

Phase 2 Study Of Autologous T Cells Engineered To Express an Anti-CD19 Chimeric Antigen Receptor (CART-19) Following First-line Autologous Stem Cell Transplantation for High-risk Multiple Myeloma

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STUDY SUMMARY

Title	Phase 2 Study of Autologous T Cells Engineered To Express an Anti-CD19 Chimeric Antigen Receptor (CART-19) Following First-line Autologous Stem Cell Transplantation for High-risk Multiple Myeloma
Short Title	CART-19 post-ASCT for Multiple Myeloma
Phase	Phase 2
Methodology	This will be a single-arm, open-label study. Patients will be enrolled during induction therapy for multiple myeloma, prior to standard-of-care consolidation with autologous stem cell transplantation (ASCT). T cells will be harvested for T cell manufacturing prior to ASCT, and CART-19 will be infused at day ~60 post-ASCT, 3 days after lymphodepleting chemotherapy. The primary endpoint is progression-free survival (PFS) after ASCT. As detailed below, the study is powered to detect an increase in two-year PFS to ~75% from a baseline expectation of 55% based on historical data. Secondary endpoints will evaluate CART-19 persistence and function, minimal residual disease, immune correlative endpoints, and associations of progression-free survival (PFS) with CART-19 persistence and clinical and biologic characteristics of multiple myeloma.
Study Duration	The study will accrue subjects over 2-3 years. Patients will be followed for two years post-ASCT.
Study Center(s)	Single-center at the University of Pennsylvania
Objectives	<p>The primary objective is to evaluate PFS in high-risk multiple myeloma patients treated with CART-19 post-ASCT.</p> <p>Secondary objectives are to:</p> <ul style="list-style-type: none"> • Describe the incidence and nature of adverse events attributable to CART-19 at this dose, schedule, and clinical setting, with specific attention to adverse events that emerge after initiation of maintenance lenalidomide. • Describe response rate and depth-of-response using both standard clinical criteria (IMWG) and MRD assessments. • Evaluate expansion, persistence, phenotype, function, and homing of CART-19 cells manufactured and administered in this low-target clinical setting. • Evaluate PFS and depth-of-response in the subset of patients, if present, with long-term (>6 months) <i>in vivo</i> persistence of CART-19 cells. • Evaluate PFS and depth-of-response in clinically and biologically defined subsets of multiple myeloma patients (e.g., subsets with certain cytogenetic abnormalities, clinical stage, multiple myeloma plasma cell immunophenotype, or gene expression profile). • Describe CART-19 manufacturing feasibility in this clinical setting and the features (dose, cellular phenotype) of the manufactured product.

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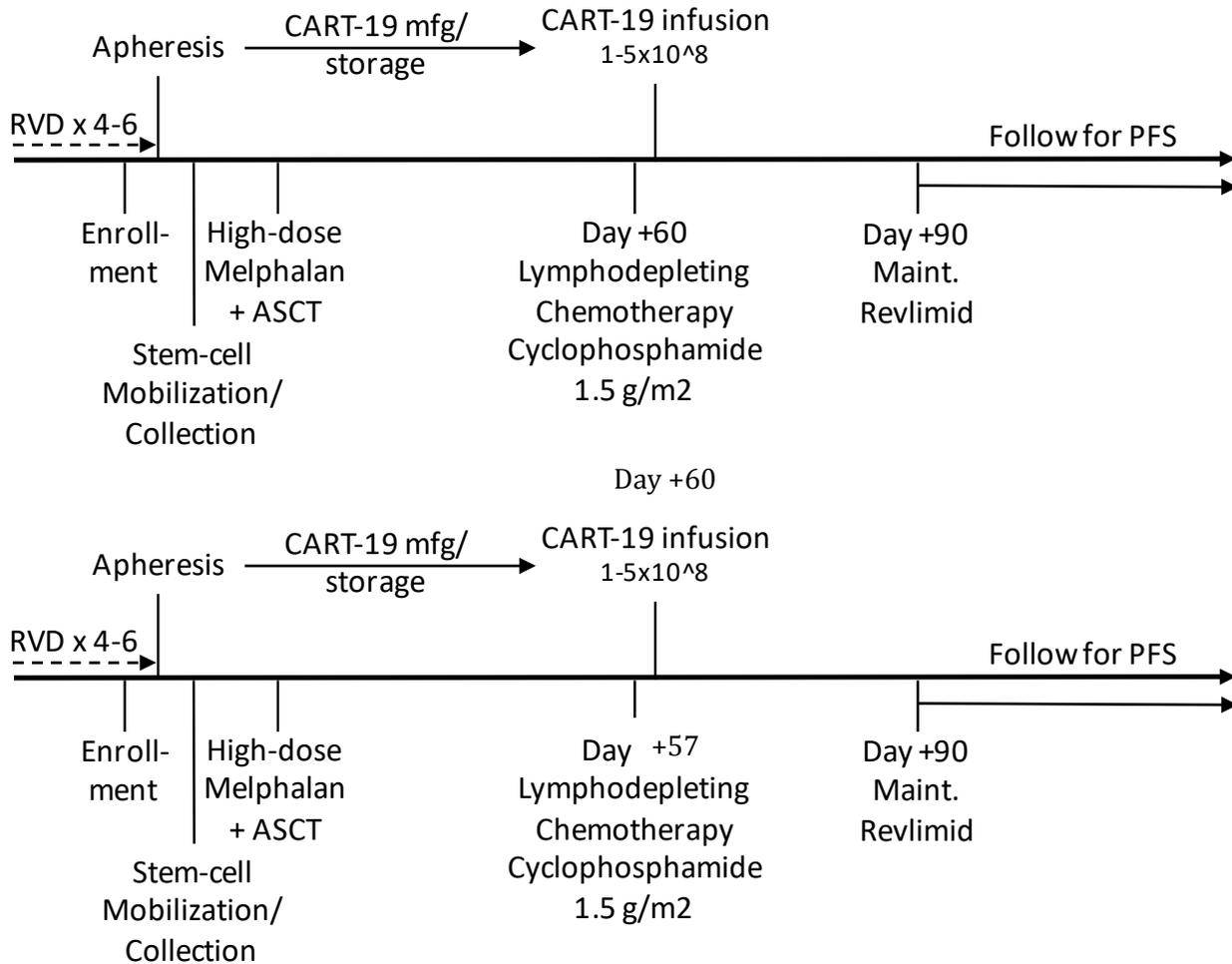
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Number of Subjects	Up to 25 evaluable subjects. An evaluable subject will be defined as a subject who receives CART-19 cells at a dose of $1-5 \times 10^8$ transduced cells.
Diagnosis and Main Inclusion Criteria	The target population includes patients between the ages of 18 and 70 (inclusive) with multiple myeloma exhibiting high-risk prognostic features (adverse cytogenetic features or R-ISS stage 3) who, following initial therapy with lenalidomide, bortezomib, and dexamethasone, are candidates for autologous stem cell transplantation and post-transplant maintenance lenalidomide.
Study Product, Dose, Route, Regimen	CART-19 cells will be administered as a single intravenous infusion. The target dose of CAR-expressing cells will be $1-5 \times 10^8$ cells. CART-19 cells will be infused three days after administration of cyclophosphamide 1.5 g/m^2 as lymphodepleting chemotherapy.
Duration of administration	CART-19 cells will be administered as a single dose.
Reference therapy	There will be no control arm in this study. Outcomes will be compared to historical expectations for PFS post-ASCT for high-risk multiple myeloma patients.
Statistical Methodology	<p>The study has been powered to detect an improvement in PFS in this high-risk population in comparison to historical expectations. Historical expectations were derived from the recently published “revised ISS” (R-ISS) staging system; R-ISS stage 3 patients who underwent ASCT in this study had a two-year post-ASCT PFS of approximately 55%. With sample size of 25 subjects, this study has 80% power to detect an increase in two-year PFS to 75.5% compared to this historical expectation. This calculation was based on assumption for exponential survival for PFSs, 2 years of recruitment, and additional 2 years of follow-up after enrollment. The distribution of PFS will be estimated by Kaplan-Meier method and median PFS will be computed. Point estimate of two-year PFS will be tested against 55% using a one-sided test at 0.05 level. The study has been structured to enable comparison to the high-risk subgroups from the BMTCTN 0702 and the DFCI/IFM 2009 studies, both of which are studies employing contemporary treatment regimens from which data will be available over the next 1-2 years.</p> <p>Secondary endpoints are descriptive in nature.</p>

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Figure 1: Study Schema



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LIST OF ABBREVIATIONS

aAPC	Artificial APC
ACC	Abramson Cancer Center
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
APC	Antigen presenting cell
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATG	Anti-thymocyte globulin
B-ALL	B-lineage acute lymphoblastic leukemia
BUN	Blood urea nitrogen
cAIX	Carbonic anhydrase IX
CAR	Chimeric antigen receptor
CART-19 cells	CD19 redirected autologous T cells
CBC	Complete blood count
CCI	Center for Cellular Immunotherapies
CD	Cluster of differentiation
CD137	4-1BB co-stimulatory molecule
CFR	Code of federal regulations
CHOP	Children's Hospital of Philadelphia
CRi	Complete Response with incomplete marrow recovery
CI	Confidence Interval
CIR	Chimeric immune receptor, interchangeable with CAR
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete Response
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical study report
CTC	Common toxicity criteria
CTL	Cytotoxic T lymphocyte
CTRC	Clinical and translational research center
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DFS	Disease free survival
DIC	Disseminated intravascular coagulation
DMC	Data monitoring committee
DMSO	Dimethyl sulfoxide
DSMB	Data and Safety Monitoring Board
DSMP	Data safety monitoring plan
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report forms
EDC	Electronic data capture
EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
GVHD	Graft versus host disease
HACA	Human anti-chimeric antibody
HAMA	Human anti-murine antibody
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLH	Hemophagocytic lymphohistiocytosis
HUP	Hospital of the University of Pennsylvania
IBC	Institutional Biosafety Committee
Ig	Immunoglobulin
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IVIG	Intravenous immunoglobulin
IWCLL	International Workshop Group on Chronic lymphocytic leukemia
kDa	Kilodalton
MAS	Macrophage activation syndrome
MED	Minimal efficacious dose
MEDRA	Medical dictionary for regulatory activities
MHC	Major histocompatibility complex
MM	Multiple Myeloma
MOI	Multiplicity of infection
MOP	Manual of procedures
MRD	Minimal residual disease

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mTOR	Mammalian target of Rapamycin
MUGA	Multiple gated acquisition scan
NaCl	sodium chloride
NHL	Non-Hodgkin's Lymphoma
PBMC	Peripheral blood mononuclear cells
PDCS	Product Development & Correlative Sciences laboratory
PDL	Product Development Laboratory
PFS	Progression free survival
PHI	Protected health information
PID	Patient identification number
PLL	Prolymphocytic leukemia
PR	Partial Response
Q-PCR	Quantitative polymerase chain reaction
Q-RT-PCR	Quantitative reverse transcriptase polymerase chain reaction
RAC	NIH Office of Biotechnology Recombinant DNA Advisory Committee
RCR/L	Replication competent retrovirus/lentivirus
RIC	Reduced intensity conditioning
R-ISS	Revised International Staging System for Multiple Myeloma
RVP	Respiratory virus panel
scFv	Single chain variable fragment
SCID	Severe combined immunodeficiency
SCT	Stem cell transplant
SLL	Small lymphocytic lymphoma
STR	Short tandem repeat analysis
SUSAR	Suspected unexpected serious adverse reaction
Tcm	Central Memory T cells
TCR	T cell receptor
TCR ζ	Signaling domain found in the intracellular region of the TCR zeta, gamma and epsilon chains
TCSL	Translational Correlative Studies Laboratory
Tem	Effector memory T cells
TLS	Tumor lysis syndrome
Treg	Regulatory T cells
UPenn	University of Pennsylvania
VSV-G	Vesicular Stomatitis Virus, Glycoprotein
V β	A rearranged T cell specific gene that can be used to determine clonality of a T cell population

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1. INTRODUCTION

This is a single-arm, open-label phase-2 study in which autologous T cells transduced with an anti-CD19 chimeric antigen receptor (CART-19 cells) will be infused to patients with high-risk multiple myeloma approximately 60 days after completion of first-line therapy. Approximately 30 days after CART-19 infusion, subjects will begin standard-of-care maintenance therapy with low-dose lenalidomide. First-line therapy will consist of standard induction/initial therapy with lenalidomide, bortezomib, and dexamethasone followed by consolidation with high-dose melphalan and autologous stem cell transplantation (ASCT). Subjects will enroll during induction therapy, undergo leukapheresis for CART-19 manufacturing, subsequently undergo hematopoietic stem cell harvesting and ASCT, and then receive CART-19 and maintenance lenalidomide. The primary objective is to assess progression-free survival (PFS); secondary objectives are to describe the maximum depth-of-response, *in vivo* CART-19 persistence and activity in this clinical setting, and association of these parameters and other correlative analyses with PFS. The rationale for CART-19 in this setting is based on data implicating CD19+ components of the myeloma clone as having unique drug-resistant and myeloma-propagating properties and clinical data from a completed pilot study suggesting that CART-19 can improve PFS after ASCT.

1.1 Background

Multiple myeloma. Multiple myeloma is a hematologic malignancy in which clonal plasma cells accumulate in the bone marrow and extramedullary sites. Potential clinical complications of multiple myeloma include the development of painful, lytic bone lesions, anemia and other cytopenias, increased susceptibility to infection, hypercalcemia, renal impairment due to toxicity of the secreted monoclonal immunoglobulin, and compromise of organs infiltrated by extramedullary plasmacytomas. In the United States, there are approximately 25,000 new cases of multiple myeloma diagnosed annually and approximately 11,000 deaths attributed to multiple myeloma annually. The lifetime risk is 1 in 143 in the United States. The median age at diagnosis is 69, and over one-third of patients are diagnosed before age 65¹. Though nearly all multiple myeloma patients respond to modern initial therapy with substantial decrease in the disease burden and improvement in the presenting complications, development of resistance to therapy is nearly inevitable. Nearly all patients eventually succumb to complications of treatment-refractory disease.

Autologous stem-cell transplantation for multiple myeloma. Based on follow-up of patients diagnosed in 2007, five-year survival for multiple myeloma patients is 45%¹. Survival has improved considerably over the last 20 years coinciding initially with the widespread adoption of ASCT as consolidation following initial/induction therapy and, more recently, with the availability of modern anti-myeloma pharmaceuticals such as thalidomide, lenalidomide, bortezomib, carfilzomib, and others. ASCT entails a single myeloablative dose of melphalan (140-200 mg/m²) followed 1-2 days later by infusion of autologous hematopoietic stem cells, which are collected and stored prior to melphalan infusion, to facilitate hematopoietic reconstitution. ASCT is typically undertaken in multiple myeloma patients following an initial period of induction therapy. The initial phase-three studies of ASCT in multiple myeloma established an overall survival advantage compared to continuous standard-dose cytotoxic chemotherapy^{2,3}. More recently, the overall survival advantage with HDM + ASCT was confirmed in a phase-3 study of patients treated with modern initial (i.e., lenalidomide- rather than chemotherapy-based) and salvage therapies⁴. Therefore, ASCT is a standard-of-care for eligible (i.e., ≤70 years of age and adequate cardiopulmonary function for high-dose chemotherapy) multiple myeloma patients, and multiple myeloma is the most common indication for ASCT worldwide. Though the optimal timing of ASCT for multiple myeloma is

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uncertain, it is most extensively studied and most commonly undertaken early in the disease course, typically once a stable response to initial therapy has been achieved.

High-risk multiple myeloma. The natural history and prognosis of multiple myeloma can vary significantly between patients. Those who achieve sustained complete response (CR) after ASCT can achieve long-term survival (e.g., 86% overall survival at 7 years in one recently reported series⁵), whereas those who fail to respond to modern therapy may survive only months. The recently published Revised International Staging System (R-ISS) defines prognostic stages based on the presence at diagnosis of unfavorable cytogenetic abnormalities (deletion 17p, t(4;14), t(14;16)) and serum LDH and beta-2-microglobulin levels (Table 1)⁶. Many clinical trials, including the BMTCTN 0702 study that may be used as a historical comparator for results of this study, define high-risk disease by unfavorable cytogenetic features alone; indeed, the median PFS for patients with unfavorable cytogenetic features alone is similar to the median PFS of R-ISS stage 3 patients (24 months)⁶. High-risk multiple myeloma comprises 15-20% of cases. Even patients with high-risk multiple myeloma typically respond well to initial therapy, but the duration of response in high-risk patients is short, and treatment-refractory disease develops relatively quickly. There is therefore a major unmet need for new strategies that maintain the response to initial therapy and prevent the emergence of treatment-refractory disease in high-risk MM patients.

Table 1: Revised International Staging System

R-ISS Stage	Criteria	5y OS
1	B2M < 3.5 mg/L, serum albumin > 3.5 g/dL, and no high-risk FISH	82%
2	Not stage 1 or 3	62%
3	B2M > 5.5 mg/L + either LDH >ULN or high-risk FISH	40%

OS: overall survival; B2M: Beta-2-microglobulin; FISH: fluorescence *in situ* hybridization; LDH: lactate dehydrogenase; ULN: upper limit of normal.

In addition to the unmet need in this population, high-risk multiple myeloma patients are well suited to the initial study of new multiple myeloma treatments in early lines of therapy, particularly when the hypothesized mechanism-of-action would be expected to prolong PFS but not necessarily induce a response as monotherapy. Expected PFS after first-line therapy in a general population of multiple myeloma patients is very heterogeneous and averages several years. By focusing on high-risk patients, the expected PFS is shorter and more homogeneous, which allows more expeditious evaluation of novel treatment strategies in early lines of therapy.

Chimeric antigen receptors (CARs). CARs are synthetic transmembrane proteins that incorporate an antigen-binding domain on the extracellular portion and T cell signaling domains on the intracellular portion (Figure 2)^{7,8}. Gene-transfer technology enables expression of CARs in autologous T lymphocytes, which redirects the specificity of the transduced T cells to the target of the CAR's antigen-binding domain. This allows highly specific targeting of autologous T cells to an intact cell-surface target in an MHC-unrestricted manner and independently of antigen processing^{9,10}. The antigen-binding function of a CAR is usually accomplished by the inclusion of a single chain variable fragment (scFv) containing the V_H and V_L chains of a target-specific antibody joined by a peptide linker of about 15 residues in length¹¹. First-generation CARs contain a minimal TCR signaling domain consisting of TCRζ. Second-generation CARs such as CART-19 contain double costimulatory signaling

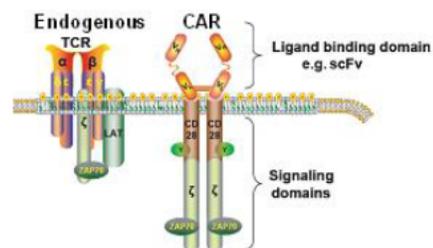


Figure 2. CAR design. Bispecific T cells are created by the introduction of genes encoding CAR proteins that recognize target surface antigens in an MHC-independent fashion.

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domains: either CD28 and TCR ζ or 4-1BB and TCR ζ . Novel CAR designs incorporating three signaling domains (third-generation CARs) and other modifications are in pre-clinical and early clinical development. CAR-transduced T cells represent a promising immunotherapy approach to cancer. Several clinical studies using CART-19 (as detailed below) and other CD19-directed CAR T cells have demonstrated impressive responses in patients with advanced B cell malignancies¹². These studies have demonstrated the capacity of CAR T cells to induce not only initial clinical responses but also long-term immunologic memory, manifest as long-term *in vivo* persistence of the CAR T cells and durable elimination of both neoplastic and non-neoplastic target cells such as, in the case of CART-19, normal CD19+ B cells. Studies of CAR T cells against other targets in a range of cancers are ongoing.

CAR T cells for multiple myeloma. Several CAR T cell targets have been explored for use in multiple myeloma. Targets in pre-clinical or early clinical development include B cell maturation antigen (BCMA), CD38, CD138, kappa light chain, Lewis-Y antigen, and CS1¹³. In particular, phase-1 studies of anti-BCMA CAR T cells are ongoing at the National Institutes of Health and the University of Pennsylvania. As described below, a pilot clinical study of CART-19 in patients with advanced multiple myeloma has been conducted at the University of Pennsylvania.

CD19 as an immunotherapy target in multiple myeloma. CART-19, also referred to as murine CTL019 (muCTL019), is a CAR directed against CD19, a cell surface protein expressed on almost all B lineage cells. Physiologic, non-neoplastic plasma cells are mostly CD19+, but the most terminally differentiated, long-lived plasma cells are CD19-negative¹⁴. The dominant population of neoplastic plasma cells in multiple myeloma patients is CD19-negative in almost all cases¹⁵. CART-19 alone would therefore not be expected to have efficacy as monotherapy in multiple myeloma. Rather, the rationale for CD19-directed therapy in multiple myeloma is the presence of CD19 on minor subsets of the multiple myeloma clone that may have unique disease-propagating properties (i.e., cancer stem-cell properties). It is hypothesized that these disease-propagating subsets resist standard MM therapies, even those to which the dominant plasma cell population is sensitive, and facilitate repopulation of the neoplastic plasma cell population with progressively therapy-resistant cells. Though a discrete and consistent definition of the myeloma-propagating subset has been elusive, subsets of cells with phenotypes along the spectrum between CD19+ B lymphocytes and terminally differentiated CD19-negative plasma cells have been consistently identified in multiple myeloma patients; in general, the less differentiated subsets have exhibited enhanced drug resistance and disease-propagating capacity in xenotransplantation models and *in vitro* clonogenicity assays¹⁶. Thus, in patients whose neoplastic plasma cell population has been successfully depleted with conventional multiple myeloma therapies, elimination of CD19+ cells with CART-19 may prevent or delay progression by depleting the less differentiated myeloma-propagating populations.

Post-ASCT maintenance lenalidomide. The development of well tolerated oral anti-myeloma agents such as lenalidomide led to investigation of low-dose maintenance therapy in clinical settings where active observation had been the standard approach. Maintenance therapy has been most intensely studied in the post-ASCT period, which is typically a period of long-term (months-to-years) disease stability. Lenalidomide is a thalidomide derivative with anti-myeloma activity that has been attributed to multiple mechanisms of action, including direct effects on myeloma plasma cells and immunomodulatory effects. Lenalidomide is FDA-approved for treatment of relapsed/refractory multiple myeloma, but it has been extensively studied as a first-line therapy and in the post-ASCT maintenance setting. Low-dose post-ASCT maintenance lenalidomide roughly doubles PFS and, in one study, significantly prolonged overall survival^{4,17,18}. Post-ASCT maintenance is widely utilized in the United States and has been incorporated

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into ongoing phase-3 studies evaluating other aspects of first-line therapy such as BMT CTN 0702, DFCl/IFM 2009, and ECOG E1A11. Lenalidomide has previously been administered in conjunction with adoptive T cell therapies for multiple myeloma in several studies conducted at the University of Pennsylvania (as reviewed¹⁹), including a study in which the transferred T cells had undergone lentiviral modification to express an affinity-enhanced T cell receptor²⁰. In these studies, maintenance lenalidomide was well tolerated with no unexpected toxicity.

Lymphodepleting chemotherapy prior to CAR T cell therapy. Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation^{21,22}, a recent finding that naive T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naive T cells are reduced below a certain threshold^{22,23}. Lymphodepletion eliminates regulatory T-cells and other competing elements of the immune system that act as “cytokine sinks”, enhancing the availability of cytokines such as IL-7 and IL-15 that are important for T cell proliferation and survival²⁴. This hypothesis has been tested clinically in patients with metastatic melanoma refractory to conventional treatments²⁵. The patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide (60mg/kg x 2 days) and fludarabine (25 mg/m² x 5 days) prior to adoptive transfer of T cells.

In prior and ongoing cellular immunotherapy clinical trials at University of Pennsylvania, the lymphodepleting chemotherapy regimen has differed according to the disease and patient population. For example, in several multiple myeloma studies, the myeloablative chemotherapy administered prior to ASCT (high-dose melphalan) was used as the lymphodepletion regimen^{20,26-28}. In these studies, infusion of *ex vivo* expanded cells on day +2 post-ASCT was associated with robust *in vivo* T cell proliferation. Infusion of CAR T cells on day +2 post-ASCT, however, risks overlapping the period of highest risk for CAR T cell toxicity with the period of highest risk for ASCT toxicity. The risk of overlapping infection, a major risk of ASCT, and cytokine release syndrome (CRS), a major risk of CAR T cell therapy, is of particular concern since overlapping CRS and severe infection could be difficult to manage. For this reason, and based on other clinical and laboratory correlative data detailed below, this study entails administration of CART-19 cells approximately two months post-ASCT, when patients will be at relatively low risk for ASCT-related infections. Due to this delay between ASCT and CART-19 infusion, however, the conditioning regimen for the ASCT will not be able to serve as lymphodepleting chemotherapy. Thus, on this protocol, subjects will receive cyclophosphamide 1.5 g/m² as a lymphodepleting chemotherapy prior to CART-19 infusion.

1.2 Investigational Agent

General description

CART-19 is the investigational agent in this protocol. CART-19 is an autologous cellular product manufactured from an autologous leukapheresis product. The apheresis product is transduced via lentiviral vector with the genetic construct encoding the anti-CD19 CAR. The anti-CD19 CAR incorporates an anti-CD19 ScFv along with the CD3 ζ and 4-1BB intracellular signaling domains. Simultaneously, the autologous product is cultured *ex vivo* in the presence of microbeads conjugated to anti-CD28/anti-CD3 antibodies to promote T cell activation and expansion. CART-19 cells will be manufactured and formulated [REDACTED] at the University of Pennsylvania according to procedures specified in [REDACTED]. CART-19 cells are resuspended in cryopreservation media containing 31.25% Plasmalyte-A, 31.25% Dextrose 5%, 0.45% NaCl, 1% Dextran 40, 5% Human Serum Albumin, and 7.5% DMSO. CART-19 cells are frozen in bags using a controlled-rate freezer. Cryopreserved CART-19 cells are stored in a monitored freezer at $\leq -130^{\circ}\text{C}$.

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Absorption, distribution and metabolism

Lymphocytes have complex trafficking and survival kinetics, and after adoptive transfer several fates have been demonstrated: 1) margination; 2) exit from the peripheral blood trafficking to lymphoid tissues; and 3) death by apoptosis. Rapid *in vivo* expansion of autologous murine CART-19 cells in peripheral blood typically occurs within 9-10 days in pediatric and adult ALL subjects and within 13 days in CLL subjects. In addition to peripheral blood, autologous murine CART-19 cells can traffic to bone marrow and cerebral spinal fluid, in some cases²⁹⁻³². Moreover, CART-19 cells have been detected in peripheral blood by qPCR and flow cytometry beyond 4 years in the first two CLL subjects treated who have sustained a complete response²⁹. In contrast, CART-19 cells were no longer detectable *in vivo* by day 100 in the phase I CART-19 multiple myeloma study, [REDACTED], discussed in Section 1.4.2.2.

Drug interactions

CART-19 cells are expected to retain many of the properties of natural T cells. As such, they will be expected to be susceptible to immunosuppressive agents such as corticosteroids, immunophilins such as cyclosporine and tacrolimus, methotrexate, mycophenolate mofetil, mTOR inhibitors such as rapamycin, alemtuzumab, daclizumab, denileukin difitox, and everolimus. Lymphocytes are especially susceptible to cytotoxic and chemotherapeutic agents that are commonly administered for hematologic malignancies such as cyclophosphamide and fludarabine.

Immune elimination

An important consideration is that CARs can be immunogenic, either because foreign sequences such as antibiotic selection genes or mouse antibody sequences are expressed, or because of novel epitopes that are created at the fusion joint of human signaling domains that are not normally juxtaposed. Immunogenicity of the CAR can lead to the rejection of the adoptively transferred T cells. The basis for this supposition is that human retrovirally-modified CTLs expressing a fusion protein consisting of hygromycin:HSV thymidine kinase were eliminated by host CTLs in patients with advanced HIV infection³³; importantly, this immune mediated elimination was not accompanied by adverse effects and required 6 to 8 weeks to occur. There is one report where CAR containing a scFv with mouse sequences has been given to cancer patients. Following a single dose of CAR T cells (0.6 to 4 x 10⁹ T cells), the CAR T cells were detected in circulation from 23, 32, and 53 days after infusion in three patients with renal cell carcinoma³⁴. All three patients developed low levels of anti-scFv antibodies between 37 and 100 days after the CAR T-cell infusion. The determinants of CAR T cell persistence and elimination are under active investigation. As described above, *in vivo* persistence of CART-19 cells is ongoing >4 years after infusion in some patients, but persistence is very brief in other patients, which could be due to immune elimination or other mechanisms.

Lymphocyte costimulation

Extensive research in the past two decades has documented that maximal activation, proliferation and persistence of T cells responding to antigenic stimuli is dependent on receipt of two discrete signals mediated by cell surface receptors. The primary "activation" signal is generated by ligation of the TCR with antigen (typically in the form of peptides presented in the groove of HLA class I molecules) and the second signal by ligation of a costimulatory molecule with its cognate ligand. T cell costimulatory molecules which have been identified to date include members of the immunoglobulin super-family (CD28), members of the tumor necrosis factor (TNF) super-family (e.g. CD40L, CD134 [OX-40], CD137 [4-1BB])³⁵.

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Signaling through the cytosolic domain of a CAR comprised of a scFv-TCR ζ single chain construct does not fully replicate the multichain TCR signaling complex^{36,37}. Chimeric receptors bearing TCR ζ signaling modules are sufficient to trigger sustained proliferation in T cell hybridomas and clones but are not sufficient to drive proliferation or cytokine production in peripheral T cells³⁶. 4-1BB is a T cell co-stimulatory receptor induced by TCR activation, and evokes various T cell responses³⁸. 4-1BB signals are critical for long term proliferation of CD8 cells, and CD28 is essential for sustained CD4 cell proliferation^{39,40}. Second-generation CARs comprised of TCR ζ and either CD28 or 4-1BB signaling modules substantially improve the function and proliferation of T cells^{41,42}.

1.3 Pre-clinical data

Extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models⁴³. Others have used electroporation or retroviral vectors to create anti-CD19 CAR T cells and have shown *in vivo* safety and efficacy of adoptively transferred T cells in immunodeficient mouse models^{44,45}. The incorporation of signaling modules such as CD28 and 4-1BB in 2nd generation CARs increases potency of the engineered T cells in pre-clinical studies^{41,46-51}. The pre-clinical data supporting CART-19 has been published^{52,53}. These data support the efficacy of CART-19 in treatment of CD19+ malignancies. They do not apply directly to multiple myeloma, in which the dominant neoplastic cell population does not express CD19. Nonetheless, these pre-clinical data indicate that anti-CD19 CAR T cells can stringently deplete CD19+ populations, which is directly relevant to the proposed mechanism of action in multiple myeloma. Use of CART-19 in multiple myeloma has not been specifically modeled pre-clinically. Nonetheless, as detailed above and reviewed elsewhere¹⁶, extensive pre-clinical and *in vitro* analysis of patient samples supports the use of CD19-directed therapy in multiple myeloma.

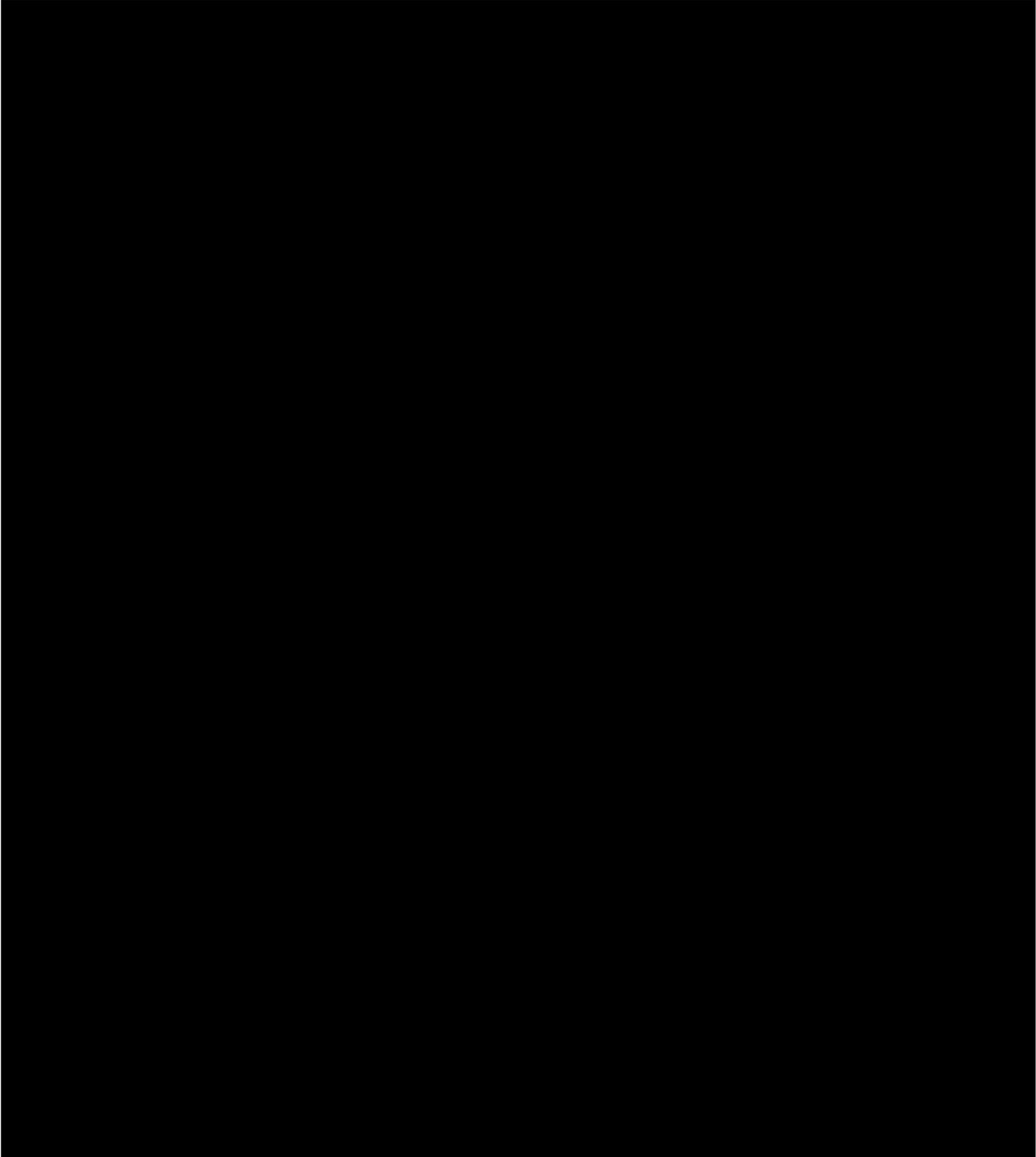
1.4 Clinical data

1.4.1 Previous Clinical Data With CART-19 Cells

[REDACTED]

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1.4.2 Autologous CART-19 cells in multiple myeloma

[Redacted text block]

[Redacted text block] The rationale for administering CART19 following ASCT in these studies was based on the data discussed in the introduction suggesting that anti-CD19 therapy, though unlikely to be effective as monotherapy in multiple myeloma patients, may prolong the duration of response to standard anti-myeloma therapy.

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1.4.2.1 [REDACTED]

[REDACTED]

[REDACTED] +2 post-ASCT, a time point at which there was less likely to be overlap of ASCT and CART-19 toxicities.

1.4.2.2 [REDACTED]

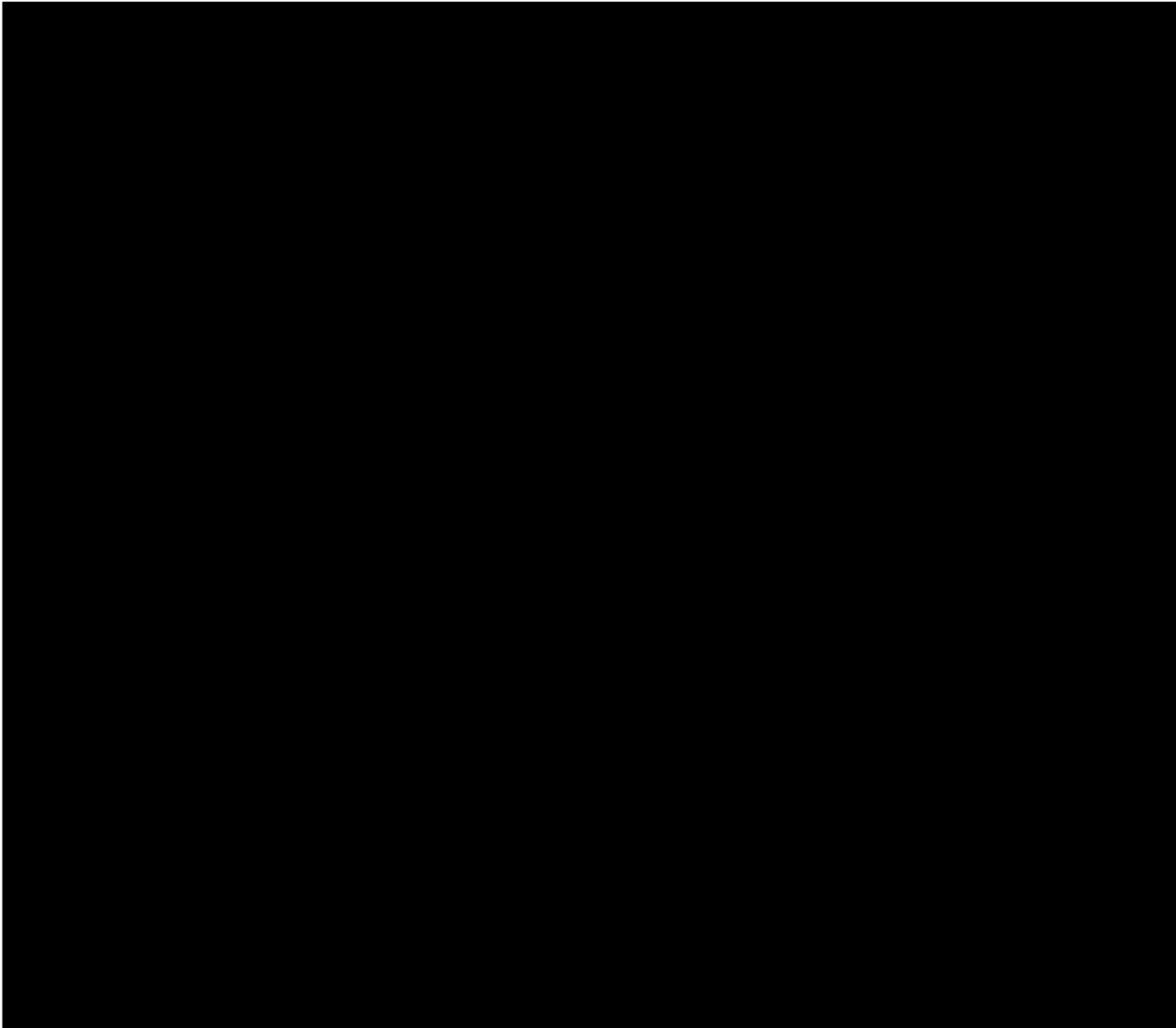
In this study, patients who had previously undergone ASCT and experienced short PFS (<12 months) underwent a second ASCT with infusion of CART-19 cells 12-14 days later. Since multiple myeloma patients generally have shorter PFS after second ASCT compared to initial ASCT, PFS after the second ASCT with CART-19 was compared in each patient to the PFS after prior ASCT as a preliminary measure of the clinical benefit from addition of CART-19. [REDACTED]

[REDACTED]

[REDACTED] patient #1, correlative studies were undertaken to confirm that the dominant neoplastic plasma cell population did not express low levels of CD19 that might have explained this response. By flow cytometry, 99.95% of this patient's multiple myeloma plasma cells were CD19-negative, and the absence of CD19 transcript was confirmed by RT-PCR performed after FACS-sorting of this population⁵⁴. [REDACTED]

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1.5 CART-19 Dose/Setting Rationale and Risks/Benefits

1.5.1 Dose and Schedule Rationale

The CART-19 dose and schedule chosen for this study is based on experience with CART-19 in multiple myeloma (██████████) and experience from previous and ongoing studies of CART-19 in ALL, CLL, and NHL. This protocol is designed to balance toxicity concerns with the desire for long-term *in vivo* CART-19 persistence. The factors that influence *in vivo* proliferation and long-term persistence are incompletely understood. In general, higher CAR T cell doses, abundance of CAR T cell target in the host (i.e., high burden of CD19-expressing cells), and the intensity of the pre-infusion lymphodepletion regimen all support *in vivo* CART-19 expansion and persistence.

██████████ and ██████ each utilized the myeloablative-dose melphalan administered prior to ASCT as lymphodepleting chemotherapy with sub-optimal results. On ██████████, robust *in vivo* CART-19

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expansion was observed, likely due to the infusion just four days after high-dose melphalan, but the overlapping toxicity of CART-19 and ASCT was excessive. In contrast, with the 10-fold lower cell dose ($1-5 \times 10^7$ CART-19 cells) and longer gap (12-14 days) between lymphodepleting chemotherapy and CART-19 infusion on [REDACTED], only minimal *in vivo* CART-19 expansion was observed, and no subjects developed long-term CART-19 persistence. In the studies of CLL, NHL, and ALL, many patients have developed long-term CART-19 persistence with infusion of $1-5 \times 10^8$ CART-19 cells within one week of non-myeloablative-dose lymphodepleting chemotherapy without synergistic toxicity between the chemotherapy regimen and CART-19. This study therefore adopts the dose and schedule used on the CLL, NHL, and ALL studies. CART-19 cells will be given at a dose of $1-5 \times 10^8$ CAR-expressing cells three days after lymphodepletion with cyclophosphamide at 1.5 g/m^2 . This lymphodepleting regimen is in use in ongoing studies of anti-BCMA and anti-mesothelin CAR T cells.

Our prior experience with manufacturing anti-CD3/CD28-stimulated autologous T cells from lymphocytes harvested in the pre-ASCT period supports the feasibility of this target dose in this patient population^{20,26-28,55-57}.

1.5.2 Setting Rationale

The rationale for administering CART-19 cells after first-line ASCT in multiple myeloma is rooted in the proposed mechanism-of-action described above for CART-19 in myeloma. Since CART-19 is hypothesized to prevent progression after effective standard anti-myeloma therapy, it is most likely to be effective early in the disease course, when the myeloma is sensitive and has been optimally cytoreduced by the accompanying standard anti-myeloma therapy. ASCT-eligible multiple myeloma patients typically achieve their lowest lifetime disease burden following first-line therapy and consolidative ASCT, especially when this line of therapy incorporates the combination of lenalidomide, bortezomib, and dexamethasone (RVD), which is the most effective standard first-line therapy for multiple myeloma. The post-RVD/post-ASCT period is therefore the optimal window for evaluation of CART-19.

1.5.3 Risks/Benefits

Safety information outlined in the risk section is largely representative of the murine CART-19 experience.

1.5.3.1 T cell proliferation

Participation in this study will expose the patient to genetically engineered autologous T cells. T cell proliferation could be uncontrolled; however we have not observed this in our pre-clinical models or in any CART-19 patient treated so far. In this case, corticosteroids and chemotherapy would be given to eradicate the CAR cells; this has been effective in previous cases⁵⁸.

1.5.3.2 Immunogenicity

Since we are using a murine-derived ScFv, it is possible the cells may be immunogenic and that the patients will have an immune response directed against the scFv; this has not had clinical consequences in previous trials of CART-19. If an immune response to the cells occurs, it is possible that the cells will be rejected. Three of 3 subjects developed HAMA and loss of T cell engraftment in the Lamers study⁵⁸, but this has generally not been observed in patients with B cell malignancies.

1.5.3.3 Hypogammaglobulinemia and B/plasma cell aplasia

Transient or permanent host B and plasma cell depletion and hypogammaglobulinemia has been observed with CART-19 cells, since normal B cells and a subset of normal plasma cells express CD19. This can be

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managed with infusions of intravenous immunoglobulin (IVIG). Hypogammaglobulinemia can be long-lived if CART-19 cells durably persist, but recovery of normal B and plasma cell counts is expected if CART-19 engraftment wanes.

1.5.3.4 Transformation

There is a risk that people who receive gene transfer may develop new tumors derived from their genetically modified cells. This risk is primarily associated with viral gene transfer vectors that integrate into the cellular DNA where they may dysregulate genes controlling proliferation. Transformation has not been observed following adoptive T cell transfer in hundreds of cancer and HIV patients receiving gammaretroviral modified T cells treated on multiple protocols at many academic centers and in the 21 HIV patients treated with lentiviral modified T cells treated at Penn⁵⁹.

1.5.3.5 Intracranial Hemorrhage

As of February 2017, there have been three events of intracranial hemorrhage on CART-19 trials under [REDACTED]. One event occurred on [REDACTED] (adult ALL) in the setting of thrombocytopenia (related to prior lymphodepleting chemotherapy and underlying leukemia), was determined to be possibly related to the CART-19 T-cell infusion, occurred with concurrent Grade 4 CRS, and resulted in death. Another event occurred on the CNS3 cohort on [REDACTED] (pediatric ALL) in the setting of active circulating leukemia, CRS, sepsis/bacteremia, and acute renal failure requiring dialysis. The subject died, and intracranial hemorrhage (suspected clinically, unconfirmed radiologically) was felt to be the immediate cause of death in this critically ill patient. A third event occurred on [REDACTED] (pediatric ALL study) in February 2017. A 3-year-old subject with refractory ALL and CNS2 disease experienced severe CRS complicated by DIC and multi-organ failure. While on extracorporeal membrane oxygen, the subject experienced an intracranial hemorrhage, with associated cerebral edema as a terminal event.

1.5.3.6 Cytokine Release Syndrome (CRS)

Overview and Clinical Manifestations: Patients treated with CART-19 cells may experience CRS, which has correlated with disease response in other CART-19 trials. Clinical manifestations have included high fevers, fatigue, anorexia, nausea, vomiting, headache, rash, hypotension (occasionally requiring vasopressor support), tachypnea, hypoxia (occasionally requiring ventilator support), delirium and confusion (in several patients), evidence of disseminated intravascular coagulation as well as macrophage activation syndrome (MAS). The CRS has been effectively abrogated with anti-cytokine therapy including tocilizumab. It is unclear if treating the CRS adversely impacts the anti-tumor response.

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

MAS is similar to HLH; it is a rare reaction to immune stimulation by infection, autoimmune diseases or other precipitants, but it is distinct from familial or genetically mediated HLH. There are no definitive diagnostic criteria for MAS, but it is typically diagnosed by meeting HLH diagnostic criteria. Some but not all features of MAS are typically observed. The clinical syndrome of MAS is characterized by high grade non-remitting fever, cytopenias affecting at least two of three lineages, and hepatosplenomegaly. It is associated with biochemical abnormalities, such as high circulating levels of serum ferritin, soluble interleukin-2 receptor (sCD25), and triglycerides, and decrease in circulating

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natural killer cell activity. Other findings include variable degrees of hepatic dysfunction ranging from mild transaminase elevation up to signs of acute liver failure and coagulopathy and DIC. A pathologic feature of MAS is the presence of hemophagocytic CD163+ macrophages (HPC) in bone marrow or lymph-node aspirates.

Diagnosis is based on the fulfillment of criteria established in 2004⁶⁰ for HLH associated with autosomal recessive disorders (familial HLH, fHLH).

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

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

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

At this time it is still unknown whether CRS/MAS is beneficial or harmful to the antitumor response. Research correlative studies have shown that IL-6 levels were extraordinarily high during the CRS, prompting us to use an anti-IL6 receptor antibody tocilizumab to treat the CRS/MAS. We have treated multiple adult patients with tocilizumab for CRS and MAS on the CLL/ALL trials. In most of the patients, this treatment resulted in rapid (within hours) resolution of high fevers, and continuous improvement in hypotension and hypoxia over hours to several days, and all showed improvement in biochemical evidence of CRS and MAS within 48 hours. Adult patients were initially treated with tocilizumab 4mg/kg x 1. Subsequently, the dose was raised to 8mg/kg. It is unclear if early treatment will negate the antitumor response. Treatment and timing of treatment of this toxicity will be at the discretion of the patient's physician and the study investigator; generally, treatment will be initiated if the syndrome progresses towards hemodynamic instability or other signs of critical illness requiring intensive care. A guide for managing CRS/MAS is described in section 8.4.2.

Pediatric ALL patients treated with CART-19 on ██████ have experienced a similar CRS and MAS. ██████ experienced a severe CRS and had high fevers, hypotension, acute vascular leak syndrome and acute respiratory distress. The patient was treated with etanercept and tocilizumab, as described in Grupp *et al.*, *NEJM*, 2013³², and all associated adverse events resolved. ██████ and ██████ 5 developed CRS after receipt of just the first dose of CART-19, which consisted of only 10% of total planned dose. ██████ 103 received the 10% and 30% doses, respectively, and experienced a mild CRS after the

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10% dose, with no CRS experienced after the 30% dose. None of these patients experienced sufficiently severe CRS to require treatment with steroids or cytokine blockade (i.e., there was no more than a transient oxygen requirement and no hypotension requiring vasopressor support).

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

Grading of CRS: The Common Toxicity Criteria (i.e., CTCAE) grading system was originally developed to capture a cytokine syndrome occurring during infusional therapy; therefore, it is inadequate to capture the delayed CRS that occurs after CAR T cell infusion. We propose to modify the CTCAE grading specifically to capture toxicity for protocols using CAR T cells. MAS/HLH signs and symptoms are a manifestation of CRS and will therefore not be graded separately (See Table 8-1 in Section 8.1).

1.5.3.7 Risk of tumor lysis syndrome (TLS) related to cytoreductive chemotherapy or CAR T cells

The risk of tumor lysis syndrome (TLS) is dependent on the disease and burden of disease. This risk is generally lower in multiple myeloma patients compared to those with other hematologic malignancies, but is present. Compared to other CART-19 studies, the risk of TLS in this protocol is expected to be low because neoplastic multiple myeloma plasma cells do not typically express CD19 and the overall burden of these cells in the post-ASCT period is low. Nonetheless, patients will be closely monitored both before and after chemotherapy and CART-19 cells for laboratory evidence of TLS (serum measurements of potassium, uric acid, phosphate, calcium, and creatinine). TLS resulting in renal insufficiency, or rapidly rising uric acid, or evidence of organ dysfunction will be managed with intravenous fluids and rasburicase as needed and determined by the treating physicians. Appropriate clinical therapy will be administered should any significant tumor lysis occur. Prophylactic administration of allopurinol is at the discretion of the clinical investigator.

1.5.3.8 Risks of cyclophosphamide

In over 10% of patients, cyclophosphamide causes dermatologic reactions (alopecia beginning 3-6 weeks) and may cause sterility; thrombocytopenia and anemia are less common than leukopenia with an onset at 7 days, nadir at 10-14 days, and recovery at 21 days. Rates of neutropenic fever range from 5 – 20%⁶¹⁻⁶⁴ at the dose used in this protocol (1.5 g/m²). Nausea and vomiting occur more frequently with large doses, usually beginning 6-10 hours after administration; subjects will be offered antiemetic prophylaxis and therapy. Acute hemorrhagic cystitis, believed to be a result of chemical irritation of the bladder by acrolein, a cyclophosphamide metabolite, occurs in 7% to 12% of patients and has been reported in up to 40% of patients in some series. Patients will be encouraged to drink plenty of fluids during and after therapy (most adults will require at least 2 L/day), and void frequently. With large IV doses, IV hydration is recommended. The use of mesna and/or continuous bladder irrigation is not indicated for doses <2 g/m². Less frequent reactions (1-10%) such as facial flushing, headache, and skin rash may occur. Nasal congestion occurs when IV doses are administered too rapidly (large doses via 30-60 minute infusion); patients experience runny eyes, rhinorrhea, sinus congestion, and sneezing during or immediately after the infusion. If needed, a decongestant or decongestant/antihistamine (eg, pseudoephedrine or pseudoephedrine/triprolidine) can be used to prevent or relieve these symptoms.

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1.5.3.9 Replication-competent lentivirus (RCL)

It is theoretically possible that RCL may be generated during the manufacturing phase or subsequently after infusion into the patient. However, an RCL resulting from the production phase is highly unlikely since elements are incorporated in the design of the vector system that minimize vector recombination and generation of RCL. Furthermore, the vector used to transduce the product undergoes sensitive assays for detection of RCL before it can be used in the manufacturing process. Nevertheless, generation of an RCL following infusion remains a theoretical possibility. The consequences of such recombination events in subjects without a known lentiviral infection are unknown, and therefore subjects with coexistent HIV infection are excluded from participation in this study in order to minimize this possibility. The development of RCL could pose a risk to both the subject and their close contact(s), and therefore, monitoring for RCL will be conducted during the course of the trial. RCL assessment (Q-PCR for VSV-G) in subjects' samples will be performed prior to treatment (as a baseline) and after T cell infusion in accordance with the Schedule of Evaluations in Appendix 1; this assessment will continue on the long-term follow-up (LTFU) protocol according to the FDA guidance. If the tests are negative during the first year post-CART19 infusion, the Month 20 sample (18 months post-CART19) will be archived in a temperature monitored and alarmed freezer at -80°C at the Translational and Correlative Studies Laboratory (TCSL).

1.5.3.10 Risks of ASCT and potential interaction with CART-19

High-dose melphalan and autologous stem cell transplantation is a standard-of-care procedure in this population. Risks of melphalan are described in the package insert. Subjects will sign a separate standard-of-care consent for ASCT. The risks of ASCT are acceptable in this population based on the significant overall survival benefit that has been repeatedly demonstrated for this procedure in this patient population (see section 1.1). Based on the ~60-day interval between ASCT and CART-19 infusion in this protocol, adverse interactions between ASCT complications and CART-19 risks are not expected.

1.5.4 Potential benefits

This trial will enroll patients with high-risk multiple myeloma. As described in section 1.1, the prognosis for this condition is poor. Given our preliminary clinical data suggesting that CART-19 may prolong responses to standard multiple myeloma therapy even in exceptionally refractory and high-risk patients, the risks and potential benefits of participation in this study are well balanced.

2. OBJECTIVES

The primary objective is to evaluate PFS in high-risk multiple myeloma patients treated with CART-19 post-ASCT.

Secondary objectives are to:

- Describe the incidence and nature of adverse events attributable to CART-19 at this dose, schedule, and clinical setting, with specific attention to adverse events that emerge after initiation of maintenance lenalidomide.
- Describe response rate and depth-of-response using both standard clinical criteria (IMWG) and MRD assessments.
- Evaluate expansion, persistence, phenotype, function, and homing of CART-19 cells manufactured and administered in this low-target clinical setting.

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- Evaluate PFS and depth-of-response in the subset of patients, if present, with long-term (>6 months) *in vivo* persistence of CART-19 cells.
- Evaluate PFS and depth-of-response in clinically and biologically defined subsets of multiple myeloma patients (e.g., subsets with certain cytogenetic abnormalities, clinical stage, multiple myeloma plasma cell immunophenotype, or gene expression profile).
- Describe CART-19 manufacturing feasibility in this clinical setting and the features (dose, cellular phenotype) of the manufactured product.

3. STUDY DESIGN

3.1 General Design

This is a single-arm, single-center, open-label study to evaluate post-ASCT administration of CART-19 cells, followed by maintenance lenalidomide, as a therapy to prolong response to ASCT in patients with high-risk multiple myeloma. **Figure 1** presents the study schema. The target population includes patients with high-risk multiple myeloma as defined by clinical and cytogenetic features who are receiving or have recently completed induction/initial therapy with a combination of lenalidomide, bortezomib, and dexamethasone (RVD) and for whom standard-of-care ASCT is planned by their treating physician. Enrollment and mononuclear cell apheresis to harvest T cells for CART-19 manufacturing will take place prior to standard-of-care hematopoietic stem cell mobilization and collection. Screening and enrollment procedures will consist of medical record review for eligibility, standard multiple myeloma response assessment, bone marrow aspiration/biopsy, and testing to confirm medical fitness for ASCT. Subjects will then undergo stem cell mobilization and collection and standard-of-care ASCT. Approximately 60 days post-ASCT, subjects will receive lymphodepleting chemotherapy with cyclophosphamide 1.5 g/m² and, three days later, 1-5x10⁸ CART-19 cells. At approximately day 90 post-ASCT, subjects will begin standard-of-care maintenance therapy with lenalidomide. A stopping rule will monitor for excess discontinuation of lenalidomide maintenance due to adverse events. The target cell dose for this protocol is 1-5 x 10⁸ transduced cells. Subjects with a manufactured cell dose that is less than the protocol-specified dose will be scored as a manufacturing failure. These subjects will receive their cell infusion, provided that the manufactured dose is above the [REDACTED] minimum acceptable dose for infusion (2x10⁷ CART-19 cells) and all other manufacturing release criteria are met. The subjects that are infused with ≥2x10⁷-<1x10⁸ CART-19 cells will be considered non-evaluable for the primary endpoint but will be included in analysis of secondary endpoints. Both primary efficacy evaluable and non-evaluable patients will be followed in the same manner according to the Schedule of Study Procedures for all evaluations, including clinical, research (correlative) and safety.

Following CART-19 infusion, subjects will be followed for toxicity, PFS, and secondary endpoints that will assess depth of response (including MRD assessments) and *in vivo* persistence and activity of CART-19 cells. Bone marrow sampled pre-ASCT and pre-/post-CART-19 infusion will be analyzed to evaluate trafficking of CART-19 cells to bone marrow, the immunophenotype of multiple myeloma plasma cells, presence of minimal residual disease, and other laboratory correlative studies. PFS will be compared to historical results reported in similar populations to preliminarily assess whether CART-19 provides clinical benefit in this setting and decide whether phase-3 evaluation of this approach is warranted. Since long-term persistence of CART-19 (>6 months) is expected to develop in some patients, PFS will also be examined in this sub-group, along with other clinically and biologically defined sub-groups, to preliminarily explore whether clinical benefit from CART-19 is restricted to certain sub-groups.

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The study is expected to enroll 25 patients over 2-3 years. The study is powered to detect an increase in two-year PFS to ~75% from a baseline expectation of 55% based on previously reported cohorts.

3.2 Primary Study Endpoint

Proportion of patients alive and progression-free (PFS) two years after ASCT. Progression will be defined by IMWG criteria (Table 5).

3.3 Secondary Study Endpoints

- Adverse events: Occurrence of adverse events and their attribution to CART-19 in this patient population and clinical setting will be described. Adverse events and criteria for their attribution are defined in Section 8.
- Incidence of discontinuation of lenalidomide maintenance due to adverse events: This will be monitored continuously, and a stopping rule will operate throughout the study to pause new enrollments if the incidence exceeds historical expectations. Details of the stopping rule and its assumptions/rationale are described in Section 7.
- Anti-myeloma responses: Full multiple myeloma response assessments will take place pre-ASCT, prior to CART-19 infusion, approximately two months after CART-19 infusion, and two years post-ASCT. Responses will be categorized by IMWG criteria (Table 4)⁶⁵ and using MRD assessment techniques. MRD assessment will be by flow cytometry and, when sufficient sample is available and when subjects are MRD-negative by flow cytometry, using immunoglobulin sequencing.
- Exploratory analysis of PFS and depth-of-response in clinically and biologically defined subgroups. The following parameters will be analyzed in all subjects and correlated in exploratory fashion with PFS and depth-of-response in an attempt to preliminarily identify sub-groups that are most likely to benefit from CART-19 therapy and to better understand the mechanism-of-action of CART-19 in multiple myeloma:
 - CART-19 persistence and activity: Presence of CART-19 cells in peripheral blood and bone marrow will be assessed by flow cytometry and qPCR. Time points for these evaluations are described in the schedule of events (Appendix 1). As an *in vivo* measure of CART-19 activity, the presence of normal CD19+ B cells will be assessed at the same time points that CART-19 persistence is assessed.
 - Plasma cell CD19 expression: Flow cytometry will be performed on all bone marrow samples to analyze CD19 expression on multiple myeloma plasma cells at pre- and post-CART-19 time points.
 - Multiple myeloma gene expression profile: Gene expression profiling (GEP) by RNA-seq will be performed on sorted multiple myeloma cells, if available, from the pre-ASCT sample. The multiple myeloma GEP-based sub-type will be determined for each patient with reference to established GEP sub-types from the MMRF CoMMpass study⁶⁶. When possible, CD19+ subsets of multiple myeloma plasma cells will be separately sorted and subjected to GEP.
 - Manufacturing feasibility: The proportion of enrolled subjects from whom CART-19 is successfully manufactured at the target dose will be described.

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Table 4: Response criteria

Response subcategory	Response criteria ^a
Stringent Complete Response (sCR)	CR as defined below plus: Normal FLC ratio and Absence of clonal cells in bone marrow ^b by immunohistochemistry or immunofluorescence ^c
Complete Response (CR)	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow ^b
Very Good Partial Response (VGPR)	Serum and urine M-Protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
Partial Response (PR)	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h. If the serum and urine M-protein M-protein are unmeasurable, ^d a ≥ 50% decrease in the difference between involved and uninvolved FLC levels in required in place of the M-protein criteria
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

^aAll response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

^bConfirmation with repeat bone marrow biopsy not needed.

^cPresence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence require a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

^dRefer to inclusion criterion #7 for definition of measurable disease.

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Table 5: Criteria for progression

Progressive disease^a requires Increase of $\geq 25\%$ from baseline in any one or more of the following:

- Serum M-component (the absolute increase must be ≥ 0.5 g/dL)^b
- Urine M-component (the absolute increase must be ≥ 200 mg/24 h)
- Only in patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels, in which case the absolute increase must be ≥ 10 mg/dL.
- Bone marrow plasma cell percentage, if the absolute % is $\geq 10\%$.
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L that can be attributed solely to the plasma cell proliferative disorder.

^a All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.

^b For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

4. SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

1. Subjects must be age 18-70, inclusive, at time of enrollment.
2. Subjects must have ECOG performance status of 0-2.
3. Subjects must have a confirmed diagnosis of active multiple myeloma according to IMWG criteria, summarized below in **Table 6**. For circumstances not encompassed by this summary of the diagnostic criteria, reference can be made to the full publication of the IMWG criteria⁶⁷. In addition, subjects must have “high-risk” multiple myeloma according to one of the following criteria:
 - a. Any of the following high-risk cytogenetic features, documented by FISH or metaphase karyotyping: deletion 17p, t(4;14), t(14;16), t(14;20).
 - b. Standard-risk cytogenetics but elevated LDH and beta-2-microglobulin > 5.5 mg/L (i.e., R-ISS stage III).
4. At time of enrollment, subjects must be within 9 months of initiation of systemic therapy for multiple myeloma.
5. Requirements for pre-enrollment therapy: Subjects must have received or be receiving, at time of enrollment, “RVD” therapy (combination therapy with lenalidomide, bortezomib, and dexamethasone). Patients must have received ≤ 6 cycles of RVD at time of enrollment and must not have progressed (by IMWG criteria⁶⁵) on RVD. Patients may have received other regimens prior to RVD if such therapy was limited to ≤ 3 cycles. Patients may have received radiation therapy prior to enrollment. Patients must not have received infusional chemotherapy (e.g., VTD-PACE or similar regimen) prior to enrollment unless such infusional chemotherapy consisted of a single cycle prior to initiation of standard RVD.
6. Subjects must be eligible for ASCT and to receive a melphalan dose of 200 mg/m² as defined by the following criteria:
 - a. Left ventricular ejection fraction $\geq 40\%$,
 - b. AST/ALT ≤ 2.5 times the upper limit of normal

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- c. Total bilirubin ≤ 1.5 mg/dL, unless hyperbilirubinemia is attributable solely to Gilbert's syndrome.
 - d. Estimated (by CKD-EPI or Cockcroft-Gault equations) or calculated CrCl ≥ 40 ml/min.
 - e. DLCO $\geq 50\%$ of predicted (corrected or uncorrected for anemia and/or alveolar volume).
7. Subjects must have measurable disease by standard serum and urine tests to enable post-transplant monitoring for progression-free survival. Any of the following criteria are sufficient to define measurable disease.
- a. Serum M-spike ≥ 0.5 g/dL
 - b. 24 hr urine M-spike ≥ 200 mg
 - c. Involved serum FLC ≥ 50 mg/L with abnormal ratio
 - d. For IgA multiple myeloma, total serum IgA level elevated above normal range.
- Note: Measurable disease does not need to be documented at enrollment but can be based on historical lab results obtained at or since diagnosis with multiple myeloma. For example, a patient who does not have measurable disease at enrollment due to complete remission after induction therapy is eligible if the disease was previously measurable by one of the above criteria.
8. Subjects must have signed written, informed consent.
 9. Subjects of reproductive potential must agree to use acceptable birth control methods, as described in protocol Section 4.3.

Table 6

IMWG Criteria for Diagnosis of Multiple Myeloma

Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
- Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL).
- Renal insufficiency: creatinine clearance <40 mL per min[†] or serum creatinine >177 μ mol/L (>2 mg/dL)
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[‡]
- Any one or more of the following biomarkers of malignancy:
- Clonal bone marrow plasma cell percentage* $\geq 60\%$
- Involved:uninvolved serum free light chain ratio[§] ≥ 100
- >1 focal lesions on MRI studies [¶]

*Clonality should be established by showing κ/λ -light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. [†]Measured or estimated by validated equations. [‡]If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. [§]These values are based on the serum FreeLite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥ 100 mg/L. [¶]Each focal lesion must be 5 mm or more in size.

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4.2 Exclusion Criteria

Subjects must not:

1. Be pregnant or lactating.
2. Have inadequate venous access for or contraindications to leukapheresis.
3. Have any active and uncontrolled infection.
4. Any uncontrolled medical or psychiatric disorder that would preclude participation as outlined.
5. Have NYHA Class III or IV heart failure (see Appendix 2), unstable angina, or a history of recent (within 6 months) myocardial infarction or sustained (>30 seconds) ventricular tachyarrhythmias.
6. Have undergone allogeneic stem cell transplantation.
7. Have received prior gene therapy or gene-modified cellular immunotherapy.
8. Have active auto-immune disease, including connective tissue disease, uveitis, sarcoidosis, inflammatory bowel disease, or multiple sclerosis, or have a history of severe (as judged by the principal investigator) autoimmune disease requiring prolonged immunosuppressive therapy.
9. Have prior or active central nervous system (CNS) involvement (e.g. leptomeningeal disease, parenchymal masses) with myeloma. Screening for this (e.g. with lumbar puncture) is not required unless suspicious symptoms are present.
10. Have a contraindication to post-ASCT maintenance lenalidomide.
11. Have active infection with HIV (negative HIV 1/2 antibody screen), hepatitis C (negative hepatitis C antibody screen), or hepatitis B (negative hepatitis B surface antigen). Any positive serologies for HIV or viral hepatitis should be confirmed with appropriate confirmatory testing before concluding that an active infection is present. Subjects with positive hepatitis core antibody are also excluded since the effect of long-term B cell depletion on the risk of hepatitis B reactivation is unknown.
12. Patients with a known history or prior diagnosis of optic neuritis or other immunologic or inflammatory disease affecting the central nervous system.

4.3 Subject Recruitment and Screening

Subjects will be identified through the clinical practices of the investigator or sub-investigators and through referrals from outside hospitals and physicians. The study will be publicized on clinicaltrials.gov, and via University of Pennsylvania or Abramson Cancer Center press releases. No direct-to-patient advertising will be performed.

Female subjects of reproductive potential (women who have reached menarche and who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone a sterilization procedure such as hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) must have a negative serum or urine pregnancy test at the time of enrollment and a negative serum pregnancy test at the Pre-Infusion Visit.

Due to the high-risk nature of this study, while enrolled, all subjects must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate or donate sperm for artificial insemination or *in vitro* fertilization). Additionally, if participating in sexual activity that could lead to pregnancy, the subject must agree to use at least one reliable method of contraception during participation in this protocol.

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Acceptable birth control includes one of the following methods:

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

Subjects who are not of reproductive potential (women who have been postmenopausal for at least 24 consecutive months or have undergone hysterectomy, salpingotomy, and/or bilateral oophorectomy or men who have documented azoospermia) are eligible without requiring the use of contraception.

Acceptable documentation of sterilization, azoospermia, or menopause consists of written or oral attestation by a physician or a physician's staff in one of the following formats:

- Physician report/letter
- Operative report or other source documentation in the subject's medical record (a laboratory report of azoospermia is required to document successful vasectomy)
- Discharge summary
- Laboratory report of azoospermia
- Follicle stimulating hormone measurement elevated into the menopausal range

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects who enroll but do not receive CART-19 cells will be prematurely discontinued from the study, will not be followed, and will be replaced in the study. Reasons for premature discontinuation prior to receipt of CART-19 cells may include, but are not limited to, the following:

1. The subject is lost to follow-up.
2. The principal investigator judges that the subject, prior to CART-19 infusion, is too ill to continue.
3. Patient noncompliance with study therapy and/or clinic appointments
4. Pregnancy is documented prior to CART-19 infusion.
5. Voluntary withdrawal: a subject may remove himself/herself from the study at any time without prejudice.
6. Significant and rapid progression of malignancy, requiring alternative medical, radiation or surgical intervention including, but not limited to, the development of CNS metastasis if this occurs prior to the CART-19 T-cell infusion.
7. A serious adverse event that requires the subject to be withdrawn from the trial if the SAE occurs prior to the CART-19 T-cell infusion.
8. Technical difficulties are encountered in the T cell genetic modification and expansion procedure that precludes the generation of clinical cell doses that meet all Quality Control release criteria as specified by FDA.
9. Termination of the study by the Principal Investigator, the Sponsor, the Funding Sponsor, the IRB, ACC CTRMC, ACC DSMC, DSMB, or the Food and Drug Administration."

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

1. The subject is lost to follow-up.
2. Voluntary withdrawal: a subject may remove himself/herself from the study at any time.

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3. Disease progression of targeted malignancy
4. Receipt of alternative treatment for their targeted disease
5. Termination of the study by the Principal Investigator, the Sponsor, the Funding Sponsor, the IRB, ACC CTRMC, ACC DSMC, DSMB, or the Food and Drug Administration.

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

4.4.2 Data Collection and Follow-up

Follow-up data collection after gene-modified cell therapy clinical trials is specified by FDA. As long as subjects have detectable cells transduced with the lentiviral vector, they should be followed for toxicity, immune reactions, and any long-term adverse events. Subjects who complete the 2 year follow-up as part of this protocol or discontinue participation early for any reason, will be encouraged to enroll in a 15-year long-term follow-up protocol to further evaluate long term adverse events related to the study product. Once subjects are enrolled on the long-term follow-up protocol, all follow-up data collection under this protocol will be discontinued.

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

In numerous previous cell therapy trials at the University of Pennsylvania, loss of follow-up is estimated to occur in less than 5% of cases. Every effort will be made to contact subjects who appear to be lost to follow-up in order to at least obtain survival data. In the event a subject fails to complete the follow-up requirements, documentation of all attempts to contact the subject includes at least 3 telephone contacts (on different days and at different times of the day), and a certified letter.

5. STUDY DRUG

5.1 Description

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

Expected toxicities associated with infusion of CART-19 cells include transient fever, chills nausea, rigors, hypotension, tumor lysis syndrome, and cytokine release syndrome. In order to minimize these events,

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patients will receive premedication as instructed below. Toxicities that could potentially occur but are unprecedented are primarily related to the gene transfer and are described in the Risk and Benefit section (refer to section 1.5) and the Investigator Brochure. These include generation of a replication competent lentivirus (RCL), insertional oncogenesis, and uncontrolled proliferation of the CART-19 cells.

5.2 Patient Eligibility to Receive CART-19 Cells

CART-19 infusion will be scheduled to occur 60 (\pm 7) days post-ASCT, and lymphodepleting chemotherapy will be scheduled for 3 (\pm 1) days prior to CART-19 infusion.

Subjects must meet the following criteria to receive CART-19 cells:

1. Disease response: Between enrollment and infusion, subjects must not have developed new disease complications or symptoms that would, in the opinion of the investigator, render it unsafe to proceed with CART-19 infusion.
2. Subjects should not experience a significant change in performance or clinical status compared to status at screening/enrollment that would, in the opinion of the investigator, render it unsafe to proceed with CART-19 infusion.
3. Female patients of child-bearing potential must not be pregnant as assessed by a negative serum beta-HCG test drawn within 7 days prior to CART-19 infusion.
4. All subjects must undergo a Respiratory Virus Panel (RVP) within 10 days prior to the planned CART-19 infusion. If the patient is positive for influenza, Tamiflu® or equivalent should be administered per package insert. The patient must complete treatment prior to receiving cyclophosphamide and CART-19 cells. The test does not need to be repeated prior to the first CART-19 cell infusion; however if influenza signs and symptoms are present, the CART-19 cell infusions should be delayed until the patient is asymptomatic. If the patient is positive for another virus on the RVP, the cyclophosphamide and CART-19 cell infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the cyclophosphamide and CAR T cell infusion will be delayed until resolution of these symptoms.
5. Subjects who develop laboratory abnormalities identified during routine care that in the opinion of the treating investigator or PI may make it unsafe to receive CART-19 cells may have their infusion delayed until both the treating investigator and PI determine that it is appropriate to proceed with the CART-19 cell infusion.
6. Subjects experiencing toxicities from ASCT or lymphodepleting cyclophosphamide may have their CART-19 cell infusions delayed until these toxicities have resolved at the investigator discretion. If a subject's CART-19 cell infusion is delayed > 4 weeks from the lymphodepleting cyclophosphamide, the cyclophosphamide dosing should be repeated.
7. The specific toxicities warranting delay of T cell infusions include:
 - a. Pulmonary: Requirement for supplemental oxygen to keep saturation greater than 95% or presence of radiographic abnormalities on chest x-ray that are progressive
 - b. Cardiac: New cardiac arrhythmia not controlled with medical management
 - c. Hypotension requiring vasopressor support
 - d. Active Infection: Positive blood cultures for bacteria, fungus, or virus within 48 hours of CART-19 cell infusion.

Administration of lymphodepleting chemotherapy and infusion of CART-19 cells may be delayed up to 4 weeks from the originally scheduled date to address any factors that make a subject ineligible for CART-

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19 infusion. Delay of lymphodepleting chemotherapy and CART-19 infusion beyond 4 weeks from the scheduled date is acceptable only with approval of the Sponsor.

5.3 Treatment Regimen

5.3.1 High-dose Melphalan and Autologous Stem Cell Transplantation

HDM + ASCT will be carried out as follows:

- Melphalan dosing: Subjects will receive HDM at a dose of 200 mg/m² unless dose-reduction is required due to new disease-related complications (e.g., new acute kidney injury) that develop between enrollment and HDM for which dose reduction is indicated. Melphalan will be administered as a single dose on day -2 or -1, or in two divided doses, according to standard institutional practice. Melphalan dose is based on ideal body weight (IBW) for patients who weigh 100-120% of their IBW. For patients who weigh less than 100% of their IBW, dosing should be based on actual body weight (ABW). For patients who weigh more than 120% of their IBW, dosing should be based on the adjusted ideal body weight (AIBW). Melphalan dose may be rounded-down to the nearest vial size per local institutional practice.
 - Ideal Body Weight Formulas:
 - Males IBW = 50 kg + (2.3 kg x number of inches greater than 60)
 - Females IBW = 45.5 kg + (2.3 kg x number of inches greater than 60)
 - For patients less than 5 feet, subtract 2.3 kg/inch
 - Adjusted Ideal Body Weight Formula: $AIBW = IBW + [(0.25) \times (ABW - IBW)]$
- Anti-emetic prophylaxis will be given per standard institutional practice.
- Peripheral blood stem cell infusion: At least 24 hours will elapse between completion of melphalan infusion and stem cell reinfusion. The typical dose of hematopoietic stem cells is $\geq 2 \times 10^6$ stem cells per kg of actual body weight. All subjects on this study must receive at least this dose, but the actual dosage will be chosen in accordance with standard institutional practice. The graft may not be CD34+ selected or otherwise manipulated to remove myeloma or other cells. Cryopreservation and thawing of stem cells will be conducted in accordance with FACT standards and local institutional practice.
- Filgrastim will be administered at a dose of 5 mcg/kg/day subcutaneously or intravenously beginning between days +3 and +5 post-ASCT until the ANC is $\geq 500/\mu\text{l}$ for two consecutive days. Filgrastim dose may be rounded to accommodate pre-formulated doses.
- Prophylaxis against infections: Anti-fungal prophylaxis with fluconazole will be initiated peri-transplant and will continue until post-ASCT neutrophil recovery. HSV/VZV prophylaxis with acyclovir or valacyclovir will be initiated according to local institutional practice and continue until six months post-ASCT. Pneumocystis and anti-bacterial prophylaxis is not required by this protocol but may be utilized at the discretion of the treating investigator.

Details of HDM + ASCT not specified above will be conducted in accordance with the site's local institutional practices and the preferences of the treating investigator.

5.3.2 Lymphodepleting Chemotherapy

Cyclophosphamide will be administered at a dose of 1.5 g/m² intravenously as a single infusion, 3 days (\pm 1 day) prior to CART-19 infusion. Cyclophosphamide is commonly used in the treatment of myeloma, and this dose has been safely used for many years to mobilize autologous stem cells in myeloma and lymphoma⁶¹⁻⁶⁴ as well as in patients receiving CAR T cell therapies⁶⁹. Although the chemotherapy is not

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investigational in itself, it is considered an integral part of this study and therefore subjects will be evaluated for toxicity that may be related to the chemotherapy conditioning regimen.

5.3.3 CART-19 Infusion

CART-19 transduced T-cells will be administered at a dose of $1-5 \times 10^8$ as a single, rapid intravenous infusion 60 (\pm 7) days post-ASCT.

5.3.4 Maintenance Lenalidomide

Subjects will receive maintenance lenalidomide at the standard-of-care dose and schedule of 10 mg daily beginning at approximately day 90 post-ASCT. Before maintenance lenalidomide is initiated, toxicities of CART-19 and lymphodepleting chemotherapy must have resolved to Grade ≤ 2 and stabilized in the judgment of the treating investigator. Maintenance lenalidomide may be withheld, delayed, or dose-reduced at the discretion of the treating investigator if there are clinical contraindications to beginning maintenance therapy on the usual dose and schedule.

5.4 Preparation and Administration of Study Drug

Cell manufacturing is [REDACTED] at the University of Pennsylvania [REDACTED] [REDACTED]). The CART-19 T cells are prepared [REDACTED] and are not released [REDACTED] until FDA approved release criteria for the infused cells (e.g., cell dose, cell purity, sterility, average copy number of vectors/cell, etc.) are met. Upon release, the cells are administered at the bedside.

Cell dose

The target cell dose for this protocol is $1-5 \times 10^8$ transduced cells. Subjects with a manufactured cell dose that is less than the protocol-specified dose will be scored as a manufacturing failure. These subjects will receive their cell infusion, provided that the manufactured dose is above the [REDACTED] minimum acceptable dose for infusion (2×10^7 CART-19 cells) and all other manufacturing release criteria are met. The subjects that are infused with $\geq 2 \times 10^7$ - $< 1 \times 10^8$ CART-19 cells will be considered non-evaluable for the primary endpoint but will be included in analysis of secondary endpoints.

Packaging and Labeling

CART-19 transduced T cells will be administered as a single infusion on Day 60 (\pm 7) days post-ASCT. Each infusion bag will contain an aliquot (volume dependent upon dose) of cryomedia containing the following infusible grade reagents: 31.25% plasmalyte-A, 31.25% dextrose (5%), 0.45% NaCl, up to 7.5% DMSO, 1% dextran 40, 5% human serum albumin.

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

Cell thawing

The cells will be transported to the subject's bedside on the day of infusion. The cells will be thawed by trained personnel using a water bath maintained between 36°C to 38°C. The bag will be gently massaged until the cells have just thawed. There should be no frozen clumps left in the container at

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the time of infusion. If the CART-19 cell product appears to have a damaged or leaking bag, or otherwise appears to be compromised, it should not be infused, and should be returned to the [REDACTED].

Premedication

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

Febrile reaction

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

Additional Safety Procedures prior to Administration

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

Emergency medical equipment (i.e., emergency trolley) must be available during the infusion in case the patient has an allergic response, or severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, pulse, and blood pressure) will be taken before infusion.

Product Return/Disposition

Any unused product will be disposed of according to local institutional procedures for the disposal of hazardous medical waste/blood product. Final disposition of the investigational product will also be documented in the site Investigational Product Accountability logs appropriately.

CART-19 T-cells may also require return to the [REDACTED] for a variety of reasons, including but not limited to: 1) Mislabeled product; 2) Condition of patient prohibits infusion/injection, and 3) Subject refuses infusion/injection.

5.5 Infusion of CART-19 Product

Trained study staff will administer the CART-19 product via i.v. infusion using precautions for immunosuppressed patients. A physician from the research team will be readily available during the complete duration of the infusion. The transduced T cells will be infused at a flow rate of approximately 10 to 20 mL per minute. A leukoreduction filter **must not be used for the infusion of the T cell product**. The duration of the infusion will be based on the total volume to be infused and the recommended infusion rate.

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Vital signs (temperature, pulse, blood pressure, and oxygen saturation by pulse oximetry) will be measured within 10 minutes prior, within 10 minutes after the infusion, and then every 15 minutes for the first hour and then every hour for the next 2 hours, until these signs are satisfactory and stable. In the event that an infusion takes longer than 15 minutes, vital signs will be taken every 15 minutes until the infusion is completed. If the subject's vital signs are not satisfactory and stable three hours post-CART-19 infusion, vital signs will continued to be monitored at a minimum of every hour or as clinically indicated until stable. The subject will be discharged after the physician managing their care on the day of the infusion has determined that they are in satisfactory condition.

5.6 *Prior and Concomitant Therapy*

All prescription and nonprescription medication, vitamins, herbal and nutritional supplements, taken by the subject during the 30 days prior to enrollment will be recorded at the screening visit. At every visit following CART-19 infusion until the subject discontinues participation on the protocol, concomitant medications will be recorded in the medical record and on the appropriate CRF. Any additions, deletions, or changes of these medications will be documented. The following guidelines will be followed regarding concomitant therapy while on-study.

- Supportive care during and after ASCT is discussed in section 5.3.1.
- GM-CSF should be avoided due to potential to worsen CRS symptoms. G-CSF is the preferred myeloid growth factor over GM-CSF, if medically indicated. G-CSF was used in some patients on [REDACTED] immediately after CART-19 infusion and did not precipitate CRS.
- Steroids or other immunosuppressant drugs should NOT be used within 14 days prior to leukapheresis. GM-CSF or G-CSF must not be used 14 days prior to apheresis, as it may increase neutrophils in the collected product and make it difficult to process.
- Patients should not have received systemic chemotherapy within 2 weeks prior to apheresis. No anti-myeloma therapy will be administered between ASCT and lymphodepleting chemotherapy. Patients should not have received treatment with monoclonal antibodies within 4 weeks prior to apheresis.
- Steroids or other immunosuppressant drugs should NOT be used as pre-medication for CART-19 infusion (refer to Section 5.4) or following CAR T cell infusion unless under life threatening circumstances.

Note: According to the HUP institutional guidance, dexamethasone is part of the prophylactic anti-emetic regimen administered before cyclophosphamide; thus, dexamethasone is allowed to be administered as a prophylactic anti-emetic therapy on the day of cyclophosphamide administration.

- Patients with severe signs and symptoms attributable to cytokine release syndrome (i.e. CRS) should be managed with administration of tocilizumab or other anti-cytokine directed therapies (Refer to Section 8.4.2 for administration details).

6. STUDY PROCEDURES

The study consists of (1) a screening phase, (2) an ASCT and CART-19 manufacturing phase consisting of apheresis and preparation of the CART-19 cell product along with standard-of-care ASCT, (3) a treatment

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phase consisting of lymphodepleting chemotherapy, infusion of CART-19 cells, and initiation of maintenance lenalidomide, and (4) a follow-up phase. Schedule of evaluations and interventions are included in Appendix 1.

6.1 Screening/Enrollment

Subjects who have signed an informed consent form will undergo a medical record review and screening procedures to assess eligibility in accordance with the Schedule of Evaluations in Appendix 1. Testing for assessment of eligibility consists of standard-of-care procedures in this patient population. All screening procedures must be performed within four weeks of enrollment. For the purposes of this study and in order to standardize the timing of study windows, enrollment will be defined as the date eligibility is confirmed by the Principal Investigator.

6.2 Enrollment

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

Protocol Monitor and Sponsor Project Manager [REDACTED] [REDACTED]
--

Documents required:

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

Assignment of subject numbers will occur at consent, will be in ascending order (i.e. 19416-XX), and no numbers will be omitted. Subject numbers will be used on all study documentation.

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

Once the monitoring visit for eligibility has been completed, the site will schedule the patient for apheresis/T cell production. If T cells have already been collected during a previous apheresis, it is not necessary to repeat the apheresis procedure.

6.3 General information concerning samples obtained for laboratory correlative studies

The following guidelines will be followed for collection of samples for research correlative studies:

For molecular studies (Q-PCR, RNAseq and Q-RT-PCR), immune phenotyping and functional assays, peripheral blood and marrow samples will be collected in purple-top (K₂EDTA) tubes. For cytokine analyses peripheral blood and marrow samples will be collected in red-top (no additive) tubes. Samples

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will be delivered, processed, and frozen as per SOP to the Translational and Correlative Studies Laboratory (TCSL) (University of Pennsylvania). Samples will be stored in the TCSL at the University of Pennsylvania for storage and bulk analyses. Documentation for sample receipt, processing, and storage and primary data from the research analyses will be collected and stored in the TCSL.

Correlative testing at this and future time points may include (but is not limited to) flow cytometry to measure both benign and malignant plasma cell populations, as well as CD19 expression on these cells, and T cell subsets within the bone marrow compartment. Deep sequencing of immunoglobulin heavy chain gene to assess for presence of the multiple myeloma clonotype and the normal B cell repertoire may also be performed.

If a clinical test or procedure is performed for clinical indications, surplus material acquired during this procedure may be utilized for research correlative analysis if the subject agrees to such use of these materials in the informed consent document. For example, if a lumbar puncture is performed to evaluate neurologic symptoms, surplus CSF not required for clinical testing may be used for correlative analysis to test for presence of CART-19 cells in CSF.

Post-infusion evaluations are specified in the Schedule of Events in Appendix 1. Additional details are provided in the sections below.

At any time point, if serum and urine studies for multiple myeloma indicate CR, a bone marrow biopsy and aspiration maybe performed at or before the next study evaluation to confirm CR and conduct MRD testing. Likewise, if serum and urine studies for multiple myeloma indicate progression, bone marrow biopsy and aspiration may be performed at or before the next study evaluation to assess the immunophenotype and genetics of disease progression and assess for CART-19 cell persistence in bone marrow. Bone marrow aspirate from procedures to confirm CR or evaluate progression will be obtained for laboratory correlative studies.

6.4 Apheresis

A large volume apheresis procedure is carried out at the Hospital of the University of Pennsylvania apheresis center. PBMC are obtained for CAR T cells during this procedure. From a single leukapheresis, the intention is to harvest at least 5×10^9 white blood cells to manufacture CART-19 cells. If a single apheresis does not yield the adequate number of cells for manufacturing, then subjects can undergo an additional apheresis as needed. Baseline blood leukocytes for FDA look-back requirements and for research are also obtained and cryopreserved (1×10^8 cells from apheresis to TCSL and $1-2 \times 10^9$ to PDL, if available after cells required for manufacturing are obtained). The cell product is expected to be ready for release approximately 3-4 weeks later. GM-CSF or G-CSF should not be used 14 days prior to apheresis, as it may increase neutrophils in the collected product and make it difficult to process. Chemotherapy, steroids or other immunosuppressant drugs should not be used within 14 days prior to leukapheresis. Treatment with monoclonal antibodies should not be used within 28 days prior to leukapheresis.

A lymphocyte subset analysis (CD3, CD4, CD8 counts) will be performed to confirm that the patient has an absolute CD3 count of $\geq 150/\mu\text{l}$. If the absolute CD3 count is $< 150/\mu\text{l}$, it is recommended that the leukapheresis procedure be delayed until their ALC is $\geq 500/\mu\text{l}$ or absolute CD3 count is $\geq 150/\mu\text{l}$.

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Historical Apheresis Sample

Cryopreserved historical apheresis products collected from the patient prior to study entry are usable for CART-19 manufacturing if collected at an appropriately certified apheresis center and the product meets adequate mononuclear cell yields, these cells may be used as the source of cells for CART-19 cell manufacturing. If a historical apheresis product is not available, an apheresis procedure (as described above) will be performed for cell procurement after study eligibility has been confirmed.

6.5 Pre-ASCT evaluation

Within 4 weeks of ASCT, but after apheresis and hematopoietic stem cell collection, subjects will undergo a full multiple myeloma response evaluation to assess response to induction therapy, assess pre-ASCT disease burden, and obtain samples for correlative analysis.

This evaluation will consist of the following testing and procedures:

- Serum protein electrophoresis and immunofixation
- Quantitative immunoglobulins (IgG, IgM, IgA)
- Urine protein electrophoresis and immunofixation from a 24-hour collection
- CBC and comprehensive metabolic panel
- Serum free light chain analysis
- Bone marrow biopsy and aspiration, for standard anatomic pathology and research correlative analysis.
- Research peripheral blood draw
- Imaging: If the treating investigator feels advanced imaging (PET-CT, CT, or MRI) is necessary for adequate characterization of the subject's response to induction therapy, these modalities will be performed. If not, a standard skeletal survey will be performed.

6.6 ASCT (Day 0)

Following apheresis, subjects will undergo standard-of-care ASCT according to the guidelines set forth in section 5.3.1. This will include, if not already performed, mobilization and collection of autologous hematopoietic stem cells. This study does not specify a particular regimen for mobilizing stem cells. Subjects will undergo routine, standard-of-care monitoring post-ASCT, and this monitoring is not specified by this protocol.

6.7 Pre-infusion visit

Subjects will undergo the following work-up 3-7 days prior to CART-19 infusion (~Day +55 ± 2d) including:

- a) Current medical conditions and physical examination including an assessment of vital sign, performance status, and concomitant medications.
- b) Complete blood count and differential
- c) Chemistry panel, consisting of the following tests: Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Calcium, Total Protein, Albumin, Total Bilirubin, Alk Phos, AST, ALT, Mg, Phos, LDH, Uric Acid.
- d) Myeloma re-staging labs (SPEP/immunofixation, quantitative immunoglobulins, serum free light chains, 24 hour urine for total protein, UPEP/immunofixation)
- e) Imaging: If the treating investigator feels advanced imaging (PET-CT, CT, or MRI) is necessary for adequate characterization of the subject's response to ASCT, these modalities will be performed. If not, a standard skeletal survey will be performed.

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- f) Serum pregnancy test (females of childbearing potential only)
- g) Baseline screens for HLH/MAS: ferritin, triglycerides, haptoglobin and CRP
- h) Coagulation factors: PT, PTT, INR, fibrinogen, D-dimer
- i) Respiratory virus panel by nasal swab (within 10 days prior to the first CART-19 infusion)
- j) Research blood draw for baseline molecular (including VSV-G), cytokine, and cellular assessments. These results are not required before CART-19 administration.
- k) Bone marrow aspirate and core biopsy. Samples will be sent for routine anatomic pathology. Additionally, bone marrow aspirate will be taken for correlative/exploratory studies.

If CART-19 infusion is re-scheduled between the pre-infusion visit and CART-19 infusion, the pre-infusion evaluations, with the exception of the bone marrow biopsy, will be repeated within 3-7 days prior to the re-scheduled CART-19 infusion.

6.8 Lymphodepleting Chemotherapy

Patients will undergo lymphodepleting chemotherapy 3 days (\pm 1d) prior to CART-19 infusion in accordance with the Schedule of Evaluations in Appendix 1. If >48 hours have passed since patient's last blood work, a complete blood count with differential, and full chemistry panel should be repeated prior to chemotherapy. Chemotherapy should be delayed if there is concern that on the scheduled day of CART-19 infusion that the subject will not satisfy criteria for CART-19 infusion specified in section 5.2.

Treatment can be given through a peripheral IV as an outpatient in the Perelman Center for Advanced Medicine (PCAM) chemotherapy unit. At the discretion of the investigator, some patients may require hospitalization for the cyclophosphamide administration. In this event, the hospitalization will not be recorded as an SAE. Intravenous hydration with normal saline is required, as is anti-emetic pre-medication. All patients will be given Zofran 24 mg and Dexamethasone 12mg pre-cyclophosphamide, and Zofran 8 mg PO BID on days 1 and 2 after cyclophosphamide.

6.9 CART-19 Cell Infusion (Day 60 +7 days)

CART T cell infusion will begin 3 days (\pm 1 day) after completion of lymphodepleting chemotherapy. Prior to infusion, subjects will undergo tests and procedures in accordance with the schedule of events in Appendix 1, including CD3, CD4, and CD8 counts. Criteria outlined in section 5.2 will be reviewed to verify all criteria for CART-19 infusion are satisfied. Section 5.2 also specifies parameters for delay of CART-19 infusion. Subjects will be premedicated and receive CART-19 cells as described in section 5.4. Subjects will be infused and premedicated as described in section 5.4 and monitored post-infusion as described in section 5.5.

6.10 Post-CART19 infusion Evaluations

Subjects will return to the clinic 4, 7, 10, 14, and 21 days (\pm 1 day) post CART-19 infusion for evaluations in accordance with the Schedule of Evaluations in Appendix 1.

6.11 Day +28 Post CART-19 Infusion (\pm 3 days)

Subjects will undergo evaluations in accordance with the Schedule of Evaluations in Appendix 1 approximately 28 days (\pm 1 days) after the CART-19 infusion. Samples for correlative analyses will also be

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obtained as detailed in the Schedule of Evaluations, including a 60 mL blood draw for research purposes and to archive T cells for analysis.

6.12 Maintenance lenalidomide

Lenalidomide will be initiated at the standard-of-care dose and schedule of 10 mg daily beginning at approximately day 90 post-ASCT and at least 4 weeks post-CART19.

6.13 Month 4 (± 7 days)

Subjects will undergo evaluations in accordance with the Schedule of Evaluations in Appendix 1 approximately 60 days after CART-19 infusion (month 4 post-ASCT).

6.14 Months 5 + 6 (± 7 days)

Subjects will undergo evaluations in accordance with the Schedule of Evaluations in Appendix 1 approximately 3 and 4 months post CART-19 infusion (months 5 + 6 post-ASCT). Standard testing for multiple myeloma progression should be performed with SPEP, UPEP from a 24-hour collection, quantitative immunoglobulin measurements, and serum free light chain analysis. Advanced imaging, however, if required to track a subject's disease, does not need to be performed at monthly intervals, and the frequency can be decided by the treating investigator based on standard clinical practice.

6.15 Months 8, 11, + 14 (± 14 days)

Subjects will undergo additional follow-up evaluations in accordance with the Schedule of Evaluations in Appendix 1 till Month 14 post-ASCT. This includes standard testing for multiple myeloma progression (SPEP, UPEP from a 24-hour collection, quantitative immunoglobulin measurements, and serum free light chain analysis). Advanced imaging, however, if required to track a subject's disease, does not need to be performed at each study visit, and the frequency can be decided by the treating investigator based on standard clinical practice.

6.16 Month 20 (± 14 days)

Subjects will undergo an additional safety follow-up visit at Month 20 in accordance with the Schedule of Evaluations in Appendix 1.

6.17 Two year post-ASCT (Month 24 ± 14 days)

Two years post-ASCT, subject will complete their Month 24/End of Study Visit, in accordance with the Schedule of Evaluations in Appendix 1. Subjects will be seen by a treating investigator and queried about any new symptoms that may represent adverse events. Subjects will undergo a full multiple myeloma response evaluation at this visit.

6.18 Long-term Follow-up

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

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7. STATISTICAL PLAN

7.1 General Design Issues

This is a single-arm, single-center, open-label study to assess the effect of post-ASCT CART-19 therapy on post-ASCT PFS. This study will also assess whether the addition of CART-19 post-ASCT improves PFS compared to historical post-ASCT outcomes in patients with high-risk multiple myeloma.

Historical expectations for post-ASCT PFS are derived from the recently published validation of the R-ISS staging system⁶. This study aggregated long-term survival outcomes from several studies of first-line therapy for multiple myeloma to derive the R-ISS; the constituent studies involved first-line regimens that incorporated “novel agents” (“-imids” such as lenalidomide or thalidomide and/or bortezomib) and, for subjects <65 years of age, ASCT and post-ASCT maintenance therapy. The publication presented separately the outcomes for subjects <65 years of age according to R-ISS stage. Among subjects who were progression-free at time of ASCT, 2-year post-ASCT PFS in this cohort was approximately 55%. An increase in 2-year PFS from 55% to ~75% is deemed a clinically meaningful improvement for the purposes of sample size and power calculations.

Though this historical cohort is used for the sample size determination below, the first-line regimens used differ significantly from the RVD regimen employed in the current study. For interpretation of PFS on this study, historical data from more contemporary cohorts such as the BMTCTN 0702 study or the DFCI/IFM 2009 studies may be utilized. Since these studies have not yet reported outcomes, they cannot be used to design this study. Results are expected to emerge from these studies over the next 1-2 years, however, and, when available, may be used for historical comparison to PFS observed on this protocol.

7.2 Sample Size

The sample size has been chosen to enable comparison to historical controls. Assuming a historical 2-year PFS of 55% in this population, the following table depicts the minimal detectable effect size with a sample size of 25 patients, 80% power, and alpha of 0.05 and 0.1 using a one-sided test. The calculation assumed a two years of recruitment and additional two years of follow-up, and exponential PFS distribution.

<u>N</u>	<u>Alpha</u>	<u>Two-year PFS</u>
25	0.05	75.5%
25	0.1	72.5%

7.3 Subject Population(s) for Analysis

- The **Enrolled Set** comprises all patients who sign an informed consent form and are enrolled in the study, excluding screen failure patients.
- The **Efficacy Evaluable Set** comprises all patients who receive the CART-19 cells at the target cell dose ($1-5 \times 10^8$ transduced cells). Subjects with a manufactured cell dose that is less than the protocol-specified dose will be scored as a manufacturing failure. These subjects will receive their cell infusion, provided that the manufactured dose is above the [REDACTED] minimum acceptable dose for infusion (2×10^7 CART-19 cells) and all other manufacturing release criteria are met. The subjects that are infused with $\geq 2 \times 10^7 - < 1 \times 10^8$ CART-19 cells will be considered non-evaluable for

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the primary endpoint but will be included in analysis of secondary endpoints. The Efficacy Evaluable Set will be used for the primary efficacy endpoint analysis.

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

7.4 Statistical Analysis of Endpoints

The primary endpoint is progression-free survival (PFS). PFS is defined as time between the ASCT to the date of the first documented disease progression (see Table 5 for definition) or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off, PFS is censored at the last adequate assessment date or date of lost to follow-up. If a patient receives a new anticancer therapy without evidence of progression, PFS will be censored. The survival function will be estimated using the Kaplan-Meier method and one-sided 95% confidence interval for 2-year survival probability will be computed. If the 55% historic 2-year PFS does not fall into this confidence interval, we will reject the null hypothesis and conclude the 2-year PFS in the current trial is statistically significant above the historic value. Median survival time along with the associated 95% confidence intervals will be presented if appropriated.

For secondary endpoints, incidence and severity of AEs will be summarized and tabulated by system organ class, preferred term and maximum toxicity grade (based on CTCAE v4.03). Changes or abnormal laboratory values and vital signs from time of infusion will be summarized descriptively. Response rate will be computed with confidence intervals. Descriptive statistics will be calculated for other correlative endpoints. Persistence and trafficking of CART-19 to blood or bone marrow over time will be presented graphically and by clinical outcomes if appropriate. Statistical methods appropriate for longitudinal data will be implemented. Subgroup analysis of PFS will be determined using appropriate parametric or non-parametric statistics. Statistical tests if performed will be limited to avoid the inflation of type I error rate.

7.4.1 Stopping rule for maintenance lenalidomide discontinuation

As described in section 1.1, we expect maintenance lenalidomide to be well tolerated after CART-19 infusion. To monitor for evidence that maintenance lenalidomide is not tolerable after CART-19, however, the stopping rule described here will monitor for lenalidomide discontinuation due to adverse events and pause the study if discontinuation is substantially in excess of baseline expectations such that there is a high probability that the true discontinuation rate will be above the maximum tolerated rate of 30%. Baseline expectations for lenalidomide discontinuation are derived from the CALGB 100104 study, which was a randomized, double-blind trial comparing maintenance lenalidomide after ASCT to placebo. In this study, 23 of 231 (10%) subjects in the lenalidomide arm discontinued maintenance therapy due to adverse events (Figure S1b in McCarthy *et al.*¹⁸). A Bayesian stopping rule will be applied with every 3 patients. Given a sample size of 25 evaluable subjects, the trial will be paused if lenalidomide discontinuation within 1 year of ASCT are observed in 3 out of 3 patients, ≥ 4 out of 6, ≥ 5 out of 9, ≥ 6 out of 12, ≥ 7 out of 15, ≥ 8 out of 18, ≥ 9 out of 21, and ≥ 10 at any time. Our calculation assumed a prior of $\text{beta}(0.6, 5.4)$ which corresponds to a 10% prior event rate. However, because the impact of receiving CART-19 infusion on lenalidomide discontinuation rate is currently unknown, we conservatively selected the values of hyperparameter in the prior distribution such that evidence of the observed discontinuation rate will outweigh over the prior rate by approximately five folds. Based on this stopping rule, the probability to stop early is

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around 71%. If this stopping rule is triggered, new enrollments will be paused, and the study will be either terminated or amended to address the excess discontinuation of maintenance lenalidomide.

8. SAFETY AND ADVERSE EVENTS

8.1 Definitions

Adverse Event

An **adverse event** (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Intercurrent illnesses or injuries should be regarded as adverse events.

Serious Adverse Event

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

- fatal
- life-threatening
- requires or prolongs hospital stay
- leads to a persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

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

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, such as preplanned study visits and preplanned hospitalizations for study procedures or treatment administration
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition.

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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

Unexpected adverse events

An adverse event is considered unexpected if the event severity and/or frequency is not described in the investigator brochure or protocol (in the absence of an investigator brochure). Please refer to the

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investigator brochure for additional detail related to severity and/or frequency of a particular event.

Related adverse events

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

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, adverse events will be reported starting at the time of administration of lymphodepleting chemotherapy and will continue until the subject is off-study or until two years post-ASCT.

If a subject is taken off study within 30 days of the T-cell infusion, all SAEs experienced within 30 days after the T-cell infusion should be reported to the sponsor. Any SAEs experienced after this 30-day period should be reported to the sponsor if the investigator suspects a causal relationship to the study treatment.

Preexisting Condition/General Physical Examination Findings

A preexisting condition is one that is present at the start of the study. At screening, any clinically significant abnormality should be recorded as a preexisting condition on the medical history eCRF. During the course of the study, a preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens. Preexisting conditions that improve should also be recorded appropriately.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. Whenever possible, a diagnosis, rather than a symptom should be provided (i.e. anemia instead of low hemoglobin).

8.2 Recording of Adverse Events

Safety will be assessed by monitoring and recording potential adverse effects of the treatment using the Common Toxicity Criteria version 4.03 at each study visit. Subjects will be monitored by medical histories, physical examinations, and blood studies to detect potential toxicities from the treatment. If CTCAE

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grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject, the investigator must seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events should be recorded in the source documentation. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis. To the extent possible, adverse events should be recorded as a diagnosis, and symptoms used to make a diagnosis recorded within the diagnosis event. Do not list symptoms if a diagnosis can be assigned.

All adverse events occurring during the adverse event reporting period (defined in Section 8.1 above) must be recorded.

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

1. The severity grade (CTCAE v4.03 Grade 1-5)
2. Its duration (start and end dates)
3. Its relationship to the study treatment- [Reasonable possibility that AE is related: No (unrelated/not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected)- is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment- [Unexpected- if the event severity and/or frequency is not described in the investigator brochure or protocol (in the absence of an investigator brochure)].
5. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (i.e. no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

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

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

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Grading System of Cytokine Release Syndrome (CRS)

A protocol specific grading system (Table 8-1) has been developed to capture cytokine release syndrome (CRS) in CAR T-cell protocols. Please refer to section 1.5 for additional detail on CRS in CAR T-cell therapy.

For the purposes of reporting and grading on clinical trials using CAR T cells, we will use the following grading for CRS Toxicity. The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (i.e. sepsis). The stop date of CRS is defined as the date when the patient has been afebrile for 24 hours and off vasopressors for 24 hours. For the purposes of defining the CRS start date, a fever is defined as a temperature of 100.4°F/38°C.

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Table 8-1: CRS Grading Criteria

CRS Toxicity Grade (Modified)				
1	2	3	4	5
Mild reaction: Treated with supportive care such as anti-pyretics, anti-emetics	Moderate reaction requiring IV fluids or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests [LFTs] related to CRS and not attributable to any other condition). Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions. This excludes management of fever or myalgias. Includes hypotension treated with IVFs* or low-dose pressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]. Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.	Life-threatening complications such as hypotension requiring high dose pressors (See Table 8-2), or hypoxia requiring mechanical ventilation	Death

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

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Table 8-2 High Dose Vasopressor Use

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

Vasopressin and Septic Shock Trial (VASST) Equivalent Equation:

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

Criteria from Russell et al, 2008⁷⁰.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the regulatory sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the regulatory sponsor. Pregnancy follow-up should be recorded on the same form and must include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

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8.3 Reporting of Serious Adverse Events

Every SAE, **regardless of suspected causality**, occurring during the adverse event reporting period defined in Section 8.1 above must be reported to the sponsor within 24 hours of learning of its occurrence. The original SAE notification may take place by email to meet the 24-hour reporting window. However, within 3 business days of knowledge of the event, the investigator must submit a complete SAE form to the Sponsor along with any other diagnostic information that will assist the understanding of the event. The Investigator will keep a copy of this SAE Form on file at the study site.

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

Report serious adverse events by email to:

Attention: Clinical Safety Manager or designee

[REDACTED]
[REDACTED]
[REDACTED]

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

1. Study identifier
2. Subject number
3. A description of the event
4. Date of onset
5. Current status
6. Whether study treatment was discontinued
7. The reason the event is classified as serious
8. Investigator assessment of the association between the event and study treatment
9. Expectedness relative to investigational product(s)

8.3.1 Investigator Reporting: Notifying the Penn IRB

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

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

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

AND

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Related to the research procedures (An event is “related to the research procedures” if in the opinion of the principal investigator or sponsor, the cause of the event was deemed probably or definitely related to the investigational product or procedure that was performed for the purposes of the research.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the IRB. This will include a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

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

Reporting Deaths: more rapid reporting requirements

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

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

For reportable deaths, the initial submission to the IRB may be made by contacting the IRB Director or Associate Director.

Other Reportable events:

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

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

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- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.3.2 Investigator Reporting: Notifying the DSMC of the Abramson Cancer Center (ACC)

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

The DSMC requires AE/SAE submission as follows:

- Unless covered by exclusions below, grade 3 or higher events must be reported within 10 days of knowledge of the adverse event.

Exceptions:

- Grade 3 and 4 events that are typical in the disease population – with the exception of those that could be symptoms/early indicators of any of the toxicities defined in the Toxicity Management section of the protocol, signs/symptoms of an allergic response, severe hypotensive crisis or any other reaction to the infusion.
- All grade 3 or 4 events that are judged by a study investigator to be clearly unrelated to protocol therapy.
- Grade 3 or 4 events that are probably or definitely related to progression of disease as judged by the study investigator.
- Grade 3 or 4 events that are probably or definitely related to an FDA approved agent.
- All unexpected deaths within one business day of knowledge
- All others deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

In the event of a grade 4 or 5 unexpected event **regardless of attribution**, the study team must meet or have a teleconference within 24 business hours of knowledge of the event to have a thorough discussion of the event. These types of events will not be vetted via e-mail. The sponsor should not be involved in discussions about attribution. The PI and Research Coordinator will schedule a meeting with the study team to discuss the grade 4 or 5 unexpected event. Meeting minutes capturing the review of any ongoing investigations of the grade 4 or 5 unexpected event, including next steps in the management of the subject and any proposed changes to the protocol will be documented appropriately.

8.3.3 Investigator Reporting: Notifying the IBC

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

8.3.4 FDA Notification by Sponsor

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

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

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

- ***Within 7 Calendar Days***

Any study event that is:

- *Unexpected* fatal or life-threatening *suspected adverse reaction*.
- Expected and unexpected Grade 3 or higher events of cytokine release syndrome per the modified CRS grading scale in Table 8-1
- All fatal events occurring within 30 days of T-cell infusion, regardless of attribution and expectedness

- ***Within 15 Calendar Days***

Any study event that is:

- unexpected
 - Suspected adverse reaction that is serious, but not fatal or life-threatening
- or-
- a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Any finding from tests in laboratory animals that:

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

Increase in rate of occurrence of serious suspected adverse reactions:

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

Additional Reporting Requirements

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

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

8.4 Toxicity Management, Stopping Rules, and Study Termination

It is expected that AEs will occur frequently in this population based on the underlying hematologic malignancy and that these can be SAEs. Therefore, there is no specific occurrence of SAEs that define a stopping rule, but the review of SAEs will form the basis for potential early stopping of the study. Only unexpected SAEs that are related to the CART-19 cells would lead to study termination (as defined below).

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

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8.4.1 Criteria for Stopping the Study

The study will be stopped if:

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

Subject accrual will be paused in the event of any death within 30 days of CART-19 infusion or if the stopping rule described in section 7.4.1 regarding excess lenalidomide discontinuation is triggered. Accrual will be held until an investigation is performed and the safety data is evaluated by the DSMB and applicable changes implemented (as appropriate). The results of DSMB review must be reviewed by the Sponsor, FDA, IRB, and ACC DSMC before additional enrollment may take place. If all parties are in agreement as to the event resolution, then the pause will be lifted.

8.4.2 General Toxicity Management Considerations

- Replication-competent lentivirus (RCL): Information on the risks of RCL is contained in Section 1.5.3.9. Regulatory agencies and the gene therapy community have previously discussed measures to be taken should an RCL be confirmed in a subject. However, because the probability and characteristics of an RCL are unknown, no guidelines have been put in place. Nevertheless, all agree that the subject must be isolated until an understanding of how to manage the subject becomes clear. Some considerations are
 - Intensive follow-up of subject in consultation with gene therapy experts, study investigators, FDA and NIH.
 - Inform local public health officials and CDC.
 - Identify sexual partners and provide appropriate counseling and intervention.

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

- Clonality and insertional oncogenesis: Four of nine treated patients in a gene therapy trial for X-linked Severe Combined Immunodeficiency (SCID) developed T cell leukemia 31-68 months post-treatment. The T cell leukemias were attributable to clonal expansion conferred by gammaretroviral vector integration sites in the CD34+ bone marrow stem cell modification (Hacein-Bey-Abina et al., 2008). This represents the most severe adverse event caused by vector

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integration. However, there is also evidence for retroviral vector integration site dominance in a gene therapy trial of β -thalassaemia without malignancy (Cavazzana-Calvo et al., 2010). The lentiviral vector used for CART-19 manufacturing is part of a vector class that may have a lower risk for integration in or near oncogenic regions than oncoretroviral vectors (Montini et al., 2009). As of May 2015, none of the patients treated with CART-19 have developed a new malignancy, T cell or otherwise, related to lentiviral vector integration. Subjects will be monitored for evidence of unexpected CART-19 expansion by CART-19 transgene quantitation by qPCR and clinical monitoring for malignancy by complete blood count (CBC) as part of the study design. If an unexpected pattern of CART-19 cell expansion is observed (i.e. CART-19 cell expansion in the absence of CD19+ target), subjects will be closely monitored clinically for new malignancies, particularly T cell, and further studies, including insertion site analysis, will be considered to investigate the molecular basis of the expansion. Investigators should consult with the Regulatory Sponsor if an unexpected pattern of CART-19 expansion and/or a new malignancy arises. Subjects will continue to be similarly monitored for clonality and insertional oncogenesis when enrolled on the long term follow-up protocol.

- Uncontrolled T cell proliferation. CART-19 cells could proliferate without control of normal homeostatic mechanisms. It is expected that the T cells will proliferate in response to signals from the malignant tumor or normal B and plasma cells. This could be beneficial or harmful depending on the extent of proliferation. Clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials²⁵. If uncontrolled T cell proliferation occurs, subjects may be treated with corticosteroids. Subjects will be treated with pulse methylprednisolone (2 mg/kg i.v. divided q8 hr x 2 days), followed by a rapid taper.
- B cell depletion. It is possible that B cell depletion and hypogammaglobulinemia will occur. This is common with anti-CD20 directed therapies⁷¹. In the event of clinically significant hypogammaglobulinemia (i.e. systemic infections or prolonged periods with total serum IgG levels <500 mg/dL), consideration will be given to intravenous immunoglobulin (IVIG) by established clinical dosing guidelines to restore normal levels of serum immunoglobulin levels, as has been done with Rituximab. Determination about IVIG therapy will be made on a case-by-case basis based on each patient's medical history, current condition, and risk of adverse reaction to IVIG.
- Infusion reaction. Acetaminophen and diphenhydramine hydrochloride may be repeated every 6 hours as needed. A course of non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved by acetaminophen. It is recommended that patients not receive corticosteroids at any time, except in the case of a life threatening emergency, since this may have an adverse effect on CART-19 cells.
- Febrile reaction. In the event of febrile reaction, an evaluation for infection should be initiated, and patients managed appropriately with antibiotics, fluids and other supportive care as medically indicated and determined by the treating physician. In the event that the patient develops sepsis or systemic bacteremia following CAR T cell infusion, appropriate cultures and medical management should be initiated. If a contaminated CART-19 T cell product is suspected, the product can be retested for sterility using archived samples that are stored in the [REDACTED]. Consideration of a cytokine release syndrome (see below) should be given.
- Macrophage activation syndrome (MAS). Based on the observations of subjects treated on UPENN protocol [REDACTED], there is some concern for macrophage activation syndrome (MAS).

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Treatment and timing of treatment of this toxicity will be at the discretion of the patient's physician and the study investigator. Suggested management might include: if the subject has a fever greater than 101°F that lasts more than 2 consecutive days and there is no evidence of infection (negative blood cultures, CXR or other source), tocilizumab 8 mg/kg can be considered. The addition of corticosteroids and anti-TNF therapy can be considered at the physician's discretion.

- Cytokine Release Syndrome (CRS) / Macrophage Activation Syndrome (MAS)
Selective tocilizumab therapy has been utilized (described below) to manage CRS/MAS toxicity without precluding CAR T cell expansion in patients. Please note, steroids or other immunosuppressant drugs should **NOT** be used as pre-medication for CART-19 cell therapy but may be considered in the management of CRS.

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

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

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

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

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

The recommended dosing for tocilizumab is 8 mg/kg i.v. single dose. Not all Grade 4 CRS reactions following CAR T cell infusions have been immediately treated with tocilizumab and decisions are, in part, based upon the rapidity of the syndrome onset and the individual patient's physiologic reserve.

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

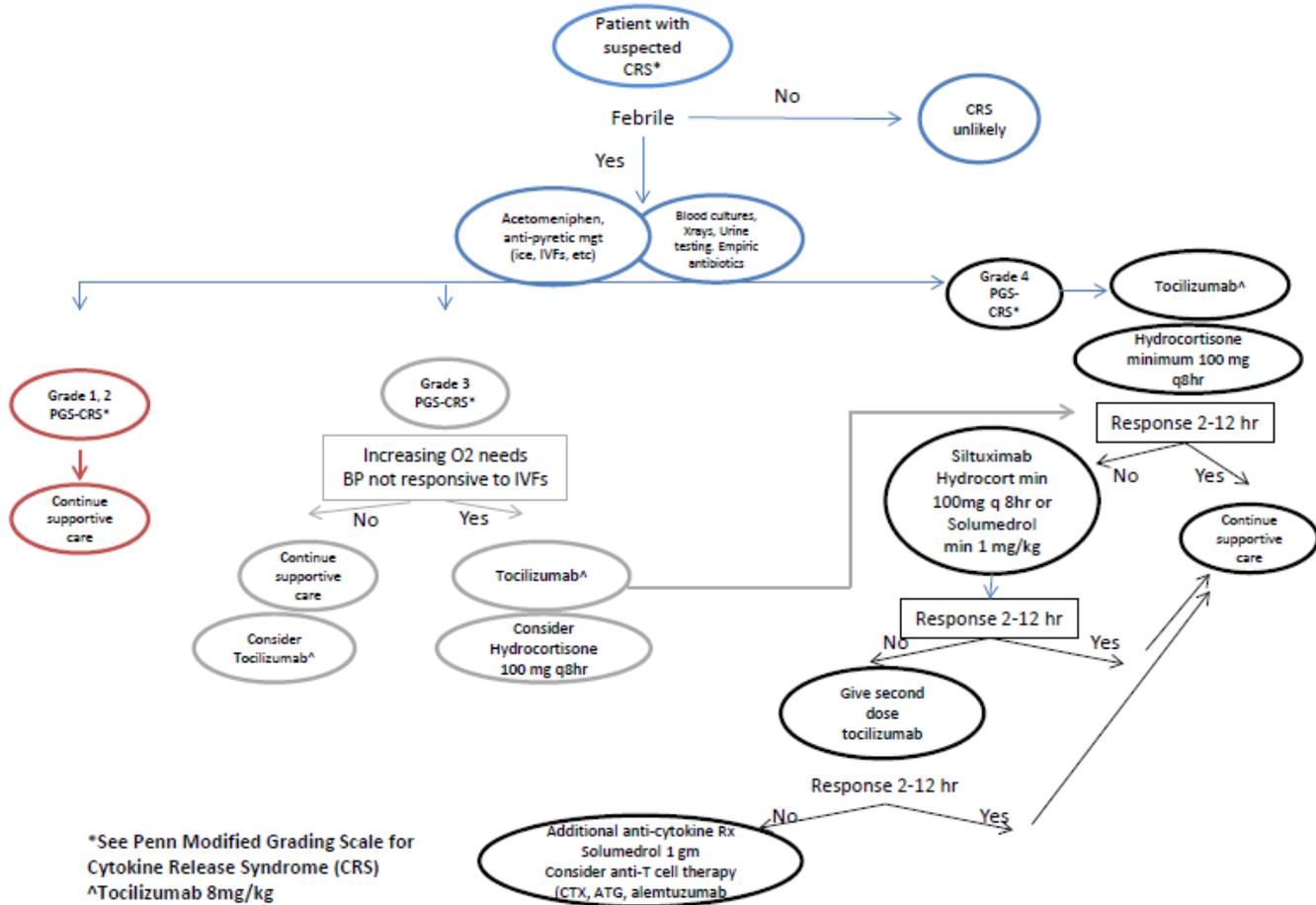
CRS has been associated with biochemical and physiologic abnormalities consistent with MAS. Moderate to extreme elevations in serum C-reactive protein (CRP) and ferritin have been seen with CART-19 associated CRS, however the magnitude and kinetics vary greatly between individual patients. CRS management decisions should be based upon clinical signs and symptoms and response to interventions, not these laboratory values *per se*. **Refer to Figure 8-1 below for a CRS Management Algorithm.**

In all cases of CRS, we will perform serum cytokine analysis at baseline using a 30-plex Luminex assay. This analysis will be repeated at all time-points collected during the event until its clinical resolution. This analysis will be batched and not available in real time; thus, it will not be used for clinical decisions. We will report these results to FDA.

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Figure 8-1 CRS Management Algorithm



- **Tumor Lysis Syndrome.** TLS resulting in renal insufficiency, or rapidly rising uric acid, or evidence of organ dysfunction will be managed with intravenous fluids and rasburicase as needed and determined by the treating physicians. Appropriate clinical therapy will be administered should any significant tumor lysis occur. Prophylactic administration of allopurinol is at the discretion of the clinical investigator.

8.5 Protocol Exceptions and Deviations

Exception

A one time, **intentional** action or process that departs from the approved study protocol, intended for **one** occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, **advance** documented approval from the Regulatory Sponsor, IRB, ACC DSMC, and other local regulatory review committees per institutional guidelines is required. Approval from the Regulatory Sponsor must be received prior to submission to the IRB, ACC DSMC, and other applicable regulatory review committees for approval.

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No exception would be granted if the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects.

Exceptions to eligibility will not be granted for this study.

Deviation

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

Any departure from the protocol that meets the following criteria should be submitted:

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

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

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

Attention: Sponsor Project Manager

[REDACTED]
[REDACTED]
[REDACTED]

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

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.7 Independent Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) comprised of four individuals including physicians with experience in oncology and/or gene transfer therapy will be assembled and will work under a charter

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specifically developed for safety oversight of this study. The DSMB will provide guidance/advice to the Regulatory Sponsor. The DSMB will evaluate patient-subject safety as specified in the DSMB Charter.

The DSMB will meet approximately every 6 months. If necessary, additional meeting of the DSMB may be held if safety issues arise in between scheduled meetings.

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

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

A sponsor representative will share the outcome of the DSMB meeting with the PI via email, for submission to local regulatory review committees as required per institutional policy.

9. DATA HANDLING AND RECORDKEEPING

9.1 Confidentiality

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

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

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

9.2 Source Documents

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

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinical medical records) containing demographic and medical information,

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laboratory data, electrocardiograms and the results of any other tests or assessments. All information recorded on the eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form, and a signed copy must be given to the patient.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All entries will be entered into an electronic data capture system (EDC) via VELOS. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Records Retention

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

10. STUDY MONITORING, AUDITING, AND INSPECTING

10.1 Study Monitoring Plan

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

Interim Monitoring Visits will be conducted during the course of the study. The Monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

At the end of the study, Monitors will conduct a close-out visit and will advise on storage of study records and disposition of unused investigational products.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

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

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

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

11. ETHICAL CONSIDERATIONS

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

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

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

The protocol is listed under clinicaltrials.gov.

12. STUDY FINANCES

12.1 *Funding Sources*

This study will be funded by Novartis Pharmaceuticals and the National Institutes of Health (NIH).

12.2 *Conflict of Interest*

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

12.3 *Subject Stipends or Payments*

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

12.4 *Study Discontinuation*

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

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13. PUBLICATION PLAN

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

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APPENDIX 1: SCHEDULE OF EVALUATIONS

	≤9 months from initiation of systemic myeloma therapy	≤4 weeks pre-ASCT	Day -2 to 0	~Day +55 (+/- 2d) ¹⁴	~Day +57 (+/-1d) ¹⁵	Day +60 (+7d)	Days Post-CART-19		Month 4 (+/-7d)	Months 5 + 6 (+/-7 d)	Month 8, 11, 14 + 17 (+/-14d)	Month 20 (+/-14d)	Month 24 (+/- 14 d)
							4, 7, 10, 14, 21 (+/- 1d)	28 (+/-3d)					
	Screening/ Enrollment ¹	Pre-ASCT Eval	ASCT	Pre-Infusion	LD Chemo	CART-19 Infusion	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Safety (RCL)	End of Study Visit
CLINICAL ASSESSMENTS													
Consent	X												
Recent Med. History Physical Examination, Performance Status	X			X	X	X	X	X	X	X	X		X
Concomitant Meds	X			X	X	X	X	X	X	X	X		X
Adverse Events					X	X	X	X	X	X	X		X
Vital Sign Assessments ⁷	X			X	X	X	X	X	X	X	X		X
Leukapheresis screening (pre-donor evaluation) ⁵	X												
Skeletal bone survey		X ¹²		X ¹²					X ¹²				X ¹²
Bone marrow biopsy and aspirate		X		X					X				X ²¹
EKG	X												
ECHO/MUGA	X												
PFTs	X												
Imaging Studies		X ¹²		X ¹²					X ¹²				X ¹²
CLINICAL LAB TESTS													
SPEP with immunofixation, quantitative immunoglobulins (IgG, IgA, IgM), serum free light chains (20 mL SST)		X		X			X ¹⁹	X	X	X	X		X

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	≤9 months from initiation of systemic myeloma therapy	≤ 4 weeks pre-ASCT	Day -2 to 0	~Day +55 (+/- 2d) ¹⁴	~Day +57 (+/-1d) ¹⁵	Day +60 (+7d)	Days Post-CART-19		Month 4 (+/-7d)	Months 5 + 6 (+/-7 d)	Month 8, 11, 14 + 17 (+/-14d)	Month 20 (+/-14d)	Month 24 (+/- 14 d)
							4, 7, 10, 14, 21 (+/- 1d)	28 (+/-3d)					
	Screening/ Enrollment ¹	Pre-ASCT Eval	ASCT	Pre-Infusion	LD Chemo	CART-19 Infusion	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Safety (RCL)	End of Study Visit
24 hour urine for total protein, UPEP and immunofixation		X		X			X ¹⁹	X	X	X	X		X
CBC, differential (5 mL EDTA)	X	X		X	X ¹⁷	X	X	X	X	X	X		X
Chemistry (3 mL SST) ³	X	X		X	X ¹⁷	X	X	X	X	X	X		X
Pregnancy test ⁸	X ⁹			X ⁹									
CD3, CD4, CD8 count (4mL EDTA)	X					X			X				X
Hepatitis serologies ² (5ml)	X												
HIV test (1 mL SST)	X												
Coagulation Factors (PT, PTT, INR, fibrinogen, D-dimer) (1 blue top – 5mL)				X									
HLH/MAS labs (serum ferritin, triglycerides, haptoglobin, CRP) (4mL SST; 3mL EDTA)				X									
Respiratory viral panel (nasal swab)				X									
INTERVENTIONS													
High-dose Melphalan			X ¹³										
Stem Cell Infusion			X ¹³										
Cyclophosphamide					X ¹⁶								
CART-19 cell infusion						X ¹⁶							
Leukapheresis	X ⁶												
Lenalidomide								X ²²					

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	≤9 months from initiation of systemic myeloma therapy	≤ 4 weeks pre-ASCT	Day -2 to 0	~Day +55 (+/- 2d) ¹⁴	~Day +57 (+/-1d) ¹⁵	Day +60 (+7d)	Days Post-CART-19		Month 4 (+/-7d)	Months 5 + 6 (+/-7 d)	Month 8, 11, 14 + 17 (+/-14d)	Month 20 (+/-14d)	Month 24 (+/- 14 d)
							4, 7, 10, 14, 21 (+/- 1d)	28 (+/-3d)					
	Screening/ Enrollment ¹	Pre-ASCT Eval	ASCT	Pre-Infusion	LD Chemo	CART-19 Infusion	Follow-up	Follow-up	Follow-up	Follow-up	Follow-up	Safety (RCL)	End of Study Visit
RESEARCH SPECIMENS¹⁰													
Marrow aspirate ~ 20 mL (Purple top tubes) for mononuclear cells		X		X					X				X
Marrow aspirate ~ 2mL (Red top tube) for serum		X		X					X				X
Total research marrow needs		22mL		22mL					22mL				22mL
Peripheral blood mononuclear cells ~25 mL (purple top tubes)	X ¹¹	X		X		X ¹⁸	X	X ²⁰	X	X	X	X	X
DNA (Q-PCR persistence)				X		X	X	X	X	X	X		X
VSV-G (Q-PCR)				X		X				X ⁴	X ²³	X ²³	X
Peripheral blood serum ~5 mL (Red top tube)				X		X ¹⁸	X	X	X	X	X		X
Immunogenicity (HAMA/HACA)				X				X					
Multiplex Cytokines				X			X	X					
Total research blood needs (mL)	25	25	0	30	0	41	30	65	30	30	30	25	30
TOTAL BLOOD DRAW (mL)	44	53	0	71	8	49	38-58	93	62	58	58	25	62

1. Screening procedures used to assess eligibility to participate must be completed within 4 weeks prior to enrollment. For the purposes of this study and in order to standardize the timing of study windows, enrollment will be defined as the date eligibility is confirmed by the Principal Investigator.
2. Required Hepatitis Serologies: Hepatitis B surface antigen (HBsAG), Hepatitis B surface antibody, Hepatitis B core antibody, and HCV antibody. If the HCV antibody is positive, a screening HCV RNA by any RT-PCR or bDNA assay must be performed. Eligibility will be

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determined based on the screening value. The HCV RNA test is not required if documentation of a negative result of a HCV RNA test performed within 60 days prior to screening is provided.

3. Chemistry Panel- Glucose, BUN, Creatinine, Sodium, Potassium, Chloride, Calcium, Total Protein, Albumin, Total Bilirubin, ALK PHos, AST, ALT, MG, Phos, LDH, Uric Acid
4. Performed at the Month 5 visit only.
5. Pre-donor evaluation of peripheral veins to determine whether apheresis can be performed without central venous access. If central venous access is felt to be necessary, catheter placement will be arranged.
6. Enrollment and mononuclear cell apheresis to harvest T cells for CART-19 manufacturing will take place prior to standard-of-care hematopoietic stem cell mobilization and collection. Cryopreserved historical apheresis products collected from the patient prior to study entry are usable for CART-19 manufacturing if collected at an appropriately certified apheresis center and the product meets adequate mononuclear cell yields, these cells may be used as the source of cells for CART-19 cell manufacturing. If a historical apheresis product is not available, an apheresis procedure will be performed for cell procurement after study eligibility has been confirmed. Please see section 6.4 for additional information.
7. Vital sign assessments include weight, temperature, pulse, blood pressure and oxygen saturation by pulse oximetry. Height will be collected at screening only. On the day of the CART-19 infusion, vital signs will be measured within 10 minutes prior, within 10 minutes after the infusion, and then every 15 minutes for the first hour, and then every hour for the next 2 hours until these signs are satisfactory and stable. If the subject's vital signs are not satisfactory and stable three hours post CART-19 infusion, vital signs will continue to be monitored at a minimum of every hour or as clinically indicated until stable. The subject will be discharged after the physician managing their care on the day of the infusion has determined that they are in satisfactory condition.
8. Female of child-bearing potential only.
9. Serum (1ml SST) or urine pregnancy test may be performed within 14 days prior to enrollment. A serum pregnancy test will be performed at the pre-infusion visit (~Day + 55 ± 2d).
10. Research bone marrow aspirates and blood draws should be sent to Translational and Correlative Studies Laboratory. TCSL has requested labs be delivered to TCSL as soon as drawn. If required to keep research labs after hours, please keep red tops upright, purple tubes should be room temperature on rotating platforms. In the event that something unexpected occurs, research sample collection may be done as necessary, not to exceed 3 tablespoons of blood twice in one week time window, in addition to the protocol-specified time points. This would be done at the PI's discretion.
11. Collected at the time of apheresis (if performed).
12. If the treating investigator feels advanced imaging (PET-CT, CT or MRI) is necessary for adequate characterization of the subject's response, these modalities will be performed per routine care. If not, a standard skeletal survey will be performed.
13. Melphalan will be administered as a single dose on day -2 or -1, or in two divided doses, according to standard institutional practice. Please see Section 5.3.1 for complete details regarding melphalan administration and ASCT.

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14. Pre-infusion visit to occur 3-7 days prior to the CART-19 infusion. If the CART-19 infusion is re-scheduled between the pre-infusion visit and CART-19 infusion, the pre-infusion evaluations, with the exception of the bone marrow biopsy, will be repeated within 3-7 days prior to the re-scheduled CART-19 infusion.
15. Lymphodepleting chemotherapy will be administered 3 days +/- 1 day prior to CART-19 infusion. Please see Section 6.8 for additional information.
16. Cyclophosphamide will be administered at a dose of 1.5 g/m² intravenously as a single infusion. Administration of lymphodepleting chemotherapy and infusion of CART-19 cells may be delayed up to 4 weeks from the originally scheduled date to address any factors that make a subject ineligible for CART-19 infusion. Delay of lymphodepleting chemotherapy and CART-19 infusion beyond 4 weeks from the scheduled date is acceptable only with approval of the Sponsor. Please refer to Section 5.2 for complete details.
17. If performed within 48 hours of the visit, these do not need to be repeated.
18. To be performed prior to the CART-19 infusion and 1-2 hours post-infusion. Pre-infusion samples: ~25mL PBMC and ~5mL serum; Post-infusion Samples: ~5mL PBMC and ~2mL serum.
19. To be performed at the D14 post-CART19 visit only.
20. A 60 ml blood draw (collected in purple top tubes) will be performed.
21. Optional; performed if clinically appropriate as determined by the treating investigator.
22. Lenalidomide will be initiated at the standard-of-care dose and schedule of 10 mg daily beginning at approximately day 90 post-ASCT and at least 4 weeks post-CART19. Before maintenance lenalidomide is initiated, toxicities of CART-19 and lymphodepleting chemotherapy must be resolved to Grade ≤ 2 and stabilized in the judgment of the treating investigator. Maintenance lenalidomide may be withheld, delayed or dose-reduced at the discretion of the treating investigator if there are clinical contraindications to beginning maintenance therapy on the usual dose and schedule.
23. RCL testing – VSV-g PCR will be performed at Months 5, 8 and 14 visits (Months 3, 6 and 12 post-CART19 infusion). Blood will be collected at Month 20 (Month 18 post-CART19 infusion) and will be archived if all tests in the first year post-CART19 infusion are negative.

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APPENDIX 2: NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASSIFICATION

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

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