CLINICAL STUDY PROTOCOL

TITLE: Descartes-11 Consolidation Treatment in Patients With High-Risk Multiple Myeloma Who Have Residual Disease After Induction Therapy

Protocol number:	DC11B
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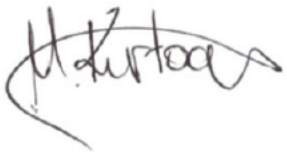
Study Product:	**Descartes-11**
Original Protocol Date:	**03-MAR-2020**
Current Version:	**1.0**

SPONSOR SIGNATURE PAGE



03-MARCH-2020

Company/Sponsor signatory

Date

[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the investigator's brochure for Descartes-11. I have read protocol and agree to conduct the study as outlined and in conformance with Good Clinical Practices (GCPs) and applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

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ABBREVIATIONS AND DICTIONARY OF TERMS

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine aminotransferase
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
AST	Aspartyl aminotransferase
AUC	Area Under the (time-concentration) Curve
BCMA	B-Cell Maturation Antigen
BSC	Biological Safety Cabinet
CA	Cytogenetic Abnormality
CAR	Chimeric Antigen Receptor
CBC	Complete blood count
CDR	Complementarity-Determining Regions
CLL	Chronic Lymphocytic Leukemia
CMC	Chemistry, Manufacturing, and Controls
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CRS	Cytokine Release Syndrome
CSF	Cerebrospinal fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMF	Drug Master File
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FHCRC	Fred Hutchinson Cancer Research Center
iFISH	Interphase Fluorescence In-Situ Hybridization
FLC	Free light chain
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-Macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
GVHD	Graft-versus-host disease
HAMA	Human anti-mouse antibody
HAS	Human Serum Albumin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio
IFN-γ	Interferon-gamma
IL	Interleukin
IMID	Immunomodulatory drug

IMWG	International Myeloma Working Group
IND	Investigational New Drug (application)
IV	Intravenous(ly)
MFC	Multi-parameter flow cytometry
MHC	Major histocompatibility complex
MM	Multiple Myeloma
MOI	Multiplicity of infection
MRD	Minimal Residual Disease
MTD	Maximal Tolerated Dose
NCI	National Cancer Institute
NDMM	Newly Diagnosed Multiple Myeloma
NGS	Next Generation Sequencing
NOAEL	No Observed Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drug
MRD	Minimal Residual Disease
MRSD	Maximum Recommended Starting Dose
MSSD	Maximum Safe Starting Dose
NDA	New Drug Application
ODD	Orphan Drug Designation (application)
OS	Overall Survival
PFS	Progression-Free Survival
PI	Proteasome inhibitor
PK	Pharmacokinetic
PR	Partial Response
PRBC	Packed Red Blood Cells
PRES	Posterior Reversible Encephalopathy Syndrome
SAE	Serious Adverse Event
sCR	Stringent Complete Response
SEM	Standard Error of the Mean
SIFE	Serum immunofixation electrophoresis
SM	Starting Materials
SPEP	Serum protein electrophoresis
SPD	Sum of the Products of the Maximal Perpendicular Diameters
TK	Toxicokinetic(s)
TLS	Tumor Lysis Syndrome
TNF α	Tumor-necrosis factor alpha
UIFE	Urine immunofixation electrophoresis
UPEP	Urine protein electrophoresis
VGPR	Very Good Partial Response

1 Introduction

1.1 Study Objectives

1.1.1 Primary Objective

To assess Minimal Residual Disease (MRD)-negative Complete Response (sCR) rate after consolidation treatment with Descartes-11 in patients with high-risk myeloma who have residual disease following induction therapy.

1.1.2 Secondary Objectives

[redacted]

1.1.3 Exploratory Objectives

[redacted]

1.2 Background and Rationale

1.2.1 Epidemiology of High-Risk Multiple Myeloma

In 2018, there were over 30,000 new cases of multiple myeloma (MM) and over 10,000 deaths from this disease.[1] MM is the second most common hematological malignancy in adults after lymphoma, with a median survival diagnosis of about 10 years.[2] A subgroup of myeloma patients carry features that confer poor risk and median survival is usually less than 4 years[3]. Historically, these poor-prognosis patients have been identified using clinical biomarkers such as β2-microglobulin and albumin. Based on these two markers, patients were classified into 3 risk-category groups in the International Staging System for Myeloma (ISS). With the advent of analytical methods that can diagnose chromosomal translocations, such as Fluorescence In Situ Hybridization (FISH), genomic changes were found to be independent risk factors for prognosis of multiple myeloma regardless of treatment. Based on the International Myeloma Working Group (IMWG) consensus, high-risk chromosomal instabilities include translocations of the IgH locus on chromosome 14 with an oncogene such as FGFR3/MMSET on chromosome 4 (t(4;14)) or c-MAF on chromosome 16 (t(14;16)) or MAFB on chromosome 20 (t(14;20)).[3] These translocations are observed in 15%, 4% and 1% of the newly diagnosed multiple myeloma (NDMM) patients, respectively.[4,5] Beside translocations, deletion of p53 on chromosome 17p, non-hyperdiploid karyotype, deletion 13 by karyotype, and gain 1q/loss of 1p (seen in 7%, 50% 44%, 30% of newly diagnosed multiple myeloma patients, respectively) are also associated with poor survival. [4,5] Each of these genomic aberrations has independently similar impact on the outcome of multiple myeloma patients while their combination further reduces overall survival. For example, the triple combination of an adverse IgH translocation, gain(1q), and del(17p) was associated with a median overall survival (OS) of 9.1 months.[6] Chromosomal aberrations showing improved outcomes were also identified, such as trisomies 3 and 5.[7,8] When both favorable and unfavorable cytogenetics coincide in the same patient, the unfavorable findings tend to dominate the clinical picture[8,9].

1.2.2 Definition of High-Risk Multiple Myeloma

High risk disease is defined by IMWG consensus.[3] IMWG defines high-risk disease as either R-ISS Stage III or by one or more high-risk cytogenetic abnormalities (CAs). [3] R-ISS Stage III is defined as serum β-microglobulin ≥5.5 mg/L and either high risk CA by iFISH or high LDH.[10] High–risk CAs are 1) t(4;14), t(14;16), t(14;20), del(17/17p), non-hyperdiploid karyotype, gain(1q), del 13, gain 1q, or a high-risk signature on gene expression profile (GEP).

1.2.3 Treatment of High-Risk Multiple Myeloma

Bortezomib partly overcomes the adverse effect of t(4;14) and possibly del(17p) on CR, PFS, and OS.[11-15] A meta-analysis of 4 randomized trials showed that the odds of post-transplantation deep response rate (VGPR or better) were similar in high-risk cytogenetics (del(17p) and t(4;14)) and standard risk cytogenetics when bortezomib was used in the induction treatment.[13] An integrated analysis of phase III trials demonstrates PFS benefit in patients with t(4;14) but lacking del(17p) and in del(17p) lacking t(4;14) but not in patients carrying both abnormalities.[16] Thus, a bortezomib-based induction regimen, and if patient is eligible followed by high dose therapy/ASCT, ideally shortly after completion of 6-8 cycles of initial therapy, is the recommended treatment in NDMM with high-risk features.[3] Typically after 3-4 cycles of multi-drug induction regimen, treatment is paused briefly for stem cell collection and then treatment is completed to 6-

8 cycles. However, this regimen results in MRD-negativity in only 20% of patients[17] and CR only in 30-35%[18,19] of patients, and the median Event-Free Survival remains at 14-24 months depending on the cytogenetic abnormality.[11] In patients who do not receive ASCT in frontline therapy but receive PI/lenalidomide based regimen, achieve 15% CR[20] and with addition of cyclophosphamide 35% CR with only half of them being MRD negative.[21] Thus, there is clear need for intensifying the upfront treatment in this patient population. Despite this need, there is no consensus on the appropriate subsequent therapy for these patients. Prevailing approaches include proteasome inhibitor/immunomodulatory drug combination maintenance, a second autotransplant, or even an allotransplant.[3,16,22] A meta-analysis of 4 European trials showed that double ASCT combined with a bortezomib-based treatment regimen partially abrogates poor PFS in patients carrying both t(4;14) and del(17p)[16], and limited data with RVD maintenance given up to 3 years post-transplant suggests some benefit in a group with del p53, del 1p; (t(4;14) or t(14;16)) with an sCR rate of 50%.[23] Although long-term PFS can be achieved with allogeneic HSCT, the benefits of graft-versus-myeloma effect are limited by high treatment-related mortality (TRM), approaching 40% for myeloablative transplantations.[24] Clinical trial enrollment for high-risk NDMM is therefore recommended by multiple expert groups.[18,22]

1.2.4 MRD as Clinical Outcome in Myeloma Patients

MRD testing in NDMM patients following first-line therapy was originally developed using multi-color flow cytometry,[25] which has been widely used in several trials for multiple myeloma.[26,27] Due to their superior sensitivity, genomic testing like Next Generation Sequencing (NGS) or IgH became the preferred method of MRD testing. Specifically, flow cytometry-based MRD assays can detect 1 myeloma cell in 100,000 bone marrow cells; current genetic MRD assays can detect 1 myeloma cell in 1,000,000 bone marrow cells.[28] This is important because the depth of MRD correlates with PFS.[29,30,31,32] Data are limited in patients with high-risk myeloma but also show that MRD is an independent risk factor in high-risk myeloma.[33] Therefore multiple expert reviews propose that MRD testing should and will become a primary regulatory efficacy endpoint.[3,22,34]

1.2.5 CAR-T Therapy in Multiple Myeloma

B-cell maturation antigen (BCMA), also known as tumor necrosis factor receptor superfamily member 17 (TNFRSF17) or CD269, is consistently and selectively expressed on normal plasma and myeloma cells.[35] For this reason, it is a preferred target antigen for CAR immunotherapy of MM. Upon engagement by its ligands, i.e., TNFSF13 (APRIL: a proliferation-inducing ligand; CD256) and TNFSF13B (BAFF: B cell-activating factor; also known as BLYS or CD257), BCMA supports survival of plasma cells.[36]

A CAR construct against BCMA was originally developed at the National Cancer Institute (NCI) and was introduced into CD3+ cells using a viral transduction system that inserts the gene permanently into the genome of the T-cell. At the maximum tolerated dose (MTD) of $9x10^6$ cells/kg, 63% of the patients achieved very good partial response (VGPR) or better.[37] Given the promising efficacy of the virally transduced anti-BCMA CAR T-cells, several other groups created permanently modified anti-BCMA CAR T-cells now in clinical testing. Bluebird Bio's anti-BCMA-CAR T-cell construct has completed its phase II trial in relapsed refractory patients who progressed after at least 2 lines of therapy demonstrated an impressive 85% overall response rate (ORR) with 45% of the patients having CR or better response.[38,39] Another product originally developed in China was recently evaluated in relapsed refractory patients during a Phase I multi-

center trial in USA and showed 100% ORR with 61% of the patients achieving CR or better.[40] Similar highly promising result are reported for several other anti-BCMA CAR-T cell products developed by different groups confirming the high potency of anti-BCMA CAR T-cells in killing myeloma cells. More importantly, this potency is seen across all risk groups, including patients with adverse cytogenetics suggesting that CAR T-cell mediated killing is independent of resistance mechanisms generated by high-risk chromosomal aberrations.

The potency of virally transduced CAR therapies comes with significant risks. All clinical trials of virally transduced CAR T-cells have recorded serious instances of cytokine release syndrome (CRS) and neurological toxicity. In the recent American Society of Blood and Marrow Transplant (ASBMT) consensus meeting, CRS was defined as "a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction."[41] CRS is a prototypical systemic inflammatory response syndrome that occurs hours to days after CAR T-cell infusion. Signs and symptoms include fever, myalgia, malaise, and, in more severe cases, a capillary leak syndrome associated with hypoxia, hypotension, and occasionally renal dysfunction and coagulopathy. Peak CAR T-cells as a result of *in vivo* proliferation has been strongly associated with the severity of CRS in many CAR T-cell studies.[42,43] The proliferation of CAR T-cells upon engagement with target antigen drives them to secrete cytokines that initiates a cascade of systemic inflammatory events. Among all cytokines elevated during CRS, IL-6 plays a central role as neutralization of this cytokine quickly and effectively reverses clinical deterioration in most cases.

The first presenting symptom of CRS is usually fever associated with mild constitutional symptoms.[42,44-46] In a number of patients, the initial mild symptoms progress over the course of hours to days and turn into a systemic inflammatory syndrome characterized by sinus tachycardia, hypotension and hypoxia. In severe cases, patients may require mechanical ventilation and vasopressors. CRS can start as early as the day of CAR T-cell infusion and in most cases it occurs within the first 14 days following the infusion. Severe cases appear to occur closer to the time of infusion and the severity of CRS was reported to correlate with peak CAR T-cell levels as mentioned above as well as disease burden[42,43] and addition of preconditioning chemotherapy.[43,44,46,47]

Neurotoxicity associated with CAR T-cell treatment, now named "Immune effector cell-associated neurotoxicity syndrome" (ICANS) in the ASBMT consensus panel document, is described as "a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Reported neurologic toxicities include headaches, confusion, alterations in wakefulness, hallucinations, dysphasia, ataxia, apraxia, facial nerve palsy, tremor, dysmetria, and seizures[43-45,48-53]. Neurotoxicity has been reported in several anti-CD19 CAR T-cell trials and severe cerebral edema lead to death in a small number of patients[54,55]. However, it has occurred less frequently in anti-BCMA CAR T-cell trials[37,39]. Factors that underlie CRS like peak CAR T-cell levels[44,46,54,56] or cytokine levels[43,48,52,57] are also associated with neurotoxicity.

Several grading systems have been developed for CAR T-cell-related CRS and neurotoxicity and this protocol uses grading developed based on ASBMT consensus criteria.[41]

1.2.6 Rationale for Current Protocol

Currently, the mainstay of treatment for high-risk NDMM is timely induction with a proteasome inhibitor/immunomodulatory drug combination followed by ASCT, which should be completed within 12 months of diagnosis. The ideal consolidation therapy in this setting would be effective in targeting myeloma clones that are resistant to the proteasome inhibitor/immunomodulatory drug combination and chemotherapy without any risk of toxicity that would delay ASCT or that would not be tolerated by a transplant-ineligible patient. A non-toxic anti-BCMA CAR T-cell therapy would provide one such therapy.

Severe CRS and neurotoxicity have only been observed in the context of CAR T-cells that are permanently modified by gene transfer. Under conditions of *genomic* modification, once CAR T-cells are engrafted, they proliferate exponentially and generate very high numbers of cells without the need for a repeat infusion. While this may provide control of the disease, rapid and uncontrolled CAR T-cell proliferation also can cause severe toxicity. In contrast, in CAR T-cells transfected with mRNA, the CAR T-cell's mRNA and CAR protein is halved with each T-cell division, effectively limiting the proliferative capacity and total circulating numbers of CAR+ T-cells. This key modification dramatically limits the potential for CRS and neurotoxicity. Furthermore, because mRNA has an inherent rate of degradation, CAR expression gradually declines to zero even in the absence of target antigen. These pharmacological properties resemble conventional drugs with predictable pharmacokinetics (PK) and pharmacodynamics (PD), properties that would be difficult or impossible to obtain with genomically modified CAR T-cells. More predictable PK in mRNA-transfected CAR T-cell activity affords the opportunity for systematic repeat dosing to maintain or, as needed, intensify anti-tumor activity. In preclinical studies, repeat dosing of mRNA-transfected CAR T-cells has shown efficacy in ALL[58], AML, breast cancer[59], neuroblastoma[60], mesothelin-expressing cancers[61] and EGFR-expressing cancers.[62]

1.2.7 Rationale for use of MRD testing as Primary Endpoint

As stated above, MRD is strongly correlated with the gold standard of PFS, which can take over 2 years to reach even in a high-risk myeloma patient population with the use of novel agents. Demonstrating MRD negativity in the context of safety and other endpoints therefore will be highly informative in assessing Descartes-11 for treatment of high-risk NDMM patients. In the era of novel agents, sCR rate in high-risk NDMM patients is reported to be 10% after induction treatment, 20% after ASCT and 50% after 3 years of RVD.[23] Similarly, CR was seen in less than 10% of high-risk patients post-induction, 20% of patients after ASCT and 50% after 2 years of bortezomib maintenance in the HOVON trial.[19] Finally, the large PETHEMA trial using bortezomib/immunomodulatory drug combination reported 35% CR rate in high-risk patients following transplant. In a smaller series in which 25% of the patients were high risk, investigators tested proteasome inhibitor-based combination as an induction therapy followed by ASCT and reported MRD-negative CR in 20% of the patients after transplant.[17] To our knowledge there is only one reported study that investigates the impact of each phase of treatment onto the depth of response which used flow cytometry for MRD assessment and showed that following induction therapy 1%, after first transplant 0.24% and after second transplant 0.1% of the cells were abnormal.[63] The greatest MRD negativity reported for high-risk patients in a small series (5 patients) in which 44% of the patients achieved MRD negativity after 8 cycles of carfilzomib, lenalidomide and dexamethasone combination which did not deepen after ASCT or 1 year of lenalidomide maintenance.[64] Thus, achieving more than 20% MRD negativity pre-ASCT in patients receiving bortezomib based regimen or 50% in all newly diagnosed patients after completing frontline therapy will be a significant improvement in NDMM with high-risk features. In this protocol, bone marrow will be evaluated by IgH/IgK gene rearrangements to search for MRD up to 1 in 10^5 cells.

1.3 Study Drug

1.3.1 Description

Descartes-11 is an autologous CD8+ T-cell product modified to express a humanized anti-BCMA CAR.

1.3.2 Route of Administration and Dosing Regimen

[redacted]

1.3.3 Nonclinical and Clinical Data

Please refer to Investigator Brochure for a detailed description of nonclinical and clinical data.

2 Eligibility and Enrollment

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

The following inclusion criteria will be applied at Screening, unless another evaluation time point is specified:

1. High-risk multiple myeloma patients (defined below) who complete pre-transplant induction treatment anti-myeloma drug combination (minimum 2 drugs).
2. Following completion of the pre-transplant induction regimen, patients must have residual disease measured by at least one of the following markers:
   a. Serum M-protein detectable by immunofixation
   b. Urine M-protein detectable by immunofixation
   c. Abnormal FLC ratio
   d. A biopsy-proven plasmacytoma or residual disease on imaging of a spot that was known to have plasmacytoma
   e. Evidence of clonal cells in immunohistochemistry defined as Kappa/Lambda <4:1 or>1:2 after counting ≥ 100 plasma cells
   f. Evidence of MRD detected by DNA-based or flow cytometry approaches
3. Patients must have high-risk multiple myeloma based on IMWG consensus as defined by R-ISS Stage III[10] or high-risk CA[3].
   a. R-ISS Stage III is defined as having serum β-microglobulin ≥5.5 mg/L and either a high risk CA by iFISH or high LDH.
   b. High–risk CAs are defined as having 1) t(4;14), t(14;16), t(14;20), or del(17/17p) in at least 20% of the cells; 2) any non-hyperdiploid karyotype, 3) gain(1q); 4) del 13; 5) gain 1q; or 6) a high-risk signature on gene expression profile (GEP).
4. There should be at least 7 days between the last dose of anti-myeloma drug and first Descartes-11 infusion.
5. Toxicities from prior therapies must have resolved to Grade 2 or less according to the CTCAE 5.0 criteria, or to the subject's pre-therapy baseline at the time of first cell infusion.
6. Patients must have signed written, informed consent.
7. Patients must be 18 years of age or older at the time of enrollment.
8. Patients must have clinical performance status of ECOG 0-2.
9. Patients must be seronegative for HIV.
10. Patients must be seronegative for hepatitis B (HBV) antigen; or, if the patient is positive for the hepatitis B antigen test, he or she must be negative for HBV DNA and must agree to use Hepatitis B prophylaxis as per institution guideline and/or principal investigator discretion.

11. Patients must be seronegative for hepatitis C (HCV) antibody; or, if the hepatitis C antibody test is positive, the patient must be tested for the presence of viremia by RT-PCR and must be HCV RNA negative.
12. Patients must have adequate vital organ function as defined by the following criteria:
    - Bone marrow function defined by absolute neutrophil count (ANC) >1000 cells/mm^3 and platelet count >50,000 cells/mm3
    - Serum ALT and AST less or equal to 3 times the upper limit of the institutional normal;
    - Total bilirubin ≤ 2.0 mg/dL, except in patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL;
    - Normal cardiac ejection fraction (≥ 45% by echocardiography) and no evidence of hemodynamically significant pericardial effusion as determined by an echocardiogram within 6 months of the start of the leukapheresis; AND
    - Creatinine Clearance (CrCl) ≥ 30 mL/min or 30 mL/min/1.73 m^2.

2.1.2 Exclusion Criteria

The following exclusion criteria will be applied at the time of Screening, unless another evaluation timepoint is specified:

1. Patients who are pregnant or lactating.
2. Patients who have any active and uncontrolled infection. No blood cultures are necessary unless clinically indicated.
3. Use of any of the following:
    a. Monoclonal antibody based anti-myeloma treatment prior to Descartes-11 infusion
    b. Experimental anti-myeloma agents prior to Descartes-11 infusion (off-label use of other FDA-approved anti-myeloma medications is allowed)
4. Ongoing treatment with the following immunosuppressants: calcineurin inhibitors (i.e. tacrolimus), mTOR inhibitors (i.e. sirolimus)
5. Patients who have active central nervous system disease.
6. Patients with second malignancies in addition to MM are not eligible if the second malignancy has required treatment within the past 3 years or is not in complete remission. There are three exceptions to this criterion are successfully treated 1) non-metastatic basal cell 2) squamous cell skin carcinoma, or 3) prostate cancer that has not required anticancer therapy.
7. Active cardiac arrhythmias, active obstructive or restrictive pulmonary disease. If there is a history of cardiac or pulmonary morbidities, the principal investigator will judge whether these conditions are active or in stable condition.
8. Any form of primary immunodeficiency (such as Severe Combined Immunodeficiency Disease).
9. History of severe immediate hypersensitivity reaction to any of the agents used in this study.

10. Subjects who have had a venous thromboembolic event (e.g., pulmonary embolism or deep vein thrombosis) requiring anticoagulation and who meet any of the following criteria:
    - Deep venous thrombosis occurred within the past 3 months OR pulmonary embolism occurred within the past 6 months
    - If on anticoagulation, based on PI discretion, anticoagulation cannot be withheld and postponed during leukapheresis
    - Have had at least Grade 2 hemorrhage in the last 30 days
    - Are experiencing continued symptoms from their venous thromboembolic event (e.g. continued dyspnea or oxygen requirement)

2.2 Screening, Evaluation and Enrollment

2.2.1 Recruitment of Patients

Subjects will be identified through the clinical practices of the investigator or sub-investigators and through referrals from outside hospitals and physicians. Patients diagnosed with high-risk multiple myeloma can be referred any time after they complete induction therapy. Patient should be enrolled and treated with Descartes-11 prior to ASCT if they are transplant eligible. If the patient does not have cells available at the time of screening (See Section 3.3.1.1 for details), they can be referred to Sponsor's Cell Collection Protocol (See Appendix B).

2.2.2 Screening Evaluation

Please refer to Section 4.1.1 for Screening visit evaluations.

2.2.3 Enrollment

To enroll a subject on this study, the following documents are required:

- Copy of signed/dated consent and HIPAA Authorization
- Source documentation to confirm enrollment/eligibility

2.2.4 Early Withdrawal of Subjects

Patients who do not complete at least one Descartes-11 infusion will be considered to have prematurely discontinued the study. The reasons for premature discontinuation must be recorded on the case report form. Final study evaluations will be completed at the time of discontinuation. Provided that all protocol requirements are satisfied for the trial to continue safely, patients who withdraw early from the study will not be counted toward study recruitment limits.

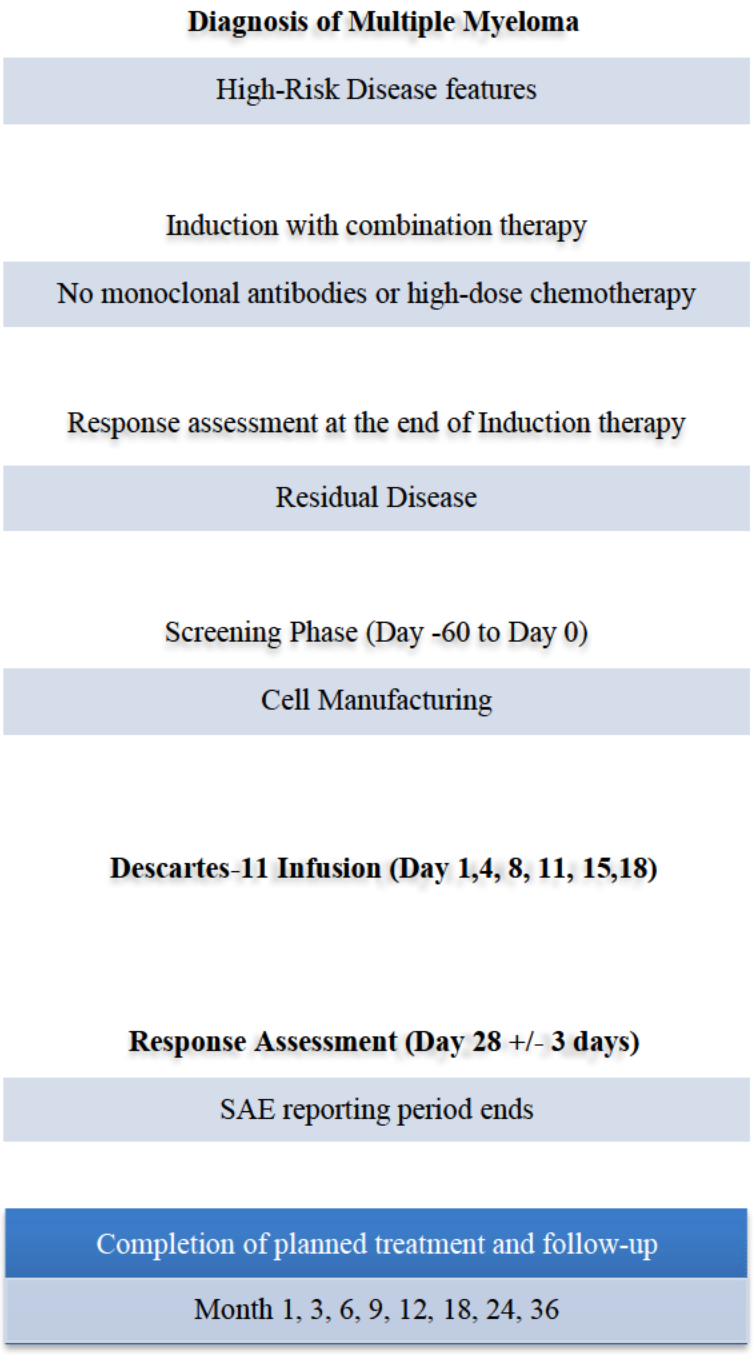
2.2.5 Data Collection and Follow-Up of Early Withdrawals

Patients who withdraw early from the study and who have provided consent for follow-up data collection will be eligible for continued data collection for up to one year. Withdrawn patients who are followed at other institutions or practices, because of preference or geographical concerns, will confer follow-up via notes from their local physician and/or phone interviews. Toxicity and other clinical assessments will be obtained from the treating physician and recorded into appropriate case report form (CRF). In the event a subject fails to complete the follow-up requirements, all attempts to contact the subject including: 1) at least three telephone contacts (on different days and at different times of the day), and 2) a certified letter will be documented.

3 Study Design

3.1 Study Schema

Figure 1. Study Schema



3.2 Study Implementation

3.2.1 Overall Treatment Design

The overall schedule of treatment for this Phase II study is illustrated in Figure 1. Steps shown prior to Screening affect eligibility but are not part of the study.

Eligible patients will receive an induction regimen with at least 2 anti-myeloma agents excluding monoclonal antibodies. After completion of the full pre-transplant induction regimen prior to high-dose chemotherapy and ASCT, eligible patients must have measurable residual disease as defined in the Eligibility Criteria. A patient can be screened and enrolled at that point. [redacted]

Descartes-11 treatment will begin at least 7 days after the patient's final dose of anti-myeloma therapy. The dose of cells will be $25x10^6$ cells/kg, and doses will be given on Days 1, 4, 8, 11, 15, 18 (i.e., total dose of $150x10^6$ cells/kg). Weight obtained during Screening Visit will be used for dose calculation. Doses are expressed as the number of live CAR+ cells. [redacted]

After completing all cell infusions, the patient will be evaluated for clinical response and then followed-up for up to 36 months unless they meet off-study criteria outlined in Section 4.5.2. During the follow-up period, if indicated, any additional induction therapy, high-dose chemotherapy and/or ASCT may be administered at the discretion of the investigator. Except for experimental agents that are not approved for myeloma treatment, treatment will be left to the investigator's discretion. The patient will be followed every 3 months for the first year, every 6 months for the second year and one time during the third year.

3.2.2 Delay of Cell Infusion

Patients experiencing toxicities from their preceding treatments will have their Descartes-11 infusion schedule delayed until these toxicities have resolved to at least Grade 2 (excluding cytopenias), unless in the documented opinion of the medical monitor and treating physician it is reasonable to proceed. During this period, the patient will be assessed to record adverse events and a decision will be made on whether the patient meets criteria for cell infusion. Infusions can also be delayed up to 24 hours for scheduling reasons. Furthermore, prior to study cell infusion, subjects must have been free from fever, infection and organ dysfunction since qualifying for the study (See Section 3.3.1.2 for details). If the patient does not meet infusion criteria, the infusion can be delayed up to 4 weeks.

3.3 Drug Administration

3.3.1 Preparation and Administration of Study Drug

3.3.1.1 Drug Preparation

3.3.1.2 Drug Administration

Prior to each infusion, patients must meet the following criteria:

1. Temperature is less than 37.9°C;
2. There are no signs of an active infection;
3. Last anti-myeloma agent was given at least 7 days prior
4. Other than a cytopenia, there are no ongoing Grade 2 toxicities from prior treatment precluding cell infusion unless PI documents that is reasonable to proceed, i.e. Grade 2 cough;
5. Pre-infusion clinical assessment does not suggest organ dysfunction and/or rapid disease progression since enrollment.

See Section 3.2.2 for conditions to delay cell infusion and Section 3.2.1 for dose definition. Administered dose must be within ±45% of defined dose. Final dose calculation will be based on actual manufactured cell numbers. Premedication for the cell infusion will be given within 15 to 120 minutes prior to the infusion. The medications are acetaminophen 500-1000 mg orally and diphenhydramine 25-50 mg intravenously or by mouth. **Prior to infusion, the cell product identity label must be double-checked by two authorized staff (MD or RN), and identification of the product and documentation of administration must be entered in the patient's chart as is done for blood banking protocols.** Please see detailed infusion instructions in the Descartes-11 Clinic Storage, Handling and Administration Manual.

3.3.2 Return or Destruction of Study Drug

The remaining thawed material should be discarded as per institution's biohazard waste removal procedures. Frozen Descartes-11 cells may require return to the Sponsor for a variety of reasons, including but not limited to: 1) condition of patient prohibits infusion/injection or 2) subject refuses infusion/injection or 3) extra product remains after completion of treatment. Sponsor will perform

ongoing reconciliation of drug shipped, drug consumed, and drug remaining. Drug destroyed on site will be documented in the study files.

3.3.3 Post-Infusion Observation

Emergency medical equipment (i.e., an emergency cart) must be available during the infusion in case the subject has an allergic response, or severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, respiration rate, pulse, blood pressure and oxygen saturation by pulse oximetry) will be measured prior to the infusion, within 10 minutes post infusion, then every 30 minutes (±5 minutes) for two hours. If the vital signs are not satisfactory or not stable two hours post-infusion, vital signs will continue to be monitored at a minimum of every hour or as clinically indicated until stable. Following the 2-hour mandatory observation, the investigator will decide whether it is safe to discharge the patient. Patients will be required to monitor their temperature daily and report to the study team if it is > 37.9°C. Follow-up assessments should include vital signs and a focused physical exam. At minimum, the following should be documented: ECOG performance status, cardiovascular exam, pulmonary exam and brief neurological exam. If clinically indicated, a more comprehensive evaluation should be added and documented in detail.

3.3.4 Management of Toxicities

For CAR T-cells, significant toxicities, if any, typically occur within one week of administration and include CRS and neurotoxicity. However, none of these have been observed in patients treated with Descartes-11 and recommendations below are based on published literature and common clinic practice.

The guidelines below are recommendations only and can be tailored to an individual patient's needs based on the judgment of the investigator or treating physician. Management that differs from these recommendations will not be considered a protocol deviation.

3.3.4.1 Febrile Reaction

Between Days 1 and 28 (or 14 days after first Descartes-11 infusion if cell infusion is delayed), fevers greater than 37.9°C will be assessed by the clinician and should be admitted for observation. To treat ordinary fever, a dose of ≥ 500 mg acetaminophen is recommended. Cooling blankets may be given if fever is greater than 40°C. In the unlikely event that the subject develops sepsis or systemic bacteremia following Descartes-11 cell infusion, appropriate cultures and medical management should be initiated. If a contaminated CAR T-cell product is suspected, the product can be retested for sterility using archived samples that are stored in the central manufacturing facility.

3.3.4.2 Infusion Reaction

Infusion-related reactions that occur during or within 24 hours following infusion were reported in less than 10% of patients participating in T-cell therapy trials, and most of the episodes were recorded as Grade 1 with a few reported as Grade 2.[43,65] [redacted]

[redacted]

The most recorded adverse event is nausea and taste disturbance (most likely due to the cryoprotectant, DMSO) and usually do not require any medical intervention. Oral ondansetron or prochlorperazine can be given for mild to moderate nausea. Additional doses of diphenhydramine and acetaminophen (if patient does not have > Grade 2 transaminitis) can be administered for mild to moderate infusion-related chills, itching, rash.

3.3.4.3 Allergic Reactions

Infusion-related allergic reactions should not occur frequently since Descartes-11 is an autologous cell product and its murine-derived sequences have been extensively humanized. Although highly unlikely, anaphylaxis has been reported in one patient who received mRNA-transfected anti-mesothelin CAR T-cell[66] and therefore an emergency cart should be present in the area where the patient receives the infusion. The clinical site's standard protocol for management of anaphylaxis should be followed. [redacted]

3.3.4.4 Cytokine Release Syndrome

This protocol has adopted the CRS grading published by ASTCT for the grading system.[41] See Appendix A for a recommended treatment algorithm, which will be used as a guidance and final treatment decision will be based on PI discretion. See Section 4.3.1.2 for CRS-related blood collection procedures.

3.3.4.5 Neurotoxicity (ICANS)

Similar to CRS, this protocol has adopted the neurotoxicity grading published by ASTCT for the grading system.[41] Management guidelines are summarized in Appendix A. One of the earliest signs of developing neurotoxicity is aphasia, and should be monitored closely as these patients may require high-dose steroids for treatment of their neurotoxicity.

3.3.5 Concomitant Medications

3.3.5.1 Antibiotic Prophylaxis

It is recommended that patients with a CD4 T-cell count less than 200 will be maintained on pneumocystis prophylaxis as per institution guidelines. Other antimicrobial (antibacterial, antiviral or antifungal) prophylaxis is left to the discretion of the investigator. Antibiotics are typically indicated in neutropenic patients.

3.3.5.2 Blood Product Support

Using CBCs as a guide, the patient will receive platelets and packed red blood cells (PRBC's) as needed. Attempts will be made to keep Hb >7.0 gm/dL and platelets >10,000/mm^3. Except for CAR T-cells, all blood products will be prepared and infused as per investigator's discretion.

3.3.5.3 Granulocyte Colony-Stimulating Factor

If the absolute neutrophil count becomes less than 1000/microliter and there is suspicion of or documented bacterial infection, then based on the investigator's discretion, growth factor support can be given. Growth factors should be discontinued once the ANC is above 1000/microliter.

3.3.5.4 Corticosteroids

Patients should not take systemic corticosteroids (including prednisone, dexamethasone or any other corticosteroid) that exceeds a dose equivalent to 40 mg/day or more of prednisone for any purpose without approval of the Principle Investigator. In addition, corticosteroids should be withheld for 12 hours before and 24 hour after the Descartes-11 infusion.

3.4 Anti-Myeloma Treatment Following Descartes-11

After all Descartes-11 infusions and the Day 28 response assessment are completed, further anti-myeloma treatment can be administered. The treatment choice is left to investigator's discretion. If the patient is eligible for transplant, high dose chemotherapy and ASCT can be given. Patient will be followed-up during this period to evaluate the clinical outcomes for secondary objectives.

4 Protocol Evaluation and Biospecimen Collection

4.1 Study Procedures

4.1.1 Baseline Evaluation (Day -60 to Day 0)

1. Obtain informed consent
2. Review of records for documentation of high-risk multiple myeloma (R-ISS Stage III or at least one of the following: t(4;14), t(14;16), t(14;20), del(17/17p), del13, gain 1q, non-hyperdiploid karyotype)
3. Complete medical history and physical examination, including, height, weight and vital signs (should always include pulse oximetry unless stated otherwise), and ECOG performance score.
4. Concomitant medications
5. Complete blood count, differential
6. Chemistry panel (Glucose, Ca, Mg, Phos, Alk Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Uric Acid, Cr, ALT, AST, lactate dehydrogenase)
7. PT/INR, PTT
8. D-Dimer, fibrinogen
9. Urinalysis
10. CRP, ferritin
11. β_2-microglobulin
12. Infectious Panel: Hepatitis B Surface Ag (HBsAg), Hepatitis B Core Total Ab, Hepatitis C Virus Ab (anti-HBc), HIV-1/HIV-2 Ab
13. Lymphocyte sub-set counts (CD19, CD3, CD4, CD8, CD56)
14. Serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE)
15. 24-h urine for urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE)
16. Serum free light chain (FLC) assay
17. Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and bone marrow flow cytometry
18. If the prospective subject has known or suspected extramedullary plasmacytomas, previous imaging results will be reviewed to confirm the status of the lesions and a repeat imaging (i.e., CT scan) can be done if the principal investigator deems it necessary to document the size/scope of the lesion.
19. ECG
20. ABO typing
21. Echocardiogram to assess left ventricular function if not performed within the last 6 months
22. β- HCG for all women of child-bearing potential. 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 (hysterectomy or bilateral oophorectomy) must have a negative serum pregnancy test performed at the time of screening and must agree not to participate in a conception process (e.g., active attempt to become pregnant or to impregnate sperm donation or *in vitro* fertilization) until 4 months after receiving preconditioning chemotherapy. Additionally, if participating in sexual activity that could

lead to pregnancy, the subject must agree to use a reliable method of contraception during their participation in the study (e.g., condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide, or intrauterine device (IUD)).

23. Research blood (See Laboratory Manual for collection details)

4.1.2 Descartes-11 Infusion (Days 1,4, 8, 11, 15, 18)

If not performed in the past 7 days and within one day of the first Descartes-11 infusion at least one of the following should be performed if abnormal at screening:

- Serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE);
- 24-h urine for urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE);
- Serum free light chain (FLC) assay

Prior to infusion of cells, the following assessments must be completed:

1. Medical history for adverse events
2. Vital signs including pulse oximetry and physical exam including brief neurological exam
3. Concomitant medications
4. ECOG performance status
5. Urine pregnancy test for all women of child-bearing potential
6. Research Blood (See Laboratory Manual for collection details)

Only on Days 1, 8, 15 the following laboratory assessments will be also be performed prior to infusion:

1. Chemistry panel (Glucose, Ca, Mg, Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, lactate dehydrogenase)
2. CRP, ferritin
3. Urinalysis

Complete blood count, differential

After infusion of cells, the following assessments must be completed:

1. Within 5±2 min of completing each infusion, Research blood should be collected. See Laboratory Manual for collection details.
2. Vital signs (See Section 3.3.3 for details)

4.1.3 Safety and Response Assessment Visit (Day 28 ± 3 days)

During the visit, the following assessment must be completed:

1. Medical history for adverse events
2. Vital signs including pulse oximetry, weight and physical exam including brief neurological exam
3. ECOG performance status
4. Concomitant medications
5. Complete blood count, differential
6. Chemistry panel (Glucose, Ca, Mg, Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, lactate dehydrogenase)
7. Urinalysis

8. Urine pregnancy test for all women of child-bearing potential
9. CRP, ferritin
10. Research blood (See Laboratory Manual for collection details)
11. If present at baseline, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
12. If present at baseline, 24-h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
13. If present at baseline, serum free light chain (FLC) assay
14. β2- microglobulin
15. If required for depth-of-response evaluation based on peripheral markers, then unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and bone marrow flow cytometry. MRD assessment (with NGS) is performed if patient is in sCR.
16. Imaging of a previously known plasmacytoma if already imaged at baseline visit

4.1.4 Follow-up Months 1, 3, 6, 9, 12, 18, 24, 36 (± 2 weeks)

1. Medical history for adverse events
2. Current medical conditions and physical examination (including weight, vital signs, pulse oximetry)
3. ECOG performance status
4. Concomitant medications
5. Complete blood count, differential
6. Chemistry panel (Glucose, Ca, Mg, Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Cr, ALT, AST, lactate dehydrogenase)
7. Urinalysis
8. If present at baseline, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
9. If present at baseline, 24-h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
10. If present at baseline, serum free light chain (FLC) assay
11. β2- microglobulin

Additional notes:

- If required for depth-of-response evaluation based on peripheral markers, then unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and bone marrow flow cytometry. MRD assessment (with NGS) is performed if patient is in sCR.
- Imaging of a previously known plasmacytoma if already imaged at baseline visit
- Research Blood (See Laboratory Manual for collection details)

4.2 Study Calendar

	Screening	Descartes-11 Infusion						Response Assessment	Follow-Up
Procedures	**Day -60 to Day 0**	**Day 1**	**Day 4**	**Day 8**	**Day 11**	**Day 15**	**Day 18**	**Day 28**	**Months 1,3,6,9,12,18,24,36**
Informed consent Eligibility Demographics	X								
Physical exam	X	X	X	X	X	X	X	X	X
Performance Score	X	X	X	X	X	X	X	X	X
Vital Signs, O_2 saturation	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X								X
Serious Adverse Events		X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Descartes-11		X	X	X	X	X	X		
CBC w/ differential	X	X		X		X		X	
Chemistry[a]	X	X		X		X		X	
PT/INR, PTT	X								
CRP, ferritin	X	X							
Urinalysis	X	X		X		X		X	
β-HCG[b]	X							X	
Urine pregnancy test[b]		X	X	X	X	X	X		
Lymphocyte subset counts[c]	X								
Serum FLC ratio	X	X[g]						X	X

	Screening	Descartes-11 Infusion						Response Assessment	Follow-Up
Procedures	**Day -60 to Day 0**	**Day 1**	**Day 4**	**Day 8**	**Day 11**	**Day 15**	**Day 18**	**Day 28**	**Months 1,3,6,9,12,18,24,36**
Serum electrophoresis and immunofixation	X	X[g]						X	X
β_2-microglobulin	X							X	X
24-hour urine for electrophoresis and immunofixation	X	X[g]						X	X
Bone marrow biopsy and aspiration	X							X[i]	X[i]
Research Blood[d]	X	X	X	X	X	X	X	X	
ECG	X								
Echocardiogram[h]	X								
Imaging	X[f]							X[j]	X[j]
Infectious Disease panel[e]	X								

[a] Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total protein, Total bilirubin, K, Na, Cl, HCO3, BUN, Uric acid, Cr, ALT, AST, LDH
[b] Child-bearing women only
[c] Lymphocyte subset includes CD19+, CD3+, CD4+, CD8+, CD56+ cells
[d] Details of Research Blood collection is explained in Laboratory Manual.
[e] Infectious Disease panel includes Hep B surface antigen, Hep B core total antibody. Hep C Virus Ab, HIV-1/HIV-2
[f] ONLY if there is known plasmacytoma at baseline.
[g] One of these should be done if not performed within the past 7 days
[h] If not done in the previous 6 months.
[i] Bone marrow aspiration and biopsy tests will be performed ONLY if needed for depth-of-response or relapse evaluation.
[j] ONLY if there is known plasmacytoma at baseline and is required for evaluating depth of response based on IMWG criteria (Table 1).

4.3 Biospecimen Collection for Exploratory Studies

4.3.1 Explanation of Research Blood Assays

4.3.1.1 Direct Measurement of Circulating Descartes-11 Cells

[redacted]

4.3.1.2 Serum Biomarkers related to CRS

[redacted]

4.3.1.3 Additional Assays

[redacted]

4.3.2 Future Studies

With patient informed consent, blood and tissue specimens collected during this research project may be banked and used in the future to investigate new scientific questions related to this study. However, this research may only be done if the risks of the new questions were covered in the consent document. If new risks are associated with the research, a protocol amendment will be

required, and informed consent will be obtained from all research subjects to whom these new studies and risks pertain.

4.3.3 Research Blood Sample and Remaining Study Drug Destruction Upon Protocol Completion

Any remaining frozen study drug after completing treatment should be returned to Sponsor. Research blood samples, and associated data, can only be permanently archived if the subject has provided informed consent for future use. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to Sponsor.

The principal investigators will contact Sponsor if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher.

4.4 Treatment Response Assessment

IMWG response criteria published in 2016 will be used for response assessment. Below is a table summarizing the parameter to stratify a response.

Table 1. IMWG Response Criteria[68]

Response Category	Parameters
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (Kappa/Lambda $\leq$ 4:1 or $\geq$1:2) or kappa and lambda patients, respectively, after counting $\geq$ 100 plasma cells
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and M-protein detectable by immunofixation but not on electrophoresis or $\geq$ 90% reduction in M-protein plus urine M-protein level <100 mg/24 hours
Partial response	$\geq$ 50% reduction of serum M-protein plus reduction in 24 hours urinary M-protein by $\geq$ 90% or to <200 mg/24 hours. If the serum and urine M-protein are unmeasurable, a $\geq$ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If the serum and urine M-protein as well as serum-free light chains are unmeasurable, $\geq$ 50% reduction in plasma cells is required, provided baseline bone marrow plasma-cell percentage was $\geq$ 30%. In addition to these criteria, if present at baseline, $\geq$ 50% reduction in size (sum of the products of the maximum perpendicular diameters (SPD) of measured lesions) of soft tissue plasmacytomas is also required.
Minimal response	$\geq$ 25% but $\leq$ 49% reduction ofserum M-protein and reduction in urine M-protein by 50-89%. In addition to these criteria, if present at baseline, $\geq$ 50% reduction in size (sum of the products of the maximum perpendicular diameters of measured lesions) of soft tissue plasmacytomas is also required.

Response Category	Parameters
Progressive disease	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: • Serum M-protein (absolute increase must be ≥0.5 g/dL) • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL • Urine M-protein (absolute increase must be ≥200 mg/24 h) • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis • ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease

To investigate disease-free survival, the following relapse criteria will be used.

Table 2. Relapse from sCR or MRD-negative Criteria

Relapse from complete response	Any of the following criteria: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% plasma cells in the bone marrow • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)
Relapse from MRD-negative complete response	Any one or more of the following criteria: • Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma) • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

4.5 Criteria for Removal from Protocol Therapy and Off-Study Criteria

4.5.1 Criteria for Removal from Descartes-11 Therapy

Off-treatment criteria mainly apply to eligibility for potential repeat Descartes-11 treatments. Completion of each cycle includes a response assessment visit. Patients will be taken off treatment for the following:

- General or specific changes in the patient's condition render the patient unacceptable for further treatment on this study in the judgment of the investigator.
- Any Descartes-11-related Grade 3 to 5 toxicity occurring within the 14 days immediately after infusion of the drug product, with the following exceptions:
  - ≤Grade 3 to 4 Tumor Lysis Syndrome (TLS) lasting <7 days
  - Grade 2 CRS associated with fever, hypotension or hypoxia lasting less than 72 hours (i.e., improves to ≤Grade 1 CRS in less than 72 hours)
    - Non-hematologic toxicities:
      - Fever of any grade, including febrile neutropenia
      - ≤Grade 3 diarrhea lasting <72 hours
      - ≤Grade 3 nausea and/or vomiting lasting <72 hours
      - ≤Grade 3 fatigue lasting <7 days
      - ≤Grade 4 transaminase, bilirubin, blood urea nitrogen (BUN), or creatinine elevation lasting <7 days
  - Hematologic toxicities:
      - ≤Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting <28 days
      - ≤Grade 3 anemia of any duration or Grade 4 anemia lasting <28 days
      - ≤Grade 3 thrombocytopenia of any duration or Grade 4 thrombocytopenia lasting <28 days
      - All cytopenias except neutropenia, anemia, and thrombocytopenia as described above

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5 will be used to grade toxicities during the trial unless specified above.

4.5.2 Criteria for Off-Study

Patients will be taken off study for the following:

- The patient voluntarily withdraws
- There is significant patient noncompliance
- Death
- Development of progressive or relapsed MM after completing Descartes-11 infusions

Patients must be followed until all adverse events have resolved to grade 2 or less other than lymphopenia or alopecia. If an adverse event is not expected to resolve to Grade 2 or less, this will be noted in the patient medical record and the patient will be taken off-study. Patients, upon obtaining consent, will also be followed for additional clinical outcomes like overall survival.

5 Safety, Adverse Events, Protocol Deviation and Stopping Rules

5.1 Definitions

5.1.1 Adverse Events (AE)

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the clinical trial associated with the use of a test article in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution.

5.1.2 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the test article caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the test article and the adverse event. A suspected adverse reaction implies less certainty about causality than adverse reaction, which means any adverse event caused by a test article.

5.1.3 Serious Unexpected Adverse Reaction (SUSAR)

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of the test article or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the test article under investigation.

5.1.4 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death within 30 days of Descartes-11 infusion
- Grade 4 or 5 CRS, infusion reaction, neurotoxicity
- Inpatient hospitalization or prolongation of existing hospitalization (except for protocol-mandated ~24-hour admission for observation due to new-onset fever)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.1.5 Protocol Deviation

A one-time, unintentional action or process that departs from the IRB-approved study protocol, involving one incident and identified retrospectively, after the event occurred. Any leukapheresis-related failure or deviation will be recorded, even if it does not constitute a per-protocol AE.

5.2 Recording of Adverse Events

5.2.1 Adverse Event Recording 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 protocol therapy completion. For this study, collection of adverse events will begin with enrollment until the subject is off-study. Serious Adverse Event reporting period starts with leukapheresis and ends at 30 days after last Descartes-11 infusion.

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

5.2.2 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise as

below. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless there is clinical worsening or an increase in frequency of hospital admissions as judged by the clinical investigator.
- Hospitalization for protocol-mandated 24-hour observation following new onset of fever following infusion of Descartes-11.

5.2.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the 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 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.

5.2.4 Recording of Adverse Events

At each contact with the subject during the adverse event recording period (defined in Section 5.2.1), the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis. To the extent possible, adverse events should be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event. Do not list symptoms if a diagnosis can be assigned.

Conditions that were already present at the time of informed consent should be recorded in the Medical History CRF. Any condition listed in a subject's medical history for which the severity increases at the time of, or post-Descartes-11 infusion, should be captured as an adverse event.

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

it has been determined that the study treatment or participation is not the cause. As detailed as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Version 5.0 Grade 1-5)
- Its duration (start and end dates)
- Its relationship to the study treatment: Is there a reasonable possibility that the AE is related to Descartes-11- No (unrelated) or Yes. If yes- is the event definitely, probably, possibly or unlikely related to the investigational treatment (Descartes-11).
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy taken (i.e., no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Whether it is serious, as defined in Section 5.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF. Adverse events should be entered into the eCRF system within 10 working days from the knowledge of the event took place. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), documented appropriately in the medical records, should not be reported as a serious adverse event. Adverse events that occur concurrently with the progression of malignancy but that are not related to disease progression (i.e., deep vein thrombosis) will be reported as an adverse event as described above.

5.2.5 SAE and SUSAR Reporting

To ensure patient safety, every SAE and SUSAR, regardless of suspected causality, occurring during the adverse event reporting period defined in Section 5.2.1 must be reported to the Sponsor within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up information is received. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

5.2.5.1 Study Sponsor Notification by the Investigator

Any SUSAR and SAE as defined in Section 5.1 must be reported to the Sponsor by **email or fax within 24 hours** of knowledge of the event. To the extent possible, adverse events should be recorded as a diagnosis. Do not list symptoms if a diagnosis can be assigned. At the time of the initial notification, a serious adverse event (SAE) report form should be filled. Following parameters will be asked in the form:

- Subject information
- A description of the event (if there is a diagnosis, it should be included)
- Date of onset

- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment
- Concomitant medications when the event happened
- Narrative summary of the event

Follow-up information on this event should be reported when received. The follow-up information should describe 1) whether the event has resolved or continues, 2) if and how it was treated, and 3) whether the patient continued or withdrew from study participation.

5.2.5.2 IRB Notification by the Investigator

Following events should be reported to IRB:

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- 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.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of subjects.

Deaths that occur during the study should be reported within the IRB-specified time frame. For reportable deaths, the initial submission to the IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

5.2.5.3 FDA Notification by the Study Sponsor

The 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 report as described in:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

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

- **Within 7 Calendar Days** any study event that is unexpected, fatal or life-threatening suspected adverse reaction.
- **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, 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.

5.3 Medical Monitor

The medical monitor will be a Sponsor physician or Sponsor-appointed physician with appropriate experience and Board Certification to oversee study conduct on the Sponsor's behalf, consult with site investigators, review and synthesize safety information from the various clinical sites, and to apply study-stopping criteria. All decisions by the medical monitor affecting study conduct, including the application of study-stopping or dose-escalation rules, will be documented in the study record.

5.4 Recording of Protocol Deviations

If the impact on the protocol disrupts the study design, may affect the outcome (objectives), or compromises the safety and welfare of the subjects, the deviation must be reported to the medical monitor within three business days. Include the following information on the Sponsor-supplied exception/deviation form: protocol number, subject study number, description of the exception/deviation from protocol and rationale. Ensure all completed exception/deviation forms are signed by the Site Investigator and submitted to the Study Sponsor and medical monitor for review. Once approval of the exception request or acknowledgement of the deviation has been granted by the Sponsor and medical monitor, the exception or deviation will be submitted to IRB and all other applicable committees.

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

5.5 Stopping Rules and Study Termination

Premature termination of the clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB or medical monitor. Additionally, recruitment may be stopped for reasons of particularly low recruitment, protocol violations, or inadequate data recording. Specifically, study will be stopped if:

- Study Sponsor or a Regulatory Body decides for any reason that subject safety may be compromised by continuing the study.
- The Sponsor decides to discontinue the development of the intervention to be used in this study.

The study will be **paused if:**

- There is death that is reasonably attributed to study drug within the first 30 days after first infusion
- Two subjects with Grade 4 adverse events to vital organs that are assessed as probably or definitely related to study drug within the 14days after last infusion

If the study is paused for the reasons above, the PI and members of the study team will meet in person or by teleconference within 24 hours of the event to have a thorough discussion of the event. Meeting minutes capturing the review of any ongoing investigations, including next steps in the management of the subject and any proposed changes to the protocol will be forwarded to the medical monitor. If all parties agree as to the event resolution, then the pause will be lifted. If the study is paused for manufacturing reasons, the Sponsor will make recommendations for process improvements to be implemented. Pending successful completion of a process validation run, the manufacturing pause will be lifted.

6 Statistical Considerations

Statistical analysis will be described in a separate Statistical Analysis Plan.

Briefly, with respect to sample size: the primary endpoint will be the proportion of responders, i.e., patients who are MRD-negative with sCR at the Day 28 Visit. This is an open-label study, and the null hypothesis is that the responder rate will not differ from the natural rate of MRD-negative sCR at the end of consolidation, as observed in the literature. We determined that this natural rate is 10%.[19,31,64,69-73] For purposes of power calculations, we assume that the response rate will be 35%. With these assumptions, a sample size of 34 will provide 80% power to detect a one-tailed difference at the 95% confidence level.

7 Ethical Considerations

7.1 General Issues

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) 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. The investigator should provide a list of IRB members and their affiliations to the Sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. 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 or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

7.2 Rationale for Subject Selection

The patients to be entered in this protocol have MM which is an almost always incurable disease and therefore these patients have limited life expectancies. Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in disease response would be expected in one group compared to another. It is not considered reasonable to administer a previously uncharacterized cell therapy to pregnant or lactating women. Children do not develop MM. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to gender or to ethnic identity are noted, accrual may be expanded, or a follow-up study may be written to investigate those differences more fully.

7.3 Evaluation of Benefits and Risks

Clinical trial summarized above demonstrated that targeting BCMA in MM by the CAR construct that will be used in the current protocol demonstrated mainly activity-associated toxicity and no off-target or on-target off-tumor effects. Furthermore, as noted above, Descartes-11 is expected to have even a better safety profile than the one used in that trial. Taken together, the potential benefits of the trial outweigh its risks.

7.4 Recordkeeping

7.4.1 Source Data

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, subject 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.

7.4.2 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 (eCRF). 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.

7.4.3 Confidentiality

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

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

If 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.

7.4.4 Records Retention

It is the sponsor'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 a Regulatory Body.

8 Pharmaceutical Information

Study drug will be provided by the Study Sponsor. For manufacturing and packaging details of the drug please see Section 1.3. FDA-approved Cyclophosphamide, Fludarabine and Tocilizumab will be sourced from commercial suppliers of the clinical site. Investigators will be referred to the approved labeling for those products.

9 References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Cancer Stat Facts: Myeloma. (Accessed July 14, 2017, at https://seer.cancer.gov/statfacts/html/mulmy.html.)
3. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood 2016;127:2955-62.
4. Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. Nat Rev Cancer 2002;2:175-87.
5. 5Munshi NC, Avet-Loiseau H. Genomics in multiple myeloma. Clin Cancer Res 2011;17:1234-42.
6. Boyd KD, Ross FM, Chiecchio L, et al. A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. Leukemia 2012;26:349-55.
7. Hebraud B, Magrangeas F, Cleynen A, et al. Role of additional chromosomal changes in the prognostic value of t(4;14) and del(17p) in multiple myeloma: the IFM experience. Blood 2015;125:2095-100.
8. Kumar S, Fonseca R, Ketterling RP, et al. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. Blood 2012;119:2100-5.
9. Morgan GJ, Gregory WM, Davies FE, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood 2012;119:7-15.
10. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol 2015;33:2863-9.
11. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). J Clin Oncol 2010;28:4630-4.
12. Neben K, Lokhorst HM, Jauch A, et al. Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p. Blood 2012;119:940-8.
13. Sonneveld P, Goldschmidt H, Rosinol L, et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. J Clin Oncol 2013;31:3279-87.
14. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010;376:2075-85.
15. Nair B, van Rhee F, Shaughnessy JD, Jr., et al. Superior results of Total Therapy 3 (2003-33) in gene expression profiling-defined low-risk multiple myeloma confirmed in subsequent trial 2006-66 with VRD maintenance. Blood 2010;115:4168-73.

16. Cavo M, Salwender H, Rosiñol L, et al. Double Vs Single Autologous Stem Cell Transplantation After Bortezomib-Based Induction Regimens For Multiple Myeloma: An Integrated Analysis Of Patient-Level Data From Phase European III Studies. Blood 2013;122:767-.
17. Jimenez-Zepeda VH, Duggan P, Neri P, et al. Bortezomib and melphalan conditioning increases the rate of complete response and MRD negativity for patients with multiple myeloma undergoing single autologous stem cell transplant. Leuk Lymphoma 2016;57:973-6.
18. Rosinol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood 2012;120:1589-96.
19. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol 2012;30:2946-55.
20. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet 2017;389:519-27.
21. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012;119:4375-82.
22. Bianchi G, Richardson PG, Anderson KC. Best treatment strategies in high-risk multiple myeloma: navigating a gray area. J Clin Oncol 2014;32:2125-32.
23. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. Leukemia 2014;28:690-3.
24. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007;356:1110-20.
25. Davies FE, Rawstron AC, Owen RG, Morgan GJ. Minimal residual disease monitoring in multiple myeloma. Best Pract Res Clin Haematol 2002;15:197-222.
26. de Tute RM, Rawstron AC, Gregory WM, et al. Minimal residual disease following autologous stem cell transplant in myeloma: impact on outcome is independent of induction regimen. Haematologica 2016;101:e69-71.
27. Flores-Montero J, Sanoja-Flores L, Paiva B, et al. Next Generation Flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. Leukemia 2017;31:2094-103.
28. Mailankody S, Korde N, Lesokhin AM, et al. Minimal residual disease in multiple myeloma: bringing the bench to the bedside. Nat Rev Clin Oncol 2015;12:286-95.
29. Avet-Loiseau H, Lauwers-Cances V, Corre J, Moreau P, Attal M, Munshi N. Minimal Residual Disease in Multiple Myeloma: Final Analysis of the IFM2009 Trial. Blood 2017;130:435-.

30. Korde N, Roschewski M, Zingone A, et al. Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma. JAMA Oncol 2015;1:746-54.
31. Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. Bone Marrow Transplant 2016;51:1565-8.
32. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis. JAMA Oncol 2017;3:28-35.
33. Hu B, Thall P, Milton DR, et al. High-risk myeloma and minimal residual disease postautologous-HSCT predict worse outcomes. Leuk Lymphoma 2019;60:442-52.
34. Landgren O. MRD Testing in Multiple Myeloma: From a Surrogate Marker of Clinical Outcomes to an Every-Day Clinical Tool. Semin Hematol 2018;55:1-3.
35. Carpenter RO, Evbuomwan MO, Pittaluga S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin Cancer Res 2013;19:2048-60.
36. O'Connor BP, Raman VS, Erickson LD, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. J Exp Med 2004;199:91-8.
37. Brudno JN, Maric I, Hartman SD, et al. T Cells Genetically Modified to Express an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor Cause Remissions of Poor-Prognosis Relapsed Multiple Myeloma. J Clin Oncol 2018;36:2267-80.
38. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. N Engl J Med 2019;380:1726-37.
39. Raje NS, Berdeja JG, Lin Y, et al. bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: Updated results from a multicenter phase I study. J Clin Oncol 2018;36.
40. Madduri DU, S.Z.; Jagannath, S.; Singh, I.; Zudaire, E.; Yeh, t.m.; Allred, A.J.; Banerjee, A.; Goldberg, j.d.; Schechter, J.M.; Zhuang,S.; Bardeja, J. Results from CARTITUDE-1: A Phase 1b/2 Study of JNJ-4528, a CAR-T Cell Therapy Directed Against B-Cell Maturation Antigen (BCMA), in Patients with Relapsed and/or Refractory Multiple Myeloma (R/R MM). Blood 2019:575.
41. Lee DW, Santomasso BD, Locke FL, et al. ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2018.
42. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood 2016;127:3321-30.
43. Santomasso BD, Park JH, Salloum D, et al. Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia. Cancer Discov 2018;8:958-71.
44. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 2016;126:2123-38.
45. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med 2015;7:303ra139.

46. Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med 2016;8:355ra116.
47. Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood 2017;130:2295-306.
48. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377:2531-44.
49. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507-17.
50. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6:224ra25.
51. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol 2015;33:540-9.
52. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels. J Clin Oncol 2017;35:1803-13.
53. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Mol Ther 2017;25:285-95.
54. Turtle CJ, Hay KA, Hanafi LA, et al. Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor-Modified T Cells After Failure of Ibrutinib. J Clin Oncol 2017;35:3010-20.
55. CAR T-cell Leukemia Trial put on hold after two Deaths. . Medscape Medical News, 2016. at http://www.medscape.com/viewarticle/865878.)
56. Kochenderfer JN, Somerville RPT, Lu T, et al. Long-Duration Complete Remissions of Diffuse Large B Cell Lymphoma after Anti-CD19 Chimeric Antigen Receptor T Cell Therapy. Mol Ther 2017;25:2245-53.
57. Gust J, Hay KA, Hanafi LA, et al. Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. Cancer Discov 2017;7:1404-19.
58. Barrett DM, Liu X, Jiang S, June CH, Grupp SA, Zhao Y. Regimen-specific effects of RNA-modified chimeric antigen receptor T cells in mice with advanced leukemia. Hum Gene Ther 2013;24:717-27.
59. Tchou J, Zhao Y, Levine BL, et al. Safety and Efficacy of Intratumoral Injections of Chimeric Antigen Receptor (CAR) T Cells in Metastatic Breast Cancer. Cancer Immunol Res 2017;5:1152-61.
60. Singh N, Liu X, Hulitt J, et al. Nature of tumor control by permanently and transiently modified GD2 chimeric antigen receptor T cells in xenograft models of neuroblastoma. Cancer Immunol Res 2014;2:1059-70.

61. Zhao Y, Moon E, Carpenito C, et al. Multiple injections of electroporated autologous T cells expressing a chimeric antigen receptor mediate regression of human disseminated tumor. Cancer Res 2010;70:9053-61.
62. Caruso HG, Torikai H, Zhang L, et al. Redirecting T-Cell Specificity to EGFR Using mRNA to Self-limit Expression of Chimeric Antigen Receptor. J Immunother 2016;39:205-17.
63. Rossi G, Falcone AP, Minervini MM, et al. Minimal residual disease and log-reduction of plasma cells are associated with superior response after double autologous stem cell transplant in younger patients with multiple myeloma. Cytometry B Clin Cytom 2019;96:195-200.
64. Kazandjian D, Korde NS, Roschewski M, et al. Sustained minimal residual disease negativity in newly diagnosed Multiple Myeloma (NDMM) patients treated with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) followed by 2 years of lenalidomide maintenance (CRd-R): Updated results of Phase 2 study. American Society of Hematology Annual Meeting. San Diego, CA2016.
65. Brudno JN, Shi V, Stroncek D, et al. T Cells Expressing a Novel Fully-Human Anti-CD19 Chimeric Antigen Receptor Induce Remissions of Advanced Lymphoma in a First-in-Humans Clinical Trial. Blood 2016;128:999-.
66. Maus MV, Haas AR, Beatty GL, et al. T cells expressing chimeric antigen receptors can cause anaphylaxis in humans. Cancer Immunol Res 2013;1:26-31.
67. Teachey DT, Lacey SF, Shaw PA, et al. Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia. Cancer Discov 2016;6:664-79.
68. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328-46.
69. Jasielec J, Dytfeld D, Griffith KA, et al. Minimal residual disease status predicts progression-free survival in newly diagnosed multiple myeloma (NDMM) patients treated with carfilzomib, lenalidomide and low-dose dexamethasone (KRd). American Society of Hematology Annual Meeting. San Francisco, CA2014.
70. Landgren O. Combination therapy for fit (younger and older) newly diagnosed multiple myeloma patients: Data support carfilzomib, lenalidomide, and dexamethasone independent of cytogenetic risk status. Semin Oncol 2016;43:703-6.
71. Landgren O, Giralt S. MRD-driven treatment paradigm for newly diagnosed transplant eligible multiple myeloma patients. Bone Marrow Transplant 2016;51:913-4.
72. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia 2009;23:1337-41.
73. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010;116:679-86.

Appendix A MANAGEMENT GUIDELINES FOR CAR T-CELL-RELATED TOXICITIES

The clinical signs and symptoms of CAR T-related toxicities guide the grading and management of CRS and neurotoxicity. This protocol adapts management recommendations described by Lee et al.[41] A copy of this reference will be provided to the investigator and staff are encouraged to review it prior to enrolling the first patient. The following is recommended:

1. All patients with suspicion of CRS or fever above 37.9°C should be admitted for at least a 24-hour observation.
2. Infectious disease work-up with blood cultures should be initiated each time CRS is suspected. Empiric broad-spectrum intravenous antibiotics are recommended.
3. Vital signs should be checked at least every 4 hours with strict urine input and output monitoring.
4. Patients with poor oral intake should be started on intravenous fluids. Patients with 80% of their baseline systolic blood pressure (or if systolic BP<90mmHg) should be given a 0.5-1 L fluid bolus. Fluid boluses can be repeated as needed; however, they should be kept to a minimum with a low threshold of starting low dose vasopressor as the capillary leak during CRS can lead to fluid overload.
5. Patients should be transferred to the Intensive Care Unit (ICU) if:
    a. the patient's systolic pressure does not respond to the first fluid bolus;
    b. the patient requires 2 or more fluid boluses within 24 hours;
    c. the patient's heart rate remains above 125/min for at least 4 hours;
    d. the patient's supplemental oxygen requirement is more than 40% FiO2; or
    e. the patient has >Grade 2 neurotoxicity.
6. Patients admitted to the ICU should have the following:
    a. vital signs checked every 2 hours;
    b. cardiac enzymes, ECG and echocardiogram evaluation;
    c. if systolic blood pressure is below 75% of baseline or below 85 mmHg, norepinephrine should be started;
    d. CBC should be checked twice a day and cytopenias should be treated as follows:
        i. blood transfusion to keep Hgb above 8.0 g/dL;
        ii. platelet transfusion to keep platelet above 20k;
        iii. growth factors for neutropenia can be started if ANC is below 1000/μL. Filgrastim is recommended due to a shorter half-life compared with pegfilgrastim.
7. Tocilizumab at the FDA-approved dose for CRS should be administered in the following circumstances:
    a. grade 3 CRS;
    b. grade 2 CRS that is not resolving within 72 hours; or
    grade 2 CRS in the context of other co-morbidities or old age.

8. TOCILIZUMAB SHOULD NOT BE GIVEN FOR ISOLATED NEUROTOXOCITY.
9. If the patient does not respond to tocilizumab within 12 hours, a repeat dose of tocilizumab can be given. If the patient does not respond to the second dose, corticosteroids (i.e. methylprednisolone 1mg/kg every 12 hours) should be prescribed.
10. Patients who are recovering from CRS should not be discharged until they are afebrile for at least 24 hours.
11. If neurotoxicity is suspected, the patient should be evaluated with the Immune Effector Cell Encephalopathy (ICE) scale[41]. Patients with Grade 2 neurotoxicity should get a neurology consult and thorough evaluation, e.g., with lumbar puncture and MRI, for other etiologies.
12. Patients who have Descartes-11 related neurotoxicity (except for headache) should receive dexamethasone in the following situations at 10mg/kg every 4-6 hours until symptoms regress to Grade 1:
    a. grade 3 neurotoxicity lasting for 24 hours;
    b. grade 4 neurotoxicity; or
    c. any generalized seizure (in conjunction with other anti-seizure therapies).

Appendix B CELL COLLECTION PROTOCOL FOR THE MANUFACTURING OF DESCARTES PRODUCTS

1 Introduction

1.1 Objective

[redacted]

1.2 Background

1.2.1 Chimeric Antigen Receptor (CAR) expressing T-cells

Chimeric antigen receptors (CARs) consist of an extra- cellular antigen-recognition domain, which is usually an antibody single-chain variable fragment (scFv), but can also be a peptide or another protein, linked to an intra- cellular signaling domain - usually the CD3ζ (CD3 zeta) chain of the T-cell receptor. The extracellular portion of the CAR permits the recognition of a specific antigen by a T cell and, subsequently, the signaling domains stimulate T-cell proliferation, cytolysis and cytokine secretion to eliminate the target cell. The patients' own T cells (or those from an allogeneic donor) are isolated, activated and genetically modified to generate CAR T cells, which are then infused into the same patient. This approach carries a very low risk of graft-versus- host disease and enables lipid, protein and carbohydrate antigens to be targeted by T cells in an MHC-unrestricted fashion. Additionally, one CAR design can be used to treat all cancers expressing the same antigen.

1.2.2 Descartes-08 and Descartes-11

In order to preserve CAR T-cell efficacy but significantly reduce toxicity, Cartesian Therapeutics pioneered development of anti-BCMA CAR T-cells with defined, controllable pharmacokinetics by transfecting T-cells with CAR mRNA instead of gene transfer. In theory, this key modification should limit uncontrolled expansion and proliferation of circulating CAR T-cells and concomitant toxicities such as CRS and neurotoxicity. The use of mRNA-transfected CAR T-cells is also expected to confer dose-linear pharmacokinetics, that is, the number of circulating CAR T-cells should remain proportional to the number of cells infused. This benefit, which cannot be obtained from permanently modified DNA-transduced CAR T-cells, should provide for more precise dose selection, prevent uncontrolled proliferation, and allow complete clearance of CAR protein to undetectable levels over time. Cartesian is currently testing this hypothesis in a repeat-dose Phase I/II clinical trial of Descartes-08, an anti-BCMA CAR T-cell product with a murine single-chain variable fragment (scFv) and a short (2 d) half-life, in patients with relapsed/refractory MM (NCT 03448978). Notably, unlike for permanently-modified CAR T-cell products, the improved benefit-risk profile of Descartes-08 have allowed its use in an outpatient setting as well as in a non-oncologic indication like myasthenia gravis (NCT04114605). The company developed a follow-up product, Descartes-11, which carries a humanized version of Descartes-08 scFv and also

the half-life of CAR expression on T-cells is increased by 2-3 fold. This product is also being tested in a Phase 1 trial in relapsed refractory multiple myeloma and demonstrates excellent safety similar to its parent product (NCT03994705).

1.2.3 Leukapheresis Procedure

[redacted]

1.3 Rationale

[redacted]

2 Eligibility Criteria

2.1 Inclusion Criteria

1. Patients must have signed written, informed consent.
2. Patients must be 18 years of age or older at the time of enrollment.
3. Patients must have clinical performance status of ECOG 0-2.
4. Patients must be seronegative for HIV.
5. Patients must be seronegative for hepatitis B (HBV) antigen; or, if the patient is positive for the hepatitis B antigen test, he or she must be negative for HBV DNA and must agree to use Hepatitis B prophylaxis as per institution guideline and/or principal investigator discretion.
6. Patients must be seronegative for hepatitis C (HCV) antibody; or, if the hepatitis C antibody test is positive, the patient must be tested for the presence of viremia by RT-PCR and must be HCV RNA negative.
7. Patients must have adequate vital organ function as defined by the following criteria:
   - Bone marrow function defined by absolute neutrophil count (ANC) >1000 cells/mm^3 and platelet count >50,000 cells/mm3
   - Creatinine Clearance (CrCl) $\geq$ 30 mL/min or 30 mL/min/1.73 m^2.
   - Abnormal PT/INR or PTT increased > 1.5-fold (unless patient is on anticoagulation therapy).

- If the patient is on anticoagulation therapy, there should be no contraindication for holding the drug during the apheresis procedure

8. If the subject is actively on a medication for treatment of an oncologic disease, there should be a minimum of 7 days between the last dose and the leukapheresis procedure. If the agent is a monoclonal antibody then wash-out should be minimum of 21 days and if it is an experimental agent then it should be 5 half-lives.

2.2 Exclusion Criteria

1. Major chronic illness that is not well managed at the time of study entry and in the opinion of the investigator may increase the risk to the patient.
2. Any other laboratory abnormality that, in the opinion of the investigator, may jeopardize the subject's ability to participate in the study.
3. Any active significant cardiac or pulmonary disease. Note: Patients with asthma and COPD controlled with inhaled medications are allowed.
4. Treatment with any investigational agent within 4 weeks of screening or 5 half-lives of the investigational drug (whichever is longer).
5. History of significant recurrent infections or any active infection at screening visit.
6. Patient is pregnant or lactating.

2.3 Screening, Evaluation and Enrollment

2.3.1 Recruitment of Patients

Subjects who are enrolled into a study using Descartes products will be referred for cell collection.

2.3.2 Screening Evaluation

Please refer to Section 4.1.1 for Screening visit evaluations.

2.3.3 Enrollment

To enroll a subject on this study, the following documents are required:

- Copy of signed/dated consent and HIPAA Authorization
- Source documentation to confirm enrollment/eligibility

3. Study Implementation

3.1 Screening Procedures

Within 28 days of leukapheresis procedure, patients who sign consent will be evaluated at a screening visit for the following procedures:

- Informed consent
- Demographics, medical history
- Concomitant medications
- Vital signs (including pulse oximetry)
- Full physical examination
- PT/INR, PTT
- CBC with differential (should include lymphocyte and neutrophil count, platelet count
- Serum Chemistry: Glucose, sodium, potassium, chloride, calcium, magnesium, phosphate, BUN, creatinine

The following laboratories should be within 7 days of collection:

- Platelet Count
- Potassium
- Magnesium

The following laboratories should be within 90 days of collection:

- Anti-HIV antibody, anti-Hepatitis B antibody, Hepatitis B antigen, Hepatitis C Antibody
- Lymphocyte subset (should include absolute number and percentages of CD19+, CD4+, CD8+, CD3+, CD16/CD56+ cells in peripheral blood)

3.2 Leukapheresis

Before leukapheresis, the following assessments should be completed:

- Vital signs (including pulse oximetry)
- Concomitant medications
- CBC

After leukapheresis, the following assessments should be completed:

- Adverse event review and evaluation
- CBC

3.3 Management of Possible Toxicities

All toxicities should be managed based on institutional guidelines and per apheresis physician's discretion. Below are recommendations and deviations from them will not be considered as protocol deviation.

3.3.1 Hypocalcemia

Hypocalcemia is a decrease in calcium levels. Hypocalcemia is a response to citrate toxicity, which can result with large volume leukapheresis. Symptoms of hypocalcemia include numbness and tingling, especially in the hands, feet, and around the mouth. Hypocalcemia can also cause painful muscle spasms that can be alleviated with calcium-rich foods and supplements. If symptoms persist during the procedure, the following protocols are advised: slowing the procedure, decreasing the amount of anticoagulation, and administering oral or intravenous calcium supplementation.

3.3.2 Vasovagal Response

Few subjects experience episodes of vasovagal responses such as lightheadedness or fainting. These occurrences are induced by extracorporeal blood flow and discomfort and/or fear of venipunctures. Major vasovagal episodes have been reported from patients receiving therapeutic leukapheresis in research for treatment of polymyositis and dermatomyositis, diseases of the muscle tissue.

3.3.3 Blood Loss

Varying, minor degrees of RBC or platelet loss have been reported. Devices separate and return blood according to different manufacturer settings that may have an influence on accounted hemoglobin or hematocrit levels. Significant blood loss, however, has not been reported. Patients with a history of anemia or thrombocytopenia should proceed leukapheresis treatments with caution.

3.3.4 Discomfort at Venipuncture Site

Discomfort, bruising, bleeding, or swelling at the venipuncture site may occur. These minor interactions may occur with any venipuncture procedure and is usually dependent on venous

structural integrity. Routine procedures are in place at each facility to help minimize the occurrence of these discomforts and, in some cases, an alternate venipuncture site may be utilized.

3.3.5 Infection

Infection, although rare, can occur at the venipuncture site due to cannula or catheter placement. Infection is minimized with proper sterilization standards and has been significantly reduced with disposable collection and storage equipment.

4 Safety, Adverse Events, Protocol Deviation and Stopping Rules

4.1 Definitions

4.1.1 Adverse Events (AE)

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the clinical trial associated with the use of a test article in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution.

4.1.2 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the test article caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the test article and the adverse event. A suspected adverse reaction implies less certainty about causality than adverse reaction, which means any adverse event caused by a test article.

4.1.3 Serious Unexpected Adverse Reaction (SUSAR)

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected"

also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of the test article or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the test article under investigation.

4.1.4 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.1.5 Protocol Deviation

A one-time, unintentional action or process that departs from the IRB-approved study protocol, involving one incident and identified retrospectively, after the event occurred. Any leukapheresis-related failure or deviation will be recorded, even if it does not constitute a per-protocol AE.

4.2 Recording of Adverse Events

4.2.1 Adverse Event Recording Period

The study period during which adverse events must be reported is normally defined as the period from the signing of consent to the leukapheresis completion. Serious Adverse Event reporting period starts with leukapheresis and ends 72 hours after the procedure.

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

4.2.2 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise as below. Any condition responsible for surgery should be documented as an adverse event if the

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

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

4.2.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the 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 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.

4.2.4 Recording of Adverse Events

Information on all adverse events should be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis. To the extent possible, adverse events should be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event. Do not list symptoms if a diagnosis can be assigned.

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

- The severity grade (CTCAE Version 5.0 Grade 1-5)
- Its duration (start and end dates)
- Its relationship to the leukapheresis procedure Is there a reasonable possibility that the AE is related to procedure- No (unrelated) or Yes. If yes- is the event definitely, probably, possibly or unlikely related

- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy taken (i.e., no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Whether it is serious, as defined in Section 5.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF. Adverse events should be entered into the eCRF system within 10 working days from the knowledge of the event took place. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), documented appropriately in the medical records, should not be reported as a serious adverse event. Adverse events that occur concurrently with the progression of malignancy but that are not related to disease progression (i.e., deep vein thrombosis) will be reported as an adverse event as described above.

4.2.5 SAE and SUSAR Reporting

To ensure patient safety, every SAE and SUSAR, regardless of suspected causality, occurring during the adverse event reporting period must be reported to the Sponsor within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up information is received. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

4.2.5.1 Study Sponsor Notification by the Investigator

Any SUSAR and SAE as defined in Section 4.1 must be reported to the Sponsor by **email or fax within 24 hours** of knowledge of the event. To the extent possible, adverse events should be recorded as a diagnosis. Do not list symptoms if a diagnosis can be assigned. At the time of the initial notification, a serious adverse event (SAE) report form should be filled. Following parameters will be asked in the form:

- Subject information
- A description of the event (if there is a diagnosis, it should be included)
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and procedure
- Concomitant medications when the event happened
- Narrative summary of the event

Follow-up information on this event should be reported when received. The follow-up information should describe 1) whether the event has resolved or continues, 2) if and how it was treated, and 3) whether the patient continued or withdrew from study participation.

4.2.5.2 IRB Notification by the Investigator

Following events should be reported to IRB:

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
- Breach of confidentiality.
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of subjects.

Deaths that occur during the study should be reported within the IRB-specified time frame. For reportable deaths, the initial submission to the IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

5. Ethical Considerations

5.1 General Issues

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) 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. The investigator should provide a list of IRB members and their affiliations to the Sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. 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 or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

5.2 Evaluation of Benefits and Risks

Cells collected from subjects enrolled into this protocol will be used to manufacture Descartes-11. There is no expected direct benefit of the procedure. These subjects will be identified by the Principal Investigator of the Sponsor's clinical trial at a site that has an open treatment protocol involving Descartes-11. Subjects identified for the Descartes-11 clinical trial protocols have either symptomatic disease that is refractory to standard of care or they are intolerant to approved regimens for their disease and therefore in need of additional investigational treatment.

The risks associated with leukapheresis are associated with the decrease in WBC count, interaction with anticoagulation solutions, and the actual venipuncture site for withdrawal and return of blood, all of which can be identified and treated easily at certified apheresis centers.

5.3 Confidentiality

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

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

If 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.