participants. Infusion of genetically modified T_{CM} cells will take place following a "standard of care" HSCT during the period of lymphopenia. $CD8^+$ T_{CM} will be isolated from research participant peripheral blood mononuclear cells (PBMC) using the CliniMACS® device to select for $CD8^+/CD45RO^+/CD62L^+$ T_{CM} precursors. These T cells

will then undergo a Dynal CD3/CD28 activation culture in combination with genetic modification using a SIN lentiviral vector that directs the expression of a CD19-specific scFvFc:ζ CAR. The activated/genetically modified $CD8^+$ T_{CM} will be expanded *in vitro* with IL-2/IL-15 and then cryopreserved. In the meantime, research participants will undergo standard practice salvage chemotherapy (if indicated), mobilization, hematopoietic progenitor cells (HPC) collection, then receive a standard myeloablative preparative regimen and HPC rescue conducted per standard operating procedures. The T cell product will be administered on approximately Day +2 or +3 following HSCT. Dose will be dependent on CAR positive (CAR+) T cells (i.e., if a product is 80% CAR+ at the first dose of 50M, then 50M CAR+ T cells will be infused which equals approximately 62.5M total cells).

The primary safety endpoints of the phase I arm of the study will address the safety of T cell product infusion, the identification of any alteration in the side effects associated with HSCT and the kinetics of engraftment and determine the (MTD) based on DLTs and to describe the full toxicity profile. The primary safety endpoints of the phase II arm of the study will determine the rate in research participants receiving T_{CM}-enriched $CD8^+$ T cells genetically-modified to express a CD19-specific CAR for. Secondary objectives of this protocol are: 1) to determine the tempo, magnitude, and duration of engraftment of the transferred T cell product as it relates to the number of cells infused; 2) to study the impact of this therapeutic intervention on the development of $CD19^+$ B-cell precursors in the bone marrow as a surrogate for the *in vivo* effector function of transferred CD19-specific T cell; and 3) to describe the progression-free and overall survival of treated research participants on this protocol.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

2.1 High-Dose Chemotherapy with Autologous Peripheral Blood Stem Cell Support for NHL

2.1.1 Introduction

Over 55,000 new cases of NHL are diagnosed each year in the United States and recent epidemiological data demonstrates that the incidence of this disease is increasing. Intermediate grade B-cell lymphomas (diffuse large cell, mantle cell, marginal zone) are the most common sub-types of NHL and account for approximately 30% of cases. Nearly 50% of these patients have widespread disease at the time of diagnosis and are treated with combination chemotherapy and/or radiation therapy. Unfortunately, over two-thirds of these patients will relapse with their disease and only 10% of these patients can be salvaged with conventional modalities. Efforts to improve the survival of these patients with recurrent disease have focused primarily on the use of consolidative myeloablative stem cell transplantation. This strategy may be curative in approximately 46% of selected patients. This selected group of salvageable patients (age <60 years, complete remission after primary treatment, and no known marrow or central nervous system disease), however, constitutes less than one-third of patients with relapsed intermediate grade lymphomas. Patients with chemotherapy-resistant recurrent disease have a <15%, 5-year event-free survival following stem cell transplantation and those with refractory disease at the time of transplant are rarely cured. Thus, the major limitation of autologous transplantation for NHL is the high incidence of relapse even at maximally

tolerated preparative regimen intensities. Autologous HCT is not curative in patients with advanced mantle cell lymphoma (MCL), even when transplanted in first remission; with a pattern of late relapse in the majority of patients so treated. Five-year overall survival rates with this approach range from 50 to 75 percent. These findings have prompted the evaluation of additional strategies to eradicate minimal residual disease (MRD) following the autologous transplantation procedure.

2.1.2 Standard Preparative Regimens for Autologous Stem Cell Transplantation Utilized in Patients with NHL

Preparative regimens including BEAM [1], and BCNU, CY, and VP-16 (CBV) [2-3] are considered standard myeloablative procedures at City of Hope (COH) for patients undergoing autologous transplant for recurrent NHL who are not on specific study protocols. With improved supportive care measures the early mortality associated with autografting has been reduced to 5% or less, and for most patients, the majority of acute regimen-related toxicities resolve within the first four weeks following stem cell rescue. Hematopoietic graft failure is defined as failure of granulocyte counts to reach 0.5×10^9/L by day 28.

Historical data indicates that engraftment failure following autologous stem cell transplantation is influenced by log-dose CFU-GM and the number of prior chemotherapy regimens. Patients who received less than 2.5×10^6 $CD34^+$ cells have delayed hematopoietic recovery of all three cell lines, and a 5% likelihood of failing to meet definition of neutrophil recovery by day +28 after transplantation. Minimum cell dose specified in the COH Hematology SOP is greater than or equal to 2×10^6 $CD34^+$ cell/kg of recipient weight. Overall survival at 100 days in patients treated at COH with the preparative regimens BEAM and CBV is 92 - 100%, per submitted institutional Research Identifiable File (RIF) data submitted to the American Society for Blood and Marrow Transplantation (ASBMT) [4]. Standard preparative regimens as described in the Heme/HCT SOP will be utilized for research participants enrolled in this protocol at the treating hematologist's discretion because of City of Hope's extensive transplant experience with these agents.

2.2 Cellular Immunotherapy for Human Disease

2.2.1 Adoptive therapy for human viral and malignant disease

The feasibility of isolating and expanding antigen-specific T cells for adoptive therapy (AT) of human disease has been validated in clinical trials [5-13]. Dr. Riddell initially studied adoptive T cell therapy with donor-derived $CD8^+$ cytotoxic T-lymphocyte (CTL) clones specific for cytomegalovirus (CMV) as a means of reconstituting deficient viral immunity in allogeneic HCT recipients; and defined the principles and methodologies for T cell isolation, cloning, expansion, and re-infusion [14-16]. A similar approach pioneered by Heslop *et al* using polyclonal Epstein Barr Virus (EBV)-specific T cells has been effective for preventing or treating post-transplant EBV-associated lymphoproliferative disease after allogeneic HCT [17-18]. These studies and others have demonstrated that virus-specific T cells, derived from donors with established viral immunity, and expanded *in vitro* can be transferred with minimal toxicity, mediate virus specific effector functions, and control viral replication as well as eradicate virally (EBV) transformed B-cell immunoblastic lymphoma [18-36].

While the adoptive transfer of tumor-specific T cells can result in tumor eradication in a variety of animal models [37-48], adoptive T cell therapy for human malignancy has been significantly more challenging and less effective than for viral diseases. Perhaps the most clinically robust AT data comes from efforts of the Surgery Branch at the National Cancer Institute to treat melanoma [49-59]. Their studies demonstrated that administration of lymphodepleting chemotherapy followed by the adoptive transfer of polyclonal tumor infiltrating lymphocytes (TILs) specific for melanocyte-lineage antigens/tumor-testis antigens and high-dose rhuIL-2, results in demonstrable tumor regressions in nearly one half of treated patients. Of note, the response rate in patients that exhibited high-level persistent engraftment of transferred T cells was nearly 90%, while no responders are seen in the approximately 50% of patients without T cell engraftment. Interestingly, persisting TILs represented only a small subset of the infused product repertoire, suggesting that the capacity for engraftment and persistence may be linked to the intrinsic programming of a rare population of T cells derived from TIL [59-60]. The generalization of the NCI group's AT results for melanoma to other tumor types, including NHL, is the subject of intense ongoing investigation.

2.2.2 Development of AT for B-lineage malignancies using chimeric antigen receptor re-directed CD20 and CD19 specific T cells

Tumor antigens presented by HLA molecules and recognized by T cells have been identified and can originate from processing of normal or over-expressed tissue-specific proteins, aberrantly expressed onco-fetal antigens and mutated proteins, or minor histocompatibility (H) antigens in the setting of allogeneic HCT [61]. However, isolating and expanding high-affinity major histocompatability complex (MHC)-restricted tumor-reactive T cells from tumor-bearing patients is technically difficult and even when successful, these T cells often fail to eliminate tumors after adoptive transfer [62-65]. Our evolving understanding of the counter-regulatory mechanisms that impede successful tumor therapy have been derived largely from murine models [66]. Because many tumor antigens are self-proteins that are expressed in some normal tissues, tolerance mechanisms shape the frequency, avidity, and function of tumor-reactive T cells. Additionally, tumors evade immune recognition through a variety of mechanisms including local recruitment of regulatory T cells (T_{REG}) and other suppressor cells, loss of antigen expression, down-regulation of MHC and co stimulatory molecules, and expression or secretion of inhibitory molecules or cytokines [67-79]. Finally, cultured tumor-reactive T cells often exhibit limited persistence *in vivo* after adoptive transfer, even if high doses of rhuIL-2 are administered to support their survival [80-83].

In order to overcome some of these obstacles, we have focused on T cell genetic engineering strategies that serve to equip T cells with tumor specificity through the expression of CARs [84-85]. We have developed CARs consisting of tumor targeting single-chain variable fragments (ScFvs) specific for CD20 and CD19 [41,86-88]. These chimeric cell-surface molecules have the ability to bind antigen and transduce activation signals via immunoreceptor tyrosine activation motifs (ITAMs) present in the CD3-ζ cytoplasmic tail [10], or both activation and co-stimulatory signals when CD28 and/or 4-1BB/OX40 domains are incorporated in series with CD3-ζ [89]. Adoptively transferred CAR-modified T cells can eradicate

established tumors in a variety of animal models [90-92]. Moreover, T cells expressing CARs consisting of co-stimulatory signaling domains appear to be more resistant to activation induced cell death, exhaustion, and T_{REG} mediated functional anergy [45,93-94]. While T cell genetic modification can address some of the issues relevant to tumor AT, our animal studies as well as data from our initial clinical trial demonstrate that the capacity of gene-modified CAR^+ effector T cells to persist following adoptive transfer is a major obstacle to achieving therapeutic responses.

2.2.3 Strategies to improve the persistence of adoptively transferred T-cells

2.2.3.1 Lymphodepletion

The induction of lymphopenia results in the proliferation of residual naïve and memory T cells to restore the size of the T cell pool [59,95-97]. A variety of mechanisms may make the lymphopenic environment favorable for T cell transfer including less competition for cytokines, such as IL-15 and IL-7, which promote lymphocyte homeostatic proliferation and survival [98-101]; the availability of "space" in the lymphoid compartment [96]; and the elimination of $CD4^+CD25^+FOXP3^+$ regulatory T cells [102-103]. Direct evidence that the induction of lymphopenia improves the persistence of transferred T cells was provided by studies from Rosenberg *et al*. in which melanoma patients were rendered lymphopenic by treatment with fludarabine and cytoxan prior to the adoptive transfer of 10^{10}-10^{11} TIL-derived polyclonal melanoma-specific T cells. As described above, a subset of these patients achieve prolonged high-level engraftment that correlates directly with tumor regression [55,57,104-105]. We hypothesize that infusing T cells shortly after a myeloablative HSCT will facilitate engraftment based on a window of lymphopenia when serum homeostatic cytokines (especially IL-15) are elevated.

2.2.3.2 Intrinsic programming of central memory T cells for persistence

The persistence of cultured T cells is improved by depletion of host lymphocytes before cell transfer and by the administration of IL-2 after cell transfer, but in half of treated melanoma patients these interventions still did not result in long-term persistence of transferred T cells or sustained tumor regression [104-105]. We hypothesized that intrinsic properties of T cells may be a critical determinant of their fate *in vivo* following adoptive transfer. The pool of peripheral blood lymphocytes from which T cell products are derived *ex vivo* consist of naïve T cells (T_N), and antigen experienced memory T cells (T_M), which can be divided into central memory T cells (T_{CM}) and effector memory T cells (T_{EM}) subsets that differ in their homing, phenotype, and function [106-108]. $CD8^+$ T_{CM} express CD62L and CCR7 which promote migration into lymph nodes, produce IL-2, and proliferate rapidly in response to antigen stimulation. $CD8^+T_{EM}$ lack CD62L/CCR7, accumulate in tissue bed niches, and exhibit immediate effector function. In response to antigen *in vivo*, both $CD8^+$ T_{CM} and T_{EM} differentiate into cytolytic effector T (T_E) cells that express high levels of granzymes and perforin, but are otherwise short-lived [109-110]. Thus, differentiation to a terminal T_E phenotype during culture has been suggested to explain the poor survival of transferred T cells in clinical trials [111-112].

In the normal host, T cell memory persists for life, suggesting that some T_M cells have the ability to self-renew or to revert to the memory pool after differentiating to T_E in response to antigen re-exposure [107]. T_{CM} and T_{EM} have distinct phenotypic and functional properties, but it is unknown if T_E cells enriched from each of these T_M subsets retain any intrinsic properties of the parental cell from which they came. Using an immunodeficient mouse model, as well as a non-human primate model (*Macaca nemestrina*) relevant for human translation, we examined whether T_E cells derived from purified T_{CM} versus T_{EM} differed in their ability to persist *in vivo* and establish T cell memory after adoptive transfer [113-114]. The studies identified a surprising dichotomy: T_E cells derived from $CD62L^-$ circulating T_{EM} that were purified by cell sorting and expanded *ex vivo*, survived in the blood for only a short duration after AT; failed to persist in lymph nodes (LN), bone marrow (BM), or peripheral tissues; and did not reacquire phenotypic markers of T_M during their brief life-span *in vivo,* while T_E cells derived from sort-purified $CD62L^+$ T_{CM} persisted in the blood long-term after adoptive transfer, migrated to memory T cell niches in the LN and BM, reacquired phenotypic properties of T_M, and responded to antigen challenge *in vivo* [113-114]. We hypothesize that human T_{CM}-derived effectors will retain their programming for persistence after their genetic modification and *ex vivo* propagation and, upon adoptive transfer to lymphoma patients shortly following a myeloablative preparative regimen, will engraft and establish a reservoir of persistent memory T cells capable of targeting $CD19^+$ lymphoma cells.

2.3 Potential Toxicities Associated with the Infusion of CD19-Specific T_{CM}-Enriched $CD8^+$ T Cell Lines

Various short-term toxicities have been associated with CD19-specific ACIT. As mentioned above, we have observed both lymphopenia and eosinophilia with possible correlation to CD19-redirected CTL administration.[115]

The NCI has also reported on a single adult patient with NHL, who received autologous CD19-specific, CD28-costimulatory CAR expressing T cells, and exhibited a fever for two days which self-resolved.[116] In a more recent publication summarizing all 8 patients with advanced B-cell malignancies that were treated on this same trial, the most prominent toxicities that were observed included fever, hypotension, fatigue, renal failure, and obtundation.[117] While these toxicities generally peaked within the first eight days after T cell administration, and resolved over time, the severity of the toxicities that were experienced by the patients appeared to correlate with serum IFN-□ and TNF-□ levels.[117]

In a trial conducted at Memorial Sloan Kettering (MSKCC) using autologous CD19-specific, CD28-costimulatory CAR expressing T cells for the treatment of chronic lymphocytic leukemia (CLL), eight of nine patients received T cells without serious adverse events (SAE), but exhibited common side effects of rigors, chills and transient fevers, all occurring within 24 hours of receiving the modified T cell infusions.[118] The one CLL patient who had an SAE with subsequent death is discussed below.[119] Autologous CD19-specific, CD28-costimulatory CAR expressing T cells were also used in an MSKCC trial for adults with relapsed acute B lymphoblastic leukemia (B-ALL).[120] After T cell infusion, transient fevers and relative hypotension, as well as transient mental status changes were observed and found to be associated with serum cytokine surges..[120]

A recent University of Pennsylvania (UPENN) trial for CLL patients who received CD19-specific, 41BB-costimulatory CAR modified autologous T cells also revealed fever as a common infusional toxicity.[121-122] Furthermore, between one and three weeks later, during which the modified T cells exhibited impressive *in vivo* expansion, the patients were re-admitted to the hospital with symptoms of tumor lysis syndrome, as well as variety of symptoms including rigors and diarrhea, which resolved over a 3-4 day period, and fevers that lasted up to two weeks. One of the three reported patients did require corticosteroids at day 18 after the first T cell infusion for heart dysfunction in the setting of fevers, rigor and dyspnea, all of which were then resolved. In a newer UPENN trial using the CD19-specific costimulatory-CAR modified autologous T cells to treat children with relapsed/refractory B-malignancies, the first two patients have also been reported to have developed fever and "cytokine release syndrome". [123] In one case the associated hypotension, acute vascular leak syndrome and acute respiratory distress syndrome was life threatening, but was reversed by cytokine blockade with etanercept and tocilizumab.[123]

It is important to note that elevated proinflammatory serum cytokines represent a common, and in certain instances severe, short-term toxicity associated with T cells expressing second generation, or costimulatory, CD19-specific CAR. The observed cytokine elevations, as reported by the NCI, MSKCC and UPENN, have been observed for a subset a patients and appears to correlate with disease burden at the time of T cell infusion.[117,120,123] For some patients, cytokine-mediated toxicities were transient. For other patients, toxicities were controlled by administration of corticosteroids[120-121] or cytokine-blockade with etanercept and tocilizumab.[123] [

Two grade 5 SAEs have been reported in the literature in relation to therapy with CAR-expressing T cells. The first was a patient receiving a CAR targeting ErbB2 who had pulmonary toxicity and cytokine release syndrome immediately following the infusion of T cells.[124] The patient had received 10^{10} T cells, and on autopsy, was found to have large numbers of transferred T cells in the lung tissue – hypothetically due to low level ErbB2 expression on lung epithelial cells. The relevance of this SAE is then considerably diminished by the fact that the current protocol is targeting CD19 and not ErbB2. The second event, as mentioned above, occurred in a CLL patient who developed a sepsis like reaction following infusion of $1.2\text{-}3\text{x}10^{7}$ T cells expressing a CD19-specific, CD28-costimulatory CAR.[119] An overt cause of death was not revealed by autopsy, but the investigators have hypothesized that the patient had low-grade sepsis prior to the infusion of T cells that was magnified in the context of the lymphodepleting preparative regimen inherent in the adoptive transfer protocol. Indeed, serum cytokine analysis revealed elevated levels of pro-inflammatory cytokines following cyclophosphamide chemotherapy and preceding the T-cell infusion, and it is this scenario which was consistent with sepsis due to infection, that was thought to lead to hypotension, acute renal failure and ultimately death. It must also be taken into consideration that infection is a leading cause of mortality in patients with advanced CLL.

The most likely acute toxicity associated with adoptive transfer is a cytokine storm syndrome when infused cells are synchronously activated by a large burden of antigen expressing target cells. Two deaths within 24-hours of infusion of CAR redirected T cell products have been reported to date. In each of these deaths patients received a large number of cells and had extensive tumor burdens ($CD19^{+}$ CLL and $HER2^{+}$ breast cancer). In order to address this risk, our protocol will treat

patients in MRD for lymphoma burden and based on the myeloablative preparative regimen and rituximab therapy, circulating $CD19^+$ B-cells will be minimal. Additionally, in light of these fatalities we have elected to stratify patients into increasing cell dose cohorts, the first cohort being 50×10^6 (5×10^7) total cells, a modest dose at which in our prior trials we have not observed infusional toxicities.

There are also at least two potential long-term toxicities to be considered in the context of CD19-speific ACIT. The first is particular to targeting CD19. The second is a general concern of genetically manipulating T cells. Since non-malignant $CD19^+$ B-cells will be subject to recognition by re-directed CTL, the long-term persistence of the adoptively transferred CD19-specific CTL has the potential to cause B-cell immunodeficiency or exacerbate the B-cell lymphopenia resulting from prior rituximab therapy. In research participants who are predicted to succumb to recurrent/progressive lymphoma, the clinical sequelae of B-cell lymphopenia may be an acceptable side effect of CD19-directed immunotherapy, especially since prolonged ablation of normal $CD20^+$ B cells in patients receiving rituximab therapy does not appear to result in clinically significant complications attributable to depleted numbers of normal B cells [125]. If the hypogammaglobulinemia becomes clinically significant, then the research participant may be given intravenous immunoglobulin (IVIG) as replacement therapy until B-cell function returns.

The second potential long-term toxicity is the potential of neoplastic transformation of the genetically modified T cell product as a consequence of insertional mutagenesis and/or lentiviral vector integration that perturbs the expression cell regulatory genes [126-128]. Dr. Alain Fischer's gene therapy trials at the Necker children's hospital in Paris [129-130] have involved a cohort of 10 patients with a SCID-X condition treated with autologous bone marrow-derived $CD34^+$ cells with a γ-retrovirus encoding the common cytokine-receptor γ-chain gene that forms a T cell growth-factor receptor. Following re-infusion of the transduced stem cells, there is a selective advantage for the survival of T cells that bear intact cytokine receptors that is manifested by the emergence of peripheral transduced T cells within 6 to 12 weeks of treatment [131-132]. However, as of October 2002 at least two of the children treated on this protocol developed a clonal "lymphoproliferation" of ($\gamma\delta$) T cells apparently manifested by an increased white blood cells (WBC), hepatosplenomegally and anemia. Preliminary analysis revealed that the retrovirus used for transduction was inserted into a child's abnormal T cells. This adverse event has raised concern that retroviral transduction may have caused the lymphoproliferation as the consequence of an insertional mutagenesis event [133].

However, it is unclear what the significance of this adverse event is for the use of CD19-specific T cell therapy. Our study differs from Dr. Fischer's protocol in several important aspects: *(a)* we are genetically modifying cells with a lentiviral vector that to date has not resulted in transformation of T cells, and not γ-retrovirus; *(b)* the targets of the genetic modification are terminally differentiated T cells and not stem cells; *(c)* we are enrolling research participants with a life-threatening lymphoma and not young patients with an immunodeficiency syndrome; and *(d)* the genetically modified CD19-specific T cells do not have an inherent selective survival advantage compared with the transduced T cells in Dr. Fischer's study which are modified to express a functional growth factor receptor.

The ScFv portion of the CD19Rop CAR does encode a murine Ig protein with human CD19 specificity and associated idiotype. The immunogenicity of this sequence is

currently not known; however, the construct has been used in previous clinical trials (COH IRB Protocol No. 01160) in plasmid form and has not been associated with immunogenicity and/or serious adverse events [115]. Furthermore, the cytoreductive chemotherapy and rituximab therapy would also minimize the possibility of a patient being able to mount significant immune responses against the T cell product.

In summary, we believe that the potential toxicities associated with the use of CD19-specific T cell therapy are outweighed by the need to develop novel treatment for patients with life-threatening lymphoma.

3.0 Therapeutic Agents

3.1 Salvage/HPC Priming Chemotherapy

The hematopoietic cell transplantation (HCT) physician may choose to use a disease-specific chemotherapy regimen for mobilization in research participants with active disease who, in the opinion of the treating physician, require additional tumor debulking. At least two cycles of salvage chemotherapy are considered a standard of therapy for debulking and demonstration of chemotherapy-sensitivity. Salvage regimens which can be used for mobilization of HPC-A includes, but is not limited to, the regimens shown in Table 1: Salvage/HPC Priming Chemotherapy.

Alternatively, the treating physician may choose to use a cytokine-only mobilization regimen using G-CSF, or Plerixafor, or a priming chemotherapy regimen used specifically for the purpose of HPC-A mobilization including varying doses of high-dose cyclophosphamide (with or without etoposide or taxol).

The chemotherapy regimens listed in Table 1, are outlined in the current COH HCT Standard Operating Policies, Procedures and Protocols. In addition, pre-printed orders are available, and will be used to order the disease-specific chemotherapy regimen when chosen for cytoreduction and mobilization.

Time interval between salvage therapy and conditioning regimen will be according to institutional standard of practice. Salvage therapy will not delay the start of the conditioning regimen beyond standard practice.

Table 1: Salvage HPC Priming Chemotherapy

REGIMEN	DRUG	TREATMENT
ICE regimen 2 Q2w x 3 cycles	Ifosfamide	5000 mg/m2 mixed with Mesna 5000 mg/m2 iv over 24 hrs d2
	Carboplatin	AUC 5 (max 800mg) iv d2
	Etoposide	100 mg/m2/d iv d1-3
		G-CSF 5 ug/kg sc qd d5-12
RICE Q2w x 3 cycles	Rituximab	375 mg/m2 iv d1 q2w x 3 cycles
	Ifosfamide	5000 mg/m2 mixed with Mesna 5000 mg/m2 iv over 24 hrs d2
	Carboplatin	AUC 5 (max 800mg) iv d2
	Etoposide	100 mg/m2/d iv d1-3
		G-CSF 5 ug/kg sc qd d5-12
ESHAP	Etoposide	40 mg/m2/d iv over 1 hr d1-4

REGIMEN	DRUG	TREATMENT
Q3-4w x 6-8 cycles	Methylprednisolone	500 mg/d iv over 15 min d1-5
	Cisplatin	25 mg/m2/d civi d1-4
	Cytarabine	2000 mg/m2 iv over 2 hr d5
DHAP Q3-4w	Dexamethasone	40 mg po qd d1-4
	Cisplatin	100 mg/m2 iv over 24 hrs d1
	Cytarabine	2000 mg/m2 iv q12 hrs for 2 doses d2
EPOCH Q3w x 6-8 cycles	Etoposide	50 mg/m2/d civi d1-4
	Prednisone	60 mg/m2/d po d1-5
	Vincristine	0.4 mg/m2/d civi d1-4
	Adriamycin	10 mg/m2/d civi d1-4
	Cyclophosphamide	750 mg/m2 iv over 14 mins d5
	Bactrim DS	1 tablet po bid tiw
	Neupogen	5 mcg/kg sc qd beginning on d6 until ANC> 10,000/uL
Hyper-CVAD/MTX-Ara-C	*Cycle 1,3,5,7 (3-4 wks/cycle)*	
	Cyclophosphamide	300 mg/m2 iv over 2 hrs q12 hrs x 6 doses d1-3
	Mesna	600 mg/m2/d civi d1-3 to start 1 h before cyclophosphamide
	Vincristine	2 mg iv d4, 11
	Adriamycin	50 mg/m2 iv over 24 hrs (over 448 hrs if LVEF <50%) d4
	Dexamethasone	40 mg po or iv qd d1-4 and d11-14
	Cycle 2,4,6,8 (3-4 wks/cycle)	
	Methotrexate (MTX)	200 mg/m2 iv over 2 hrs followed by 800 mg/m2 civi over 22 hrs d1
	Cytarabine (Ara-C)	3 g/m2 (1 g/m2 for patients over 60 yo) iv oer 2 hrs q12 hrs x 4 doses d2-3
	Leucovorin	50 mg iv q6 hrs starting 12 hrs after completion of MTX untill MTX level < 0.05 uM
	Intrathecal Chemotherapy	
	Prophylaxis	
	MTX 12 mg d2 of each cycle for a total of 3-4 treatments	
	Ara-C 100 mg d8 of each cycle for a total of 3-4 treatments	
	Therapeutic	
	Intrathecal chemotherapy twice a week (MTX 12 mg and Ara-C 100 mg respectively) until no more cancer cells in CSF, then decrease intrathecal chemotherapy to once a week x 4, followed by MTX 12 mg d2, Ara-C 100 mg d8 for the remaining chemotherapy cycles	

3.2 Rituximab (Rituxan, IDEC-C2B8)

Rituximab may be used as part of the cytoreduction and mobilization regimen if desired by the treating physician, and if so, will be ordered in the pre-printed order sheets as noted above. Rituximab infusion will be per COH standard practice

including possible premedication with diphenhydramine, acetominophen and possibly hydrocortisone.

3.3 Granulocyte-Colony Stimulating Factor (Figrastim, Amgen)

Granulocyte-Colony Stimulating Factor (G-CSF) will initially be administered to the research participant according to COH standard of care. In autologous donors, there is a dose-response relationship for G-CSF with higher doses of G-CSF (16 – 24 µg/kg/day given in two divided doses 10 to 12 hours apart) resulting in better $CD34^+$ cell yields than conventional mobilization doses. Thus the HCT physician or the Blood Bank staff physician may choose to order a higher dose of G-CSF or alter the G-CSF dose if deemed necessary. G-CSF will begin 24 hours after the last dose of chemotherapy and will continue until the end of stem cell collection. It will be administered at approximately the same time each day as defined in the institutional standard operating procedures. The dose should be given at least one hour prior to HPC(A) apheresis on the days of apheresis. Daily dosing of G-CSF will continue until the last day of stem cell collection has been reached.

3.4 Plerixafor (Mozobil™, Genzyme Corp.)

Plerixafor, a hematopoietic stem cell mobilizer, is indicated in combination with G-CSF to mobilize hematopoietic stem cells and may be used in combination with or as an alternative to GCSF for stem cell mobilization at the discretion of the primary COH hematologist as outlined in the Hematology standard operating procedure (SOP).

3.5 Hematopoietic Progenitor Cell, Apheresis, Collection, Cryopresevation, and Re-Infusion

Current institutional operating procedures shall be used in collection, processing and cryopreservation of the autologous peripheral blood stem cell product. Current institutional operating procedures shall also be used during infusion of the HPC(A) product.

3.6 Cryopreserved Autologous T_{CM}-Enriched CD19R-CAR^+ $CD8^+$ T cell Product

Peripheral blood mononuclear cell (PBMC) preparations from research participants' leukapheresis products will be isolated by Ficoll separation followed by a cell wash/concentration procedure. PBMC's will then undergo a two-step CliniMACS® immunomagnetic selection procedure to derive $CD8^+$ T_{CM} enriched T cell preparations. The first step is to deplete PBMC's of cells expressing CD4 (CD4 T cells), CD14 (monocytes), and CD45RA (naïve T cells). The second step is an enrichment step for cells expressing CD62L, a marker on $CD45RO^+$ T cells for the central memory subset. The resulting cell preparation, highly enriched for $CD8^+CD45RO^+CD62L^+$ $T_{CM,}$ will then be activated with anti-CD3/CD28 beads. After activation the T_{CM} cells will undergo a lentiviral transduction to express the CD19-specific CAR.

Following transduction cells will be expanded *in vitro* with IL-2/IL-15 to achieve cell numbers sufficient for the research participant's planned clinical cell dose and all related product release testing. At the end of the culture, cells will be harvested, washed and formulated in cryopreservation media, and transferred to a cryopreservation bag. Samples will be taken from each product prior to cryopreservation, and cryopreserved bag(s) will be frozen using a controlled rate

freezer. Cryopreserved cells will be stored in the vapor phase in a controlled access LN_2 freezer until released for clinical use.

3.6.1 Lentiviral Vector CD19Rop-epHIV7

The cloned DNA that will be used for the genetic modification of autologous T cells consists of a CD19-specific chimeric immunoreceptor (designated CD19R), which was generated by fusion of the human GM-CSF receptor alpha signal, CD19-specific ScFv, IgG4 Fc hinge, CD4 transmembrane and CD3zeta cytoplasmic signaling domain sequences, and was synthesized *de novo* by Geneart after codon optimization (thus, the name CD19Rop). This CD19Rop sequence was inserted into the multiple cloning site of the epHIV7 lentiviral vector, so that its transcription is driven by the EF1 promoter. The CD19Rop-epHIV7 construct does not contain an intact 3' long terminal repeat (LTR) promoter, so the resulting expressed and reverse transcribed DNA proviral genome in targeted cells will have inactive LTRs.

As a result of this design, no HIV-I derived sequences will be transcribed from the provirus and only the therapeutic CD19Rop sequence will be expressed. The removal of the LTR promoter activity in this self-inactivating vector is also expected to significantly reduce the possibility of unintentional activation of host genes [134]. Furthermore, this study will employ replication-incompetent lentivirus produced by the 4-plasmid co-transfection of producer cells (i.e., 293T renal carcinoma cells) [135].

Briefly, the crippled CD19Rop-epHIV7 containing lentivirus was harvested from cultures of 293T cells that had been transiently transfected with the following four plasmids encoding the required components: 1) pCgp containing the HIV-1 gag and pol genes required for viral vector assembly; 2) pCMV-G containing the VSV-G gene required for viral vector infectivity; 3) pCMV-rev containing the rev gene which assists in the transportation of the viral genome for efficient packaging; and 4) the above described CD19Rop-epHIV7 transfer vector.

4.0 Staging Criteria

4.1 Pre-Enrollment

4.1.1 Verification of Lymphoma

Verification of history of intermediate grade B-cell lineage lymphoma (e.g., diffuse B-cell lymphoma, Mantle Cell lymphoma, transformed Follicular lymphoma), including histological verification.

4.1.2 Imaging and/or Histophatological Confirmation

Imaging and/or histopathological confirmation of relapsed disease after achieving first remission with primary therapy, or failure to achieve remission with primary therapy.

4.1.3 Relapsed Disease

Standard staging studies for extent of relapsed disease.

5.0 Research Participant Eligibility

5.1 Inclusion Criteria at Time of Enrollment

5.1.1 Confirmation of Diagnosis

COH pathology review confirms that research participant's diagnostic material is consistent with history of intermediate grade B-cell NHL (e.g., diffuse B-cell lymphoma, Mantle Cell lymphoma, transformed Follicular lymphoma).

5.1.2 History of Relapse

History of relapse after achieving first remission with primary therapy, or failure to achieve remission with primary therapy.

5.1.3 Life expectancy

Life expectancy >16 weeks

5.1.4 Age

Age at time of enrollment is ≥18 years.

5.1.5 KPS

KPS ≥70%

5.1.6 Pregnancy

Negative serum pregnancy test for women of childbearing potential.

5.1.7 Selection Criteria

Research participant has an indication to be considered for autologous stem cell transplantation.

5.2 Exclusion Criteria at Time of Enrollment

5.2.1 Study Specific Exclusion Criteria

- Fails to understand the basic elements of the protocol and/or the risks/benefits of participating in this phase I/II study. Evidence of understanding includes passing the Protocol Comprehensive Screening given by the Research Subject Advocate (RSA). A legal guardian may substitute for the research participant.
- Any standard contraindications to myeloablative HSCT per standard of care practices at COH.
- Dependence on corticosteroids.
- Currently enrolled in another investigational therapy protocol.
- HIV seropositive based on testing performed within 4 weeks of enrollment.
- History of allogeneic HSCT or prior autologous HSCT.
- Active autoimmune disease requiring systemic immunosuppressive therapy.
- Research participants who are to receive radioimmunotherapy (Zevalin-based)-based conditioning regimens.

- Research participants with known active hepatitis B or C infection.

5.3 Pre Transplant Tests

The following pre-study tests should be obtained prior to stem cell transplantation in accordance with good medical practice. Results of these tests do not determine eligibility. Minor deviations would be acceptable if they do not impact on research participant safety in the clinical judgment of the treating physician.

- CMV Titer
- Hepatitis Panel (which includes Hep A antibody, Hep B surface antigen, Hep B core antibody, and Hep C antibody)
- Hepatitis B Surface Antibody
- EBV, HSV and VZV Titer
- LDH measurement
- HIV 1/2 Antibody

5.4 Eligibility to Undergo Autologous Myeloablative Transplantation with HPC(A) Rescue

5.4.1 Candidate for Autologous Transplant

Research participant meets all standard clinical parameters for candidates of autologous transplant as described in the current COH Hematopoietic Cell Transplant Standard Operating Policies, Procedures and Protocols – Patient Evaluation & Selection or Deferral for HCT.

5.4.2 Scheduled for Chemotherapy

Research participant is scheduled to receive a standard chemotherapy-based conditioning regimen, such as CBV or BEAM.

5.4.3 Cryopreserved HPCA Product

Research participant has a cryopreserved unselected HPCA product of at least 2 x 10^6/kg $CD34^+$ cells.

5.4.4 Evidence of Stable or Improved Disease

Research participant has evidence of improvement or stable disease after salvage therapy.

5.5 Eligibility Criteria at Time of Infusion of Genetically Modified Autologous T Cells

5.5.1 Released T Cell Product

Research participant has a released cryopreserved T cell product.

5.5.2 Cryopreserved Back-up

Research participant has a cryopreserved back-up unselected HPC(A) product of at least 2 x 10^6/kg $CD34^+$ cells.

5.5.3 Autologous HPC(A) Procedure

Research participant has undergone an autologous HPC(A) procedure.

5.5.4 Pulmonary

Not requiring supplemental oxygen or mechanical ventilation, oxygen saturation 90% or higher on room air.

5.5.5 Cardiovascular

Not requiring pressor support, not having symptomatic cardiac arrhythmias.

5.5.6 Renal Function

Adequate renal function defined as: Lack of acute renal failure/requirement for dialysis, as evidenced by creatinine <1.6.

5.5.7 Liver Function

Adequate liver function defined as: Total bilirubin $\leq$5.0.

5.5.8 Neurological

Research participant without clinically significant encephalopathy/new focal deficits.

5.5.9 Infectious diseases

No evidence of uncontrolled active infectious process.

5.6 Criteria for Delaying or Cancelling T Cell Dose

5.6.1 Delaying T Cell Dose

Research participants who do not meet eligibility for T cell infusion on day +2 or day +3 may receive T cell infusion at a later date, after the medical issues are appropriately addressed, and once eligibility criteria for this event is achieved.

5.6.2 Canceling the T Cell Dose

Following are the criteria for canceling the T Cell Dose

- Failure to meet eligibility criteria on **Section 5.5**: (Eligibility Criteria at Time of Infusion of Genetically Modified Autologous T Cells) by day +45 post HPC(A) rescue
- Significant and rapid progression of lymphoma requiring alternative medical intervention that, in the opinion of the principal investigator or his/her designee, is not compatible with T cell therapy.

6.0 Study Design

This will be a Phase I/II, open-label, nonrandomized study in which adult research participants with high-risk intermediate grade B-cell lymphomas who are candidates for an autologous myeloablative stem cell transplant procedure will receive post-transplant immunotherapy with adoptively transferred autologous T_{CM}-Enriched $CD19R^{+}$ $CD8^{+}$ T cells. The trial consists of dose escalation by cohort (phase I portion), followed by expanded enrollment at the tolerable dose (phase II portion) for a potential total enrollment of fifty-seven research participants. Cryopreserved T cell products will be infused at approximately day +2 or day +3 following HPC(A) reinfusion. Research participants whose modified cellular product cannot be generated in sufficient numbers to achieve the assigned cell dose level will not be removed from the study and may

receive the modified cell dose generated. Cell dose cohort advancement will be rule-based as described in **Section 12** (Statistical Considerations). The research participant's primary COH hematologist will manage the non-study specific aspects of their patient's medical management throughout the duration of this protocol and indefinitely thereafter.

7.0 Treatment Plan

7.1 PBMC Collection

The leukapheresis product will be collected at COH Donor Apheresis Center (DAC) according to DAC operating procedures. The research participant must be evaluated by a physician prior to leukapheresis and not have a standard contraindication for this procedure per COH standard practices, this process may take approximately 1 hour. The procedure will be a single apheresis run of approximately 2-4 hours. Apheresis duration may be modified by the DAC physician as required by DAC policies without prior notification to the PI and will not result in a deviation. Should a technical issue arise during the procedure or in the immediate processing of the product, such that it cannot be used for T cell production, a second procedure may be needed.

7.2 Salvage/Priming Chemotherapy

Research participants will commence with standard salvage chemotherapy per standard practice as prescribed by their treating hematologist who will use agents best suited for individual research participants based on their response to prior therapy and organ toxicity considerations. Mobilization for autologous stem cell collection with cytoreductive chemotherapy and G-CSF and/or Plerixafor will be conducted per current COH HCT Clinical Program Standard Operating Policies, Procedures and Protocols. Research participants with evidence of progressive disease after salvage chemotherapy will not be considered for this study (see **Section 5.4.4**).

7.3 Pre-transplant Rituximab Therapy for B-Cell Depletion

Since CD19-specific T cells will also target normal $CD20^+$ ($CD19^+$) B cells, the B cell numbers will be lowered using rituximab to reduce infusional toxicities attributable to T_{CM} cell activation upon receiving the genetically modified CTL and also increase availability of infused T cells to immediately target lymphoma cells. Furthermore, rituximab may blunt a humoral immune response against the genetically modified T cells. If rituximab is not given as part of the Salvage/Priming chemotherapy regimen, research participants will receive a single intravenous infusion of rituximab (chimeric anti-CD20 antibody) at the discretion of the PI at 375 mg/m^2 within 4-weeks of the planned auto-HSCT procedure. Rituximab infusion will be per COH standard practice including premedication with diphenhydramine and acetaminophen and hydrocortisone

7.4 Mobilization with G-CSF and/or Plerixafor

Mobilization with G-CSF and/or with Plerixafor will be started after completion of salvage/priming chemotherapy and rituximab, if salvage chemotherapy is required. G-CSF and/or Plerixafor will be used per institutional standard of practice (HCT SOP

"Mobilization of Peripheral Blood HPCs for Apheresis") for mobilization of peripheral blood stem cells and will be started after stem cell transplant at Day +5.

7.5 Hematopoietic Progenitor Cell, Apheresis and Product Manipulation

7.5.1 HPC, Apheresis Procedure

Apheresis will be performed on a continuous flow cell separator according to Donor Apheresis Center guidelines and standard of care.

7.5.2 Cryopreservation of Back-Up HPC Product – Phase I Arm

During the time of initial stem cell collection, an additional number of $CD34^+$ cells will be collected to re-establish normal hematopoiesis after high dose chemotherapy (minimum of 2.0×10^6 cells/kg) for research participant's within the Phase I Arm of the study.

7.6 Myeloablative Conditioning Regimen

Conditioning regimen for the autologous stem cell transplant will be administered per institutional standards, as outlined in the current COH HCT Clinical Program Standard Operating Policies, Procedures, and Protocols.

7.7 HPC(A) Cell Infusion

The cryopreserved HCT product will be thawed and infused according to institutional standard of practice on Day 0 of transplantation. Premedication with diphenhydramine, mannitol, hydrocortisone and acetaminophen will be as per institutional policy.

7.8 Adoptive Transfer of Cryopreserved T_{CM}-Enriched $CD19R^+CD8^+$ T Cell Products

The autologous cryopreserved T cell product will be manufactured and released for use in accordance with SOPs provided in an FDA IND for this project. A description of the manufacturing and release for use requirements are provided within the IND which is managed by COH Office of IND Development and Regulatory Affairs (OIDRA). On Day +2 or Day +3 after HSCT, when research participants meet protocol specified eligibility criteria for T cell infusion (**Section 5.5**: Eligibility Criteria at Time of Infusion of Genetically Modified Autologous T Cells), the cryopreserved unit will be thawed, washed, reformulated based on % CAR positivity and then transported to research participant's bedside. Research participants will be pre-medicated at least 30 minutes prior to T cell infusion with 15 mg/kg of acetaminophen P.O. (max. 650 mg.) and diphenhydramine 0.5-1 mg/kg I.V. (max dose 50 mg). Clinically acceptable alternatives may be used if research participant is intolerant.

The morning of T cell infusion preparation a sample of the T cell product will be sent for sterility analysis. Results will be obtained after the product has been infused. In the event that there is a positive microbiology culture the PI or designee must be notified immediately. Standard practice of care will be followed to treat participants having a bacterial, fungal or viral infection in addition to standard prophylaxis, with the agent chosen to cover the specific organism identified while taking into account any patient specific antibiotic allergies. Treatment will be at the PI or designee's discretion.

7.9 Summary of Correlative Studies

Peripheral blood, bone marrow and lymph node samples will be collected from research participants at the designated time points defined in **Section 8.0**: Study Parameters and Calendar, and **Appendix B**: Study Parameters and Calendar. Samples will be delivered, processed, stored, and evaluated in accordance with established laboratory practices at COH. Correlative studies performed, but not limited to, are as follows:

7.9.1 WPRE Q-PCR Determination of Frequency of Gene Modified Cells in the Circulation/Bone Marrow

The magnitude and duration of persistence of adoptively transferred T_{CM} cells and accumulation of infused T cells in bone marrow and lymph node will be measured by Q-PCR with primers specific for the lentiviral WPRE (woodchuck hepatitis virus post-transcriptional regulatory element) sequence normalized to cell numbers to read out frequency of gene marked cells in mononuclear cell preps.

7.9.2 *Ex vivo* Immunophenotyping/Functional Analysis

Direct *ex vivo* analyses of persisting infused cells will be performed directly on peripheral blood, bone marrow samples or lymph node samples using multiparameter flow cytometric analyses. *In vivo* activation/memory/effector phenotype of persisting and expanded infused cells will be analyzed if at least 1% of total lymphocytes in samples collected is shown to be immunoreceptor–positive and appropriate antibody reagents are available to detect immunoreceptor-positive cells in whole blood samples. A panel of specific antibodies will be used to evaluate the differentiation status (such as naïve, effector, memory, effector memory, central memory) of persisting gene-modified T cells. Correlation of initial activation status of infused cells and *in vivo* T cell persistence and direct *ex vivo* characterization of anti-tumor effector functions of persisting infused cells will also be performed.

7.9.3 Cytokine Analysis

Research participants will have weekly peripheral blood draws for the first month post T cell infusion, and then monthly for the first year, which will be analyzed for the presence of cytokines such as IFN-g. We will also test the level of IFN-g and other cytokines released by the corresponding final cell product after *in vitro* antigen stimulation.

7.10 Supportive Care

7.10.1 Supportive Care for Regimen Related Toxicities

All standard supportive care measures for patients undergoing HSCT will be used at the discretion of the research participant's COH oncologist. Standard supportive care guidelines are outlined in Hematopoietic Cell Transplant Clinical Program Standard Operating Policies, Procedures, and Protocols.

Decisions regarding antibiotics choices, when hyperalimentation is used and when to use blood products will be determined by the treating clinician. Menstruating females should receive an anovulatory agent during the

thrombocytopenic period. The use of cytokines, such as G-CSF to facilitate engraftment, is permitted per institutional guidelines.

7.10.2 Infectious Disease Prophylaxis and Monitoring

Active infections occurring after study enrollment will be treated according to the standard of care as defined by the COH HCT Clinical Program Standard Operating Policies, Procedures, and Protocols.

7.10.3 Contra-Indicated Medications

Unless the Principal Investigator or her designee provides an exception, the following agents, other than specified in the protocol, are not allowed once T cell infusion commences through day 100:

- systemic corticosteroids
- chemotherapy
- immunosuppressive agents
- immunotherapy
- other investigational agents

8.0 Study Parameters and Calendar

COH Standard Policies and Procedures will be performed and followed in addition to the listed study procedures below. Bone marrow examination and lymph node sampling may be cancelled by the PI or designate. Note that the planned amount of blood drawn for this protocol in the first year (time of enrollment to month +12 post T cell infusion) is approximately 669 cc. Additional diagnostic test may be performed as required for AE reporting under **Sections 11.5** of the protocol to delineate AEs.

8.1 Enrollment

8.1.1 Evaluation of Eligibility

Evaluation of research participant's eligibility after signing the informed consent will include the following; however, procedures completed within 30 days of the informed consent signing will not be duplicated and will, therefore, be used to document eligibility:

- Documented protocol comprehension assessment by Research Subject Advocate
- Review by COH pathologists of available pathologic specimens to confirm history of intermediate grade B-cell NHL (e.g., diffuse B-cell lymphoma, Mantle Cell lymphoma, transformed Follicular lymphoma).
- Documentation of relapsed disease after achieving first remission with primary therapy or failure to achieve remission with primary therapy.
- Review of available CT and nuclear medicine scans.
- History and Physical Exam, Vital Signs, KPS.
- Females and males of reproductive potential must use a physician-approved contraceptive method for at least two weeks prior to, during, and two months after T cell infusion.

- Serum pregnancy test for post-menarchal women without a history of tubal ligation or hysterectomy
- Initiation of the following tests:
  - EBV, CMV and HIV serologies
- BSA (will be re-calculated throughout treatment as needed)
- CBC, Differential, Platelet Count
- Comprehensive Metabolic Panel
- Bone marrow examination per COH standard policies and procedures for HCT (may be cancelled at the PI or designees discretion)
  - *Ex vivo* Immunophenotyping / Functional Analysis Correlative Studies

8.2 HPC(A) Transplant

8.2.1 Prior to HPC(A)

Prior to HPC(A) the following must be performed.

- CT and FDG-Pet or PET/CT combination to evaluate lymphoma disease status.
- Bone marrow examination that in addition to standard disease specific pathologic evaluation includes Correlative Studies (may be cancelled at the PI or designees discretion).
- 55 cc peripheral blood collected for Correlative Studies and Cryopreservation of PBMC and Plasma

8.2.2 Day 0 - HPC(A) Transplant

On Day 0 of HPC(A) Transplant, COH standard policies and procedures for HCT must be followed.

8.2.3 Day +2 or Day + 3 Post HPC(A) Transplant

T Cell Infusion on Day +2 or Day +3 post HPC(A) Transplant, the following must be performed. If, in the opinion of the PI, or her designee this must be delayed, the procedure may be delayed up to Day+45 following HSCT.

- Progress notes including vital signs (pulse rate, temperature, respiratory rate, blood pressure)
- KPS
- Complete blood count, differential, platelet count
- Chemistry panel - per COH standard policies and procedures for HCT
- 35 cc peripheral blood will be collected for Correlative Studies (drawn prior to T_{CM} cell infusion) including, but not limited to, the following:
  - WPRE Q-PCR
  - *Ex vivo* Immunophenotyping/Functional Analysis
- CTCAE evaluation using version 4

8.2.4 Day +5 (+/-3) Post Stem Cell Transplant

At Day +5, begin G-CSF (5 µg/kg/day) following institutional standard of practice.

8.2.5 Day +60 (+/- 3) Post Stem Cell Transplant

- CT and FDG-Pet or PET/CT combination
- Bone marrow examination that in addition to standard disease specific pathologic evaluation (may be cancelled at the PI or designees discretion), includes Correlative Studies. Correlative tests to include, but not limited to, the following:
  - WPRE Q-PCR
  - *Ex vivo* Immunophenotyping/Functional Analysis

8.2.6 Day +100 (+/- 3) Post Stem Cell Transplant

- Bone marrow examination that in addition to standard disease specific pathologic evaluation (may be cancelled at the PI or designees discretion), includes:
  - WPRE QPCR
  - *Ex vivo* Immunophenotyping/Functional Analysis
- Lymph node biopsy/removal of a pathologic lymph node that is accessible (such as in the axilla or groin) if lymph node is detectable within 100 days post transplant.

8.2.7 6 month Evaluations: +6, +12, +18 and +24 months Post Stem Cell Transplant

- CT and FDG-Pet or PET/CT combination
  Scans may be cancelled if they were/are performed as part of standard of care within +/- 1 month.

8.3 T Cell Infusion

8.3.1 Within 24 hours Post T Cell Infusion

35 cc peripheral blood will be drawn for Correlative Studies including, but not limited to, the following:

- WPRE QPCR
- *Ex vivo* Immunophenotyping/Functional Analysis

8.3.2 Day 7 (+/- 3) Post T Cell Infusion

At Day 7 (+/- 3) Post T Cell Infusion 35 cc peripheral blood will be drawn for Correlative Studies including, but not limited to, the following:

- WPRE QPCR
- *Ex vivo* Immunophenotyping/Functional Analysis

8.3.3 Day 14 (+/- 3) Post T Cell Infusion

At Day 14 (+/- 3) 35 cc peripheral blood will be drawn for Correlative Studies including, but not limited to, the following:

- WPRE QPCR
- *Ex vivo* Immunophenotyping/Functional Analysis

8.3.4 Day 21 (+/- 3) Post T Cell Infusion

At Day 21 (+/- 3) Post T Cell Infusion, 35 cc peripheral blood will be drawn for Correlative Studies including, but not limited to, the following:

- WPRE QPCR
- *Ex vivo* Immunophenotyping/Functional Analysis

8.3.5 Day 28 (+/- 3) Post T Cell Infusion

Day 28 (+/- 3) Post T Cell Infusion:

35 cc peripheral blood will be drawn for Correlative Studies including, but not limited to, the following:

- WPRE QPCR
- *Ex vivo* Immunophenotyping/Functional Analysis

Unilateral Bone Marrow Aspirate (may be cancelled at the PI or designees discretion)

- Standard pathological evaluation
- WPRE Q-PCR
- *Ex vivo* Immunophenotyping/Functional Analysis

8.3.6 Monthly Post T Cell Infusion for 1 year (starting at Month 2)

35 cc peripheral blood will be drawn for Correlative Studies including, but not limited to, the following:

- WPRE QPCR
- *Ex vivo* Immunophenotyping/Functional Analysis
  - B cell and IgG analysis
- CBC, Differential, Platelet Counts, Comprehensive Metabolic Panel and LDH measurements

8.3.7 3 month Evaluation: Post T Cell Infusion (may be combined with Day +100 visit)

- Additional 25 cc peripheral blood will be drawn for Correlative Studies for a total of 60 cc at this time point. Correlative tests to include, but not limited to, the following:
  - WPRE QPCR
  - *Ex vivo* Immunophenotyping/Functional Analysis
- HIV-1/2 antibody testing for short-term follow-up plan (reference **Section 8.4**)

8.3.8 6 Month Evaluation Post T Cell Infusion

- HIV-1/2 antibody testing for short-term follow-up plan (reference **Section 8.4**)

- Up to 60 cc peripheral blood will be drawn for Correlative Studies including, but not limited to, the following:
    - WPRE QPCR
    - *Ex vivo* Immunophenotyping/Functional Analysis (B cell and IgG analysis)
    - CBC, Differential, Platelet Counts, Comprehensive Metabolic Panel and LDH measurements
- Bone marrow examination that in addition to standard disease specific pathologic evaluation (may be cancelled at the PI or designees discretion), includes:
    - WPRE QPCR
    - *Ex vivo* Immunophenotyping/Functional Analysis

8.3.9 Yearly Evaluations: 12, 24 and 36 Months Post T Cell Infusion

- CT and FDG-Pet or PET/CT combination
- Up to 60 cc peripheral blood will be drawn for Correlative Studies including, but not limited to, the following:
    - WPRE QPCR
    - *Ex vivo* Immunophenotyping/Functional Analysis (B cell and IgG analysis)
    - CBC, Differential, Platelet Counts, Comprehensive Metabolic Panel and LDH measurements
- Bone marrow examination that in addition to standard disease specific pathologic evaluation (may be cancelled at the PI or designees discretion), includes:
    - WPRE QPCR
    - *Ex vivo* Immunophenotyping/Functional Analysis
- HIV-1/2 antibody testing for short-term follow-up plan (reference **Section 8.4**)

8.4 Short-term Follow-up Plan

COH patients who are recipients of gene transfer products involving the use of lentiviral vectors are required by the FDA to undergo follow-up testing for replication competent lentivirus (RCL) for no less than 15 years. The short-term follow-up testing for RCL will be performed under COH IRB 09174 until the research participant completes the protocol specified follow-up period of 36 months and will consist of analysis of whole blood samples for Human Immunodeficiency Virus (HIV-1/2) antibody at the pre-treatment (baseline), 3 month, 6 month, 12 month, 24 month, and 36 month time points.

8.5 Long-term Follow-up Plan

Research participants treated on this study will be asked to participate in two of COH's long-term follow-up protocols: (1) COH IRB 02025: Long-Term Follow-up of Recipients of Gene Transfer Research at City of Hope, as specified in the guidance "Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events" and (2) COH IRB 00029: Long-Term Following Hematopoietic Cell Transplantation per institutional policy.

COH patients who are recipients of hematopoietic cell transplantation enroll onto COH IRB 00029 after receiving transplantation. COH IRB 00029 consists of the use of an annual status short form, a periodic Long-Term Follow-up Complications form, and a secondary malignancies form. In the event of the death of a research participant in the time period between the follow-up time-points, information will be obtained from the responsible physician or a specified family member (usually a parent or a spouse).

COH patients who are recipients of gene transfer products enroll onto COH IRB 02025 upon completion of the protocol required follow-up period. COH IRB 02025 consists of the continued testing for RCL (initial testing at the pre, 3, 6, 12, 24 and 36 month time points previously required under COH IRB 9174 follow-up, reference **Appendix B**). Follow-up under COH IRB 02025 will include the following:

- Physical examination which will include assessment for reproductive risk and risk to the fetus; autoimmune toxicities (such as new evidence or exacerbation of a prior rheumatologic or other autoimmune disorder);
- Continued testing for RCL (initial testing at the pre, 3, 6, 12, 24 and 36 month time points previously required under COH IRB 09174 follow-up) which will be performed by analysis of whole blood samples for Human Immunodeficiency Virus (HIV-1/2) antibody on an annual basis;
- Evaluation of T cell persistence which will include testing for long-term vector persistence and insertional mutagenesis until at such time T cells become undetectable.

All long-term toxicities will be reported to the Agency in accordance with CFR 312.32.

9.0 Monitoring Toxicities

9.1 Management of Constitutional Symptoms Associated with T cell Infusion

Mild transient symptoms have been observed with LAK, TIL, and T cell clone infusions and may occur in research participants being treated with T_{CM}-enriched $CD19R^{+}CD8^{+}$ T cell infusions. The management of these symptoms is outlined below.

9.1.1 Fever

Fever, chills and temperature elevations >101°F will be managed with additional Tylenol as clinically indicated. Demerol I.V. (max dose 50 mg) may be given for chills. Additional methods such as cooling blankets may be employed for fevers resistant to these measures. Research participants that develop fever or chills will have a blood culture drawn. Appropriate selection of empiric antibiotics for treatment of neutropenic fever will be administered to research participants who, in the opinion of the physician in attendance, appear septic; alternate antibiotic choices will be used as clinically indicated.

9.1.2 Hypotension

Transient hypotension will initially be managed by intravenous fluid administration; however, research participants with persistent hypotension will be admitted for definitive medical treatment.

9.1.3 Hypoxemia

Hypoxemia will be managed with supplemental oxygen. An etiology for hypoxemia will be worked up per standard clinical practice.

9.2 Management of Acute Adverse Event(s) Attributable to This Study

9.2.1 Management of Acute Adverse Event(s) Attributable to Infused T Cells

Following T cell infusions, the following rules will be applied for adverse events that are greater than grade 2 and are probably or definitely attributed to T cell infusion:

- Research participants experiencing a new grade 3 or higher toxicity with an attribution of ≥4 (probable or definite) to the infused T cells rather than expected toxicities attributable to the myeloablative preparative regimen, that in the opinion of the Principal Investigator puts the research participant in significant risk of an untoward outcome if measures are not taken to ameliorate the toxicity and commence with corticosteroid treatment (reference **section 9.3**).
- Additional measures may also be taken to resolve the toxicity should the protocol specified corticosteroid treatment plan failure to ablate side effects associated with T cell infusion such as, but not limited to, immunosuppressive medications such as ATG/Campath and calcineurin inhibitors, or chemotherapy agents with immunosuppressive properties the administration of other immunosuppressive agents.
- If applicable, all research participants will be hospitalized for at least the first 72 hours of receiving corticosteroids.

9.2.2 Management of aHSCT Engraftment Failure

Back-up cryopreserved HPC(A) product (reference **section 7.5.2**) will be available to those research participants experiencing engraftment failure (reference **section 12.3.1**).

9.2.3 Management of Infectious Complications from Prolonged Lymphopenia

Standard of practice will be used for the treatment of infectious complications from prolonged lymphopenia including, but not limited to, trimethoprim-sulfamethoxazole (or an equivalent) for the prevention of pneumocystis jiroveci, acyclovir for herpes simplex and herpes zoster infection, and an azole drug for prevention of invasive fungal disease. Routine screening and treatment of CMV reactivation will also be performed in these research participants.

9.3 Schedule of Systemic Corticosteroids to Ablate Side Effects of Genetically Modified T cells

The following table (**Table 2**: Steroid Dose Schedule for Ablation of T cell Side Effects) shows the dose schedule for steroids dose used to ablate any side effects observed upon T cell infusion:

Table 2: Steroid Dose Schedule for Ablation of T cell Side Effects

Day of Dose	Steroid Dose
1	Intravenous Solu-Medrol at 2 mg/kg divided q 8hr
2	Intravenous Solu-Medrol at 1 mg/kg divided q 8hr
3-4	Prednisone at 1 mg/kg P.O. BID or Intravenous Solu-Medrol at 0.8 mg/kg BID (begin wean if symptom improvement)
5-6	Prednisone at 0.5 mg/kg P.O. BID or Intravenous Solu-Medrol at 0.4 mg/kg BID
7-8	Prednisone at 0.25 mg/kg P.O. BID or Intravenous Solu-Medrol at 0.2 mg/kg BID
9-10	Prednisone at 0.1 mg/kg P.O. BID or Intravenous Solu-Medrol at 0.08 mg/kg BID
11+	Prednisone at 0.1 mg/kg P.O. q day or IV Solu-Medrol at 0.08 mg/kg q day

*Corticosteroid dosing may be extended at the discretion of the PI or designee should significant symptoms fail to resolve.

Such steroid treatment strategies have been clinically shown to reverse the side effects of adoptively transferred cytolytic immune cells such as T cells [136-138].

9.4 Expected Adverse Events Associated with this Protocol

CTCAE v4.0 parameters will be used for toxicity grading. The table below (**Table 3**: Expected Adverse Events Attributable to Stem Cell Transplant or T Cell Infusion) lists regimen related toxicities attributable to the following treatment procedures listed below.

Table 3: Expected Adverse Events Attributable to Stem Cell Transplant or T Cell Infusion

Expected Adverse Events Attributable to Stem Cell Transplant	
Treatment/Procedure	**Symptoms Associated with Treatment/Procedure**
Placement of Hickman catheter	Pain, Bruising, Bleeding, Pneumothorax, Insertion site infection, Bacteremias
High dose chemotherapy	Nausea, Vomiting, Mucositis, Fatigue, Alopecia, Anorexia, Diarrhea, Neutropenic Fevers, Amemorrhea, Infertility, Pancytopenia, Bacteremia, Myelodysplastic syndrome, Elevations of liver enzymes, Veno-occlusive disease of the liver (VOD), Pneumonitis, Neuropathy, Myalgias, Palmar-plantar erythema
Rituximab	Fever, Chills, Rigors, Nausea, Urticaria, Angioedema, Bronchospasm, Hypotension
Expected Adverse Events Attributable to T Cell Infusion	
Treatment	**Adverse Events Associated with Treatment**

T Cell Infusion	• ≤ Grade 4 Fever for less than 48 hours after T cell infusion • ≤ Grade 2 Chills lasting for less than 24 hours after T cell infusion • ≤ Grade 3 Cough lasting for less than 24 hours after T cell infusion • ≤ Grade 3 Transaminases for lasting for less than 7 days after T cell infusion • ≤ Grade 2 Tachycardia lasting for less than 48 hours after T cell infusion • ≤ Grade 3 Hypotension lasting for less than 48 hours after T cell infusion • ≤ Grade 3 Cytokine release syndrome lasting for less than 48 hours after T cell infusion

Adverse events from the above list occurring within the specified time will:

- Not result in an expedited adverse event reporting to the FDA
- Not result in ablation of T cells with corticosteroids

9.5 Adverse Events to Be Monitored

Toxicity criteria for this protocol will be per the NCI Common Toxicity Criteria For Adverse Events (CTCAE) v4.0.[1] A copy of the complete CTCAE may be downloaded from the CTEP home page (http://ctep.info.nih.gov/). Any toxicity reported by research participants while receiving treatment or in follow-up for which there is no specific CTCAE designation will be graded on the following scale:

- ***Grade 0*** - no toxicity,
- ***Grade 1*** -mild toxicity, usually transient, requiring no special treatment and generally not interfering with usual daily activities,
- ***Grade 2*** - moderate toxicity that may be ameliorated by simple therapeutic maneuvers, and impairs usual activities,
- ***Grade 3*** -severe toxicity that requires therapeutic intervention and interrupts usual activities. Hospitalization may be required or may not be required.
- ***Grade 4*** - life-threatening toxicity that requires hospitalization
- ***Grade 5*** - death related to adverse event

To ensure that treatment-related conditions are distinguished from disease-related conditions, attribution of causality will be established in grading adverse events. All symptoms, signs, or diseases (including abnormal laboratory findings), that might be associated with investigational agents or therapies will be captured and graded. For each event, the Principal Investigator or his/her designee in conjunction with the physician or research nurse who examined and evaluated the research participant, will assign the attribution. Data managers who are removed from the clinical assessment of the research participant will not perform this. Attribution of adverse events attributed to the infused genetically modified T cells should be determined using the following criteria:

- ***Definite*** – (5) The adverse event is *clearly related* to the infused T cells

[1] ncictephelp@ctep.nci.nih.gov

- ***Probable*** – (4) The adverse event is *likely related* to the infused T cells
- ***Possible*** – (3) The adverse event *may be related* to the infused T cells
- ***Unlikely*** – (2) The adverse event is *doubtfully related* to the infused T cells
- ***Unrelated*** – (1) The adverse event is *clearly not related* to the infused T cells

Deaths occurring 30 days or later from T cell infusion and death from tumor progression will be scored as a grade 5 toxicity; however, those with an attribution of unlikely or not related, as determined by the Principal Investigator and his/her designee, will not result in termination of the study.

All Serious Adverse Events (SAEs) regardless of attribution shall be reported in an expedited manner according to Section 11.5: Adverse Event Reporting.

Common Toxicity and Adverse Events shall be documented on an approved Case Report Form (see Appendix C).

9.6 Criteria for Research Participant Accrual

9.6.1 Phase I Accrual Interval

9.6.1.1 Accrual within a Cohort

- Cohort Advancement Rule for Dose Level 0 ($50x10^6$ CAR^+ T_{CM}): The minimum time interval between infusion of T_{CM} cells in one research participant and infusion of T_{CM} cells in the next research participant receiving Dose Level 0 ($50x10^6$ CAR^+ T_{CM}) is four weeks.
- Cohort Advancement Rule for Dose Level 1 and Above: Research participants will receive their assigned T cell dose in cohorts of 3 (reference **Section 12** [Statistical Considerations]).

9.6.1.2 Accrual for Cohort Advancement

The minimum time interval between first infusion of T_{CM} cells at a set dose and the first infusion of T_{CM} cells at the next dose escalation is 3 months and is dependent on the dose escalation guidelines provided in **Section 12.1.1**, Table 5: Dose Escalation Guidelines.

9.6.2 Accrual for Advancement into the Phase II Arm

The minimum time interval between infusion of T_{CM} cells in the last research participant on the Phase I arm of the study and infusion of T_{CM} cells in the first research participant on the Phase II arm of the study is 3 months.

9.7 Research Participant Premature Discontinuation

Research participants who do not receive the T cell infusion will be considered to have prematurely discontinued the study. The reasons for premature discontinuation (for example, voluntary withdrawal, toxicity, and death) must be recorded on the case report form. Research participants who do not receive T cell therapy may continue to be monitored as stipulated in the protocol. Potential reasons for premature discontinuation include:

- In the judgment of the PI, or his/her designee, the research participant is too ill to continue.
- Research participant/family is noncompliant with study therapy and/or clinic appointments.

- Pregnancy.
- Voluntary withdrawal; a research participant or his/her parents/legal guardians may remove himself/herself from the study at any time without prejudice.
- Significant progression of lymphoma requiring alternative medical interventions that in the opinion of the PI or his/her, designee, are not compatible with T cell therapy.

9.8 Study Closure

The study will be halted:

9.8.1 Lack of Improvement

If any research participant receiving systemic corticosteroids for ablation of T cell-mediated side effects does not show an improvement to a toxicity grade of <3 within 14 days of initiating ablation procedures or;

9.8.2 Persistence of T_{CM} Cells

If there is no identifiable persistence of infused T_{CM} cells in 0 of the first 6 research participants after reaching the MTD or highest manufactureable dose (reference **Section 12.3.2**).

9.8.3 Study Termination

The study is terminated by the PI or her designate, the COH IRB, or the Food and Drug Administration.

10.0 Criteria for Evaluation and Endpoint Definitions

10.1 Criteria for Evaluation

Toxicity and adverse event will be assessed using CTCAE v4.0 from data obtained at each clinical assessment as outlined in **Appendix B**. Symptoms and toxicities will be evaluated as follows:

- Physical exam and Blood Chemistry/Hematology results
- Adverse event reporting

10.2 Disease Status

The grading of the tumor responses will be performed according to the Revised IWG response criteria (Cheson *et al.*, J Clin Oncol 25:579, 2007), reference **Appendix A**.

10.3 Dose Limiting Toxicity (see also Section 12.0)

Definition of Dose Limiting Toxicity (DLT):

- any grade 3 or higher toxicity, with the exception of those listed in **Section 9.4**; and designated as definitely or probably related (level of attribution) to the infusion of the T_{CM} cells; and occurring within 28 days of T-cell infusion;
- any toxicity requiring the use of steroids to ablate side effects attributable to the infusion of the T_{CM} cells, and occurring within 28 days of T-cell infusion;
- any toxicity which is a lower grade, but that increases in grade to a grade 3 or higher as a direct result of the T_{CM}, and occurring within 28 days of T-cell infusion; and

- any grade 2 or greater autoimmune toxicity, and occurring within 28 days of T-cell infusion.

Toxicities of any grade normally expected with an autologous stem cell transplant, as defined in Section 9.4, will not be considered a DLT with respect to protocol continuation, or dose escalation/de-escalation of T_{CM} cell dose.

11.0 Data and Safety Monitoring

11.1 Definition of Risk Level

This is a Risk Level 4 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx involving COH as the IND holder and a first-in-human gene therapy for *ex vivo* expanded autologous T_{CM}-Enriched CD19R-CAR^{+} CD8^{+} T cells in conjunction with myeloablative chemotherapy and autologous HSCT rescue for patients with recurrent/refractory B-lineage non-Hodgkin lymphomas.

11.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA/protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy (as listed in **Section 12.3**).

This study will utilize the Phase I tracking log to monitor data and safety for dose escalation, recording doses administered, and resultant adverse events. The tracking log will contain dose levels administered, DLT-defining adverse events, and documentation that the data from a dose level is complete before dose escalation. Those data and safety elements will be reported to the COH DSMC as applicable within the PMT report, which will be submitted quarterly from the anniversary date of activation, as noted in Table I below.. Protocol specific data collection will include the following items:

- Phase I arm:
  Assessment of Feasibility (i.e., ability to manufacture the required T cell dose from research participant's leukapheresis product) data.

- Phase II arm (in addition to review listed in Phase I arm above):
  (1) Assessment of Hematologic engraftment,
  (2) Assessment of T_{CM} persistence/Futility (the inability to achieve T_{CM} persistence).

In addition to the above, a Safety Committee will be convened, which is responsible for review of all adverse events associated with this protocol.

General responsibilities of the committee include review of adverse events associated with the protocol, including grading of severity, and assignation of level of attribution to the stem cell transplant and the T cell infusion.

Members

The Committee shall consist of the following three members:

- Protocol PI
- Physician from the Department of Hematology/Hematopoietic Cell Transplantation with expertise in transplantation, (one required, two allowed)
- Protocol Statistician, Suzette Blanchard (Dr. Longmate and Dr. Palmer can serve as alternate in Dr. Blanchard's absence)

Table I: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Compassionate Use Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

11.3 Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event* that results in any of the following outcomes:

- Death

- Is life-threatening event (places the subject at immediate risk of death from the event as it occurred);
- Requires in-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect
- Secondary Malignancy, or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience or outcome that *meets all three* of the following criteria:

- Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

11.4 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table II below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the continuation reports and PMT reports (see Table II below).

Table II: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grade 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

Externally Sponsored Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED[1]**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 1 and 2	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

ADDITIONAL REPORTING REQUIRMENTS

SAEs meeting the requirements for expedited reporting to the FDA, as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting which can found at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the following:

- any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];
- any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

Special instructions

Under COH-sponsored IND 14645, OIDRA, along with study staff, will prepare and submit the SAEs that meet the requirements of 21 CFR 312.32 to the FDA, followed by any required reporting to the NIH.

National Institutes of Health-Office of Biotechnology Activities (NIH-OBA) and FDA Reporting

Since this study involves gene therapy, and City of Hope holds the IND, adverse events must also be reported to the NIH-OBA

The PI/designee will submit the adverse event report through the City of Hope electronic reporting system, and then OIDRA will take responsibility for reporting of the adverse event to NIH-OBA.

Follow up of study participants

As required by the FDA, study patients will be followed long term (up to 15 years) and the PI will continue to report data and safety concerns to the FDA, DSMC, and IRB as they arise during this follow-up period.

12.0 Statistical Considerations

12.1 Phase I Study Arm

12.1.1 Design and Sample Size for Phase I Arm of Study

The objectives of the Phase I arm of the study are to assess the safety of cellular immunotherapy utilizing *ex vivo* expanded autologous T_{CM}-Enriched $CD8^+$ T cells genetically-modified to express a CD19-specific CAR in conjunction with a standard myeloablative autologous HSCT for patients with high-risk intermediate grade B-lineage non-Hodgkin lymphomas, and determine the MTD based on DLTs and describe the full toxicity profile.

This study will use a two stage design based on the target toxicity equivalence range design [139] patterned after Ji, Li, Bekele (2007) [124,] and Ji, Liu, Li, Bekele (2009).[140-141] to define the escalation and de-escalation rules to evaluate select doses of T_{CM} to determine the MTD. The decision to escalate to a higher dose, stay at the same dose, or de-escalate to a lower dose is determined by the portion of the toxicity probability scale (0-1) in which our toxicity rate lands. The toxicity probability scale is portioned into three pieces based on the target toxicity probability (pT) and the identified range of equivalence (pT-ε1 to pT+ ε2). If the study DLT rate is in the 0 to pT- ε1 range the guideline indicates escalate, if it is in the pT-ε1 to pT+ ε2 range the guideline indicates stay, and if the rate is in the pT+ ε2 to 1 range the guideline mandates de-escalate. Further we also implement the additional rules: 1) terminate the trial if dose level 1 is too toxic, and 2) if the current dose is safe but based on the data the next dose is deemed too toxic, stay at the current dose.

Research participants will enter the protocol in cohorts of 3. The dose schedule is provided in **Table 4**. The dose guidelines will be assessed after 3 evaluable participants receiving the T cell dose being studied have completed the 28 day post T cell infusion follow-up. In the first stage dose escalation will take whole steps (even numbered doses labeled in black starting at Dose 0) until a DLT is seen. If a DLT is not seen, dose escalation will continue in whole steps using only the even numbered doses. Once a DLT is seen, the dose will decrease to a dose (odd numbered doses labeled in grey) that is half way between the current dose and the next lower whole step dose. All further escalation will be done in

half-steps. For example if a DLT is seen at the 100M dose, the next dose studied would be 75M.

The starting dose is 50M CAR+ T cells.

Table 4: CAR^+ Cell Dose Schedule							
Dose -1	Starting Dose Dose 0	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
10M	**50M**	**75M**	**100M**	**300M**	**500M**	**750M**	**1000M**

* M = 10^6 CAR+ T cells

Table 5 below provides the dose escalation/de-escalation guidelines for a target toxicity of 20% and $\varepsilon_1 = \varepsilon_2 = 5\%$ giving an equivalence range of 15%-25%. The numbers of research participants treated at the current dose is provided in the columns and the number of research participants experiencing a DLT in the rows. Note that this design is slightly more conservative than a 3+3 design as it de-escalates at 1 DLT in 3 research participants, stays at 1 DLT in 6 research participants and escalates at 1 DLT in 9 research participants. The Phase I portion of the study will end when 12 research participants are studied at a single dose level. Toxicity levels of 0.34 or higher are considered too toxic and doses that achieve that level will not be revisited. The MTD will be the dose closest to target of 0.20 below 0.34 based on isotonic regression.

Note in the case that the cell sample manufactured is smaller than the defined dose, but is in the dose schedule range, we will allow the research participant to enter the study at the lower T_{CM} dose level. This data will be included in the calculation of the MTD using isotonic regression at the end of the study.

Table 5: Dose escalation guidelines
(E= escalate, D=de-escalate, S=stay, DU=de-escalate and do not return to this dose).

	No. of Research participants Treated on the Current Dose Level				
No. of Research participants Experiencing a DLT		**3**	**6**	**9**	**12**
	0	E	E	E	E
	1	D	S	E	E
	2	DU	D	S	S
	3	DU	DU	D	S
	4		DU	DU	D

Table 5: Dose escalation guidelines (E= escalate, D=de-escalate, S=stay, DU=de-escalate and do not return to this dose).					
	No. of Research participants Treated on the Current Dose Level				
No. of Research participants Experiencing a DLT		**3**	**6**	**9**	**12**
	5		DU	DU	DU

Based on the results of 1,000 simulated trials considering 4 toxicity probability schedules (**Table 6**) for the 8 doses in combination with the trial specifications listed above, the median sample size was 24 with 95% confidence limits of 15 and 39 and the sample size at the MTD was ≥ 12 in at least 93% of trials. Note **Table 6** provides the rates at which each dose level for each schedule was chosen as the MTD (MTD rate) and the average number of research participants seen at each dose (Ave # Pts.).

Table 6: Four Dose toxicity probability schedules for the above dose schedule and associated rates each dose level is identified as the MTD.								
Toxicity ProbabilitySchedules	**Dose levels**							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Schedule 1	0.025	**0.05**	0.10	**0.15**	0.20	**0.25**	0.35	**0.45**
MTD rate	0.01	**0.1**	0.14	**0.25**	0.20	**0.22**	0.06	**0.02**
Ave # Pts.	0.62	**4.6**	3.1	**5.9**	3.6	**4.4**	1.6	**0.9**
Schedule 2	0.025	**0.10**	0.20	**0.37**	0.53	**0.69**	0.79	**0.84**
MTD rate	0.04	**0.37**	0.41	**0.17**	0.01	**0**	0	**0**
Ave # Pts	1.5	**7.3**	6.6	**4.9**	0.8	**0.56**	0	**0**
Schedule 3	0.01	**0.02**	0.05	**0.1**	0.15	**0.2**	0.35	**0.50**
MTD rate	0.00	**0.03**	0.07	**0.19**	0.19	**0.39**	0.11	**0.02**
Ave # Pts	0.2	**3.6**	1.9	**5.7**	4.0	**6.5**	2.8	**1.2**
Schedule 4	0.025	**0.025**	0.025	**0.20**	0.20	**0.20**	0.40	**0.40**
MTD rate	0	**0.02**	0.21	**0.29**	0.14	**0.27**	0.04	**0.03**
Ave #Pts	0.2	**3.5**	4.0	**6.7**	2.8	**4.5**	1.6	**1.0**

Based on the above trial simulation data, the maximum sample size we expect for the Phase I portion of the trial will be 39 research participants +3 for replacement of unevaluable research participants, for a total of 42 research participants. Participants who do not receive T cells will be replaced.

12.1.1.1 Amendments to Dose Plan

- Protocol Amendment V07 dated 11/20/2012:

This study was initiated and has treated a total of two (2) patients where the T cell infusion dose was defined as *total T cells* (i.e., a dose of 50M equaled 50M total T cells infused). However, the protocol has been revised to define the infusion dose as *total **CAR+** T cells* (i.e., a dose of 50M CAR+ T cells where the product is 80% CAR+ equals ~62.5M total T cells infused).

The definition of T cell infusion dose was revised to more accurately review toxicities associated with a cell dose of the active product (i.e., it is only the CD19-specific CAR + T cells that are expected to exhibit anti-tumor activity). Toxicities attributable to CAR+ T

cells are believed to be due to the interaction between CAR+ T cells and cells presenting the target antigen and as such our colleagues have also moved toward the approach of infusing doses based on CAR positivity.[118,121] However, based on the manufacturing capacity of the GMP platform, the maximal dose that could be administered to a research participant (i.e., at Dose 6, 1000M CAR+ T cells) is limited to $3.0x10^9$ total T cells (3000M).

The first 4 research participant's manufactured products have revealed a range of 46 to 92% CAR+ T cell products. With this range in CAR+ T cells, and our minimal range between doses, it will be difficult to evaluate dose level toxicities (reference figure 1 below).

Based on this change in definition of dose, the following decision has been made: Patient Numbers 01, 03 and 04 will be included in the cohort evaluation of dose level 0 (50M). Patient Number 02 (since their T cell product was only 46% CAR+) will be evaluated at dose level -0.5 (25M). Moving forward, all doses will be based on the new definition of "T cell infusion dose = total **CAR+** T cells".

Figure 1: Review of First 4 Research Participant's Product and Dose Level

Patient #	Product % CAR +	Infusion Details		Dose Level for Evaluation	
		Infused Dose	Corrected Based on % CAR+	Dose Level	Anticipated # CAR+ T Cells
01	86%	50M total	43M	0	50M
02	46%	50M total	23M	-0.5	25M
03	92%	50M total	46M	0	50M
04	91%	50M CAR+	50M	0	50M

- Protocol Amendment V08 dated 03/01/2013:

Since we have not seen T cell related toxicity on this protocol, we are requesting a revision to the accrual guidelines to allow study participants to accrue in cohorts of 3. This change will make it easier to accrue patients to this study in a more timely fashion. The changes are in **Sections 9.6.1.1** (Accrual within a Cohort) and **12.1.1** (Design and Sample Size for Phase I Arm of Study).

12.1.2 Endpoints for Phase I Arm of Study

The objectives for the Phase I Arm of the Study are the determination of the MTD based on DLTs as previously defined in Section 10.3, and defining the full toxicity profile. Determination of the full toxicity profile will include analysis of adverse events attributable to T_{CM} adoptive transfer as reporting using CTCAE version 4.0.

12.2 Phase II Study Arm

12.2.1 Design and Sample Size for Phase II Arm of Study

The objectives of the Phase II arm of the study are 1) to determine the tempo, magnitude, and duration of engraftment of the transferred T cell product as it relates to the number of cells infused, 2) to study the impact of this therapeutic intervention on the development of $CD19^+$ B-cell precursors in the bone marrow as a surrogate for the *in vivo* effector function of transferred CD19-specific T-cells and 3) to describe the progression-free and overall survival of treated research participants on this protocol.

The Phase II study is a prospective treatment study to estimate the rate of research participants receiving T_{CM}-derived $CD8^+$ T cells genetically-modified to express a CD19-specific CAR for which the transferred cells are detected in the circulation for 28 days (+/- 3 days) by WPRE Q-PCR. The Phase II dose will be the MTD dose from the Phase I portion of the trial and the Phase I research participants seen at this dose will be included in the analysis for Phase II. Based on 1000 simulated trials, 93% of the simulated trials had at least 12 research participants at the MTD. The Phase II portion of the trial will begin when after we follow the last patient on the Phase I portion for 3 months and determine the MTD. We will then add 12-15 more research participants at the MTD dose to achieve an overall the Phase II sample size of 24. Given a sample size of 24 research participants the widest half-width of the confidence limit for the rate of T_{CM} persistence will be less than or equal to 0.21. If, for example, a T_{CM} persistence rate of 0.50 (12 research participants showing persistence/24 evaluable research participants) was observed, the 95% lower and upper confidence limits would be 0.29 and 0.71, respectively.

12.2.2 Endpoint for Phase II Arm of Study

WPRE detection above background 28 days (+/- 3 days) after T cells are infused.

12.3 Stopping Rules

12.3.1 Failure of hematologic engraftment at 21 days

Although a higher than usual engraftment failure rate is not expected, additional guidelines and criteria have been established which will be used to flag an unexpected number of research participants who fail to engraft within 21 days of the autologous hematopoietic stem cell infusion (reference **Section 9.2.2**: Management of HSCT Engraftment Failure for management of engraftment failure).

The **risk set** to be used in the safety monitoring decision (to trigger a review of the protocol) will include all research participants that have received the T cell product as part of the T_{CM} protocol.

Every time a research participant fails to engraft within 21 days of transplant, we will look at the column for the total number of research participants that failed to engraft (X), and compare the number of research participants, N, who are in the risk set to N_X. If the number of research participants, N, is greater than N_X, the number given in the bottom row of **Table 7**, then accrual will continue. If N is less than or equal to N_X, then the monitoring boundary has been crossed and a careful review of the trial data will be mandated.

Table 7: Criteria for Suspending Accrual to Evaluate Safety				
X: # research participants who fail to engraft within 21 days	1	2	3	4
N_x: safety boundary crossed if # research participants in risk set (N) is less than or equal to N_x (if $N \leq N_x$)	≤ 1	≤ 26	≤ 51	≤ 60

These rules were selected to ensure a low probability that the safety boundary would be crossed, indicating excessive failure to engraft, if the true chance of failure to engraft were less than 1% and a high probability that the boundary would be crossed if the true chance of failure to engraft reached 10%. Criteria for flagging an excessive number of research participants that fail to engraft within 21 days are based on the sequential probability ratio test with α=0.10, β=0.05, p_o=0.01 and p_a=0.10. **Table 8** below summarizes these probabilities. The values in the table below are based on 10,000 simulations.

Table 8: Probability of Crossing the Safety Boundary (i.e., too many research participants have TOX)					
True Chance of failure to engraft in 21 days	1%	2.5%	5%	7.5%	10%
Probability of Crossing the Safety Boundary	0.04	0.21	0.56	0.81	0.93

12.3.2 Futility

The study will stop if 0 out of 6 research participants experience T_{CM} persistence 28 days (+/- 3 days) post T cell infusion after reaching the MTD (or highest dose), as the probability of 50% of the research participants achieving T_{CM} persistence for 28 days (+/- 3 days) is <0.02. Note that if there is no toxicity, this result will be achievable after 15 evaluable research participants have been followed through 28 days (+/- 3 days) on this protocol (3 research participants on each dose (50,100, 500M) and 6 on a dose of 1000M). The concept is similar to stopping after the first stage of a Gehan test [142].

12.3.3 Feasibility

Feasibility will be examined separately in research participants that have 1) received any salvage chemotherapy prior to leukapheresis and 2) those that have not. If we reach a rate of greater than 50% inability to manufacture the needed number of cells for the research participant's assigned dose level after at least 6 research participants in the research participant group that has received salvage chemotherapy prior to leukapheresis, we will rewrite the protocol to make those patients ineligible for entry. If we reach a rate of greater than 50% inability to achieve the needed number of cells for the research participant's

assigned dose level after at least 6 research participants in the patient group that have not received salvage chemotherpay prior to leukapheresis we will stop the study.

12.4 Statistical Analysis

Tables will be created to summarize all toxicities and side effects by dose, course, organ and severity. Rates and associated 95% confidence limits will be estimated for failure to engraft from the HSCT within 21 days, and rates of engraftment and persistence for T_{CM} for 28 days (+/- 3 days). Time to engraftment and Progression free survival, and overall survival will be estimated using Kaplan-Meier methods. Descriptive statistics will be provided for the research participant demographics.

12.5 Accrual

Accrual is expected to be 10 evaluable research participants per year, where an evaluable research participant is defined as having received the protocol prescribed T cell infusion. The median sample size based on simulations of 1000 similar trials is 24 research participants assuming a minimum of 9 and a maximum of 39 plus 3 for replacement of evaluable research participants. With the addition of up to 15 research participants to fill out the MTD dose to 24 for the Phase II portion of the study, the total sample size should not exceed 57. Thus, we expect to complete the study in 5 years.

13.0 Registration Guidelines

To register a research participant, the PI or his/her designee will contact the responsible protocol nurse to begin research participant education to assist with the informed consent process. After signing of the informed consent, administration of protocol comprehension will be performed and documented by Research Subject Advocate, and eligibility criteria will be verified. Once all the eligibility testing data is finalized the Protocol Management Team will review the data for determination of eligibility and proceed with protocol enrollment. Enrolled research participants will then be scheduled for leukapheresis.

13.1 Procedures for On-Study and Treatment Deviations

The treating physician must contact the Principal Investigator or her designate to approve all waivers (i.e., deviations in eligibility) prior to research participant registration, and all treatment deviations prior to treatment.

14.0 Records to be Kept and Data Submission Schedule

Essential documents, as listed below, will be retained by the investigator for as long as needed to comply with national and international. Essential documents include:

14.1 Data Collection Forms

The original data collection forms will be secured per institutional policies for patient medical records.

14.2 Research Participant Consent Forms

At the time of registration, signed and dated copies of the research participant Informed Consent form with the Experimental Bill of Rights must be available for the

research participant and the research participant's study binder. The original shall be forwarded to the research participant's medical record file.

14.3 Documentation of Registration Eligibility

At the time of registration, the information requested on the On-Study/Eligibility Form will be obtained by CRA and appropriate data collection forms shall be completed in a timely manner. Only current approved data collection forms and checklists may be used.

14.3.1 Results Reporting

Following completion of the study the PI or his/her designee will assemble a summary report for the FDA and COH regulatory committees. This data will be subject to submission as a manuscript to an appropriate peer-reviewed journal.

15.0 Minorities and Gender Statement

All eligible research participants will be included in this study without regard to gender or ethnicity, so that the distribution of the research participants should be representative of the gender/ethnicity makeup of the adult/pediatric population in the Southern California Area and the broader United States.

16.0 Ethical and Regulatory Considerations

16.1 Institutional Review Board

In accordance with federal regulations (21 CFR 312.66), an Institutional Review Board (IRB) that complies with regulations in 21 CFR 56 must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, Federal, and State of California regulations concerning the Informed Consent will be fulfilled.

16.1.1 Informed Consent

The PI or his/her designee must explain verbally and in writing the nature, duration, and purpose of the study and possible consequences of treatment to adult research participants, and if the research participant is a minor or is incapacitated, to both the child and his/her legal guardians. Research participants/legal guardians must also be informed that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment. After signing the informed consent, research participants will undergo eligibility testing.

Following eligibility testing, but prior to enrollment, to the assigned Research Subject Advocate will assess the potential research participant or their legal guardian's comprehension of the study. Should sufficient doubt be raised regarding the adequacy of comprehension, further education will be administered and the evaluation repeated until a satisfactory result is obtained. Potential research participants or legal guardians who cannot adequately comprehend the fundamental aspects of the protocol with a reasonable amount of education and proctoring will be ineligible for enrollment. Following completion of the eligibility testing and study comprehension assessment the research team will determine if

the research participant may be enrolled. After enrollment the research participant may proceed with leukapheresis.

16.2 Termination of Study

The PI reserves the right to terminate this study at any time. Furthermore, the FDA, NIH-OBA or IRB may also terminate the study.

17.0 Pathological Review

All available pathology samples documenting intermediate grade B-cell lineage lymphoma (e.g., diffuse B-cell lymphoma, Mantle Cell lymphoma, transformed Follicular lymphoma) at diagnosis, response(s) and relapse(s) will be submitted to the COH pathology service for confirmation of diagnosis. Should material be available that is in excess of that need for standard pathologic studies, then excess material may be used for correlative studies to assess susceptibility to re-directed T cell effector mechanisms.

18.0 Research Participant-Specific Biological Materials

At the completion of the T cell infusion for a particular research participant, the fibroblasts, T cells and leukapheresis product, serum samples, and cryopreserved PBMC will not be returned to the research participant or their family/families. They will become property of COH and may be used in non-therapeutic experiments.

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