CLINICAL STUDY PROTOCOL

TITLE: Phase I safety study of Descartes-11 in patients with relapsed/refractory multiple myeloma

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Investigators:	Multi-center
Sponsor:	Cartesian Therapeutics, Inc.
Address:	704 Quince Orchard Rd., Suite 210A Gaithersburg, MD 20878
Phone:	+1-301-348-8698
Website:	www.cartesiantherapeutics.com
e-mail:	metin.kurtoglu@cartesiantx.com
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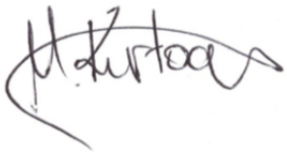

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Company/Sponsor signatory | Date

Metin Kurtoglu, MD, PhD
Cartesian Therapeutics, Inc.
704 Quince Orchard Rd. Suite 210A
Gaithersburg, MD 20878
Tel 301-348-6898

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

TABLE OF CONTENTS

SPONSOR SIGNATURE PAGE 2
INVESTIGATOR'S AGREEMENT 3
ABBREVIATIONS AND DICTIONARY OF TERMS 9
1 INTRODUCTION 11
1.1 Study Objectives 11
1.1.1 Primary Objectives 11
1.1.2 Secondary Objective 11
1.1.3 Exploratory Objectives 11
1.2 Background and Rationale 11
1.2.1 Epidemiology of Multiple Myeloma 11
1.2.2 Treatment of Relapsed/Refractory Multiple Myeloma 11
1.2.3 Engineering of CAR T-cells 12
1.2.4 CAR-T Therapy in Multiple Myeloma 12
1.2.5 Summary of CAR T-cell Related Adverse Events 13
1.2.6 Rationale for Current Protocol 15
1.2.7 Rationale Behind Preconditioning Chemotherapy 15
1.2.8 Preface to Protocol Version 1.5 16
1.2.9 Preface to Protocol Version 1.6 16
1.3 Study Drug 16
1.3.1 Description 16
1.3.2 Route of Administration and Dosing Regimen 16
1.3.3 Preclinical Data 17
2 ELIGIBILITY AND ENROLLMENT 18
2.1 Eligibility Criteria 18
2.1.1 Inclusion Criteria 18
2.1.2 Exclusion Criteria 19
2.2 Screening, Evaluation and Enrollment 20
2.2.1 Recruitment of Patients 20
2.2.2 Screening Evaluation 20
2.2.3 Enrollment 21
2.2.4 Early Withdrawal of Subjects 21
2.2.5 Data Collection and Follow-Up of Early Withdrawals 21
3 STUDY DESIGN 22
3.1 Study Schema 22
3.2 Study Implementation 22

3.2.1 Overall treatment design 22
3.2.2 Dose Levels 23
3.2.3 Dose Escalation / Stopping Rules 24
3.2.4 Delay of Cell Infusion 25
3.3 Drug Administration 25
3.3.1 Leukapheresis 25
3.3.2 Administration of Cyclophosphamide and Fludarabine 26
3.3.3 Preparation and Administration of Study Drug 26
3.3.4 Return or Destruction of Study Drug 27
3.3.5 Post-Infusion Observation 27
3.3.6 Management of Toxicities 27
3.3.7 Concomitant Medications 28
4 PROTOCOL EVALUATION AND BIOSPECIMEN COLLECTION 30
4.1 Study Procedures 30
4.1.1 Baseline Evaluation (Day -60 to Day -8) 30
4.1.2 Leukapheresis (Day -59 to Day -7) 31
4.1.3 First day of Pre-conditioning chemotherapy (Day 1 (± 1 d) of Cycle 1) 31
4.1.4 Second and Third day of Preconditioning chemotherapy (Day 2 to Day 3 of Cycle 1) 32
4.1.5 Descartes-11 infusion 32
4.1.6 Safety Review and Response Assessment Visit (Day 21+3 days) 33
4.1.7 Follow-up Months 3, 6, 9, 12 (+ 2 weeks) 34
4.2 Study Calendar 35
4.3 Biospecimen Collection for Exploratory Studies 37
4.3.1 Explanation of Research Blood Assays 37
4.3.2 Future Studies 37
4.3.3 Research Blood Sample and Remaining Study Drug Destruction Upon Protocol Completion 38
4.4 Treatment Response Assessment 38
4.5 Criteria for Removal from Protocol Therapy and Off-Study Criteria 40
4.5.1 Criteria for Removal from Descartes-11 Therapy 40
4.5.2 Criteria for Off-Study 40
5 SAFETY, ADVERSE EVENTS, PROTOCOL DEVIATION AND STOPPING RULES 41
5.1 Definitions 41
5.1.1 Adverse Events (AE) 41
5.1.2 Suspected Adverse Reaction 41

5.1.3 Serious Unexpected Adverse Reaction (SUSAR) 41
5.1.4 Serious Adverse Event (SAE)....42
5.1.5 Dose Limiting Toxicity (DLT) 42
5.1.6 Protocol Deviation 43
5.2 Recording of Adverse Events 43
5.2.1 Adverse Event Recording Period....43
5.2.2 Hospitalization, Prolonged Hospitalization or Surgery 43
5.2.3 Pregnancies 43
5.2.4 Recording of Adverse Events 44
5.2.5 SAE and SUSAR Reporting 45
5.3 Medical Monitor 47
5.4 Recording of Protocol Deviations....47
5.5 Stopping Rules and Study Termination 47
6 STATISTICAL CONSIDERATIONS....49
6.1 Primary Endpoints 49
6.1.1 Safety and Tolerance....49
6.1.2 Feasibility....49
6.2 Secondary Endpoints 49
6.2.1 Efficacy....49
6.3 Exploratory Endpoints 49
6.3.1 Descartes-11 Biology....49
6.3.2 Immunogenicity Assessment 49
7 ETHICAL CONSIDERATIONS....50
7.1 General Issues 50
7.2 Rationale for Subject Selection....50
7.3 Evaluation of Benefits and Risks....50
7.4 Recordkeeping 51
7.4.1 Source Data....51
7.4.2 Case Report Forms....51
7.4.3 Confidentiality 51
7.4.4 Records Retention....51
8 PHARMACEUTICAL INFORMATION....52
9 REFERENCES 53
10 APPENDIX 1 MANAGEMENT GUIDELINES FOR CAR T-CELL-RELATED TOXICITIES....59

List of In-Text Tables

Table 1. CRS Grading Scale 14
Table 2. Dose Levels and Infusion Schedule per Cycle 23
Table 3. Dose Escalation Rules 25
Table 4. IMWG response criteria[82] 38
Table 5. Relapse from sCR or MRD-negative Criteria....39

List of In-Text Figures

Figure 1. Study Schema 22

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
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
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
NGS	Next Generation Sequencing
NOAEL	No Observed Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drug
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 Objectives

1. Determine the safety of Descartes-11 in patients with relapsed/refractory multiple myeloma (MM)
2. Determine the feasibility of manufacturing Descartes-11 from apheresis products of patients with relapsed/refractory MM

1.1.2 Secondary Objective

1. Describe anti-myeloma responses after Descartes-11 infusion
   a. Determine best response according to the IMWG response criteria
   b. Determine progression-free survival (PFS) after Descartes-11 infusion

1.1.3 Exploratory Objectives

1. Characterize Descartes-11 persistence, homing, phenotype, and function in patients with MM
2. Determine impact of Descartes-11 on systemic soluble immune factors and BCMA levels
3. Test for immunogenicity of Descartes-11

1.2 Background and Rationale

1.2.1 Epidemiology of 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. and median survival after diagnosis is around five years.[2] MM is still considered an incurable disease, as almost all patients eventually relapse after each line of treatment.

1.2.2 Treatment of Relapsed/Refractory Multiple Myeloma

First-line therapy of MM with autologous stem cell transplant (ASCT), a proteasome inhibitor (PI), and immunomodulatory agent (IMID) has extended the time to relapse of disease progression. However, until recently, limited treatment options existed when the disease became resistant to both PI and IMID, with a median survival of 13 months after documentation of symptomatic progression.[3] In the past decade, discovery of several new myeloma-specific pathways and antigens has changed this paradigm by providing several potent options for second-line treatment. Newly approved agents for myeloma include carfilzomib,[4,5] ixazomib,[6] daratumumab,[7,8] elotuzumab,[9] panobinostat[10] and pomalidomide[11]. These agents are used in combination with either dexamethasone, bortezomib-dexamethasone, or lenalidomide-dexamethasone for patients who are refractory to, or relapsed after, first-line treatment. While these combinations are highly effective in achieving deep responses when given as second-line therapy, disease almost always

relapses, leaving patients with limited approved options for third-line therapies and beyond. Among various experimental options for advanced MM, Chimeric Antigen Receptor (CAR) T-cell therapy has drawn significant attention due to its unprecedented activity in patients who have relapsed after multiple lines of therapy. The concept and reported clinical activity of CAR T-cell treatment are summarized below.

1.2.3 Engineering of CAR T-cells

Chimeric antigen receptors (CARs) are fusion proteins that include an extracellular antigen-recognition domain linked to an intracellular signaling domain.[12] When the CAR is expressed in a T-cell, the cell recognizes a specific antigen and subsequently stimulates T-cell proliferation, cytolysis, and cytokine secretion to eliminate the target cell. Autologous T-cells carry negligible risk of graft-versus-host disease (GVHD). The process theoretically allows any specific surface antigen to be targeted by T-cells in a manner unrestricted by the major histocompatibility complex (MHC).

1.2.4 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.[13] For this reason, it is considered the most promising 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.[14]

A CAR construct against BCMA was originally developed at the National Cancer Institute (NCI). The scFv portion of this CAR was derived from a mouse anti-human-BCMA monoclonal antibody. [13] The construct also contains the hinge and transmembrane regions of the CD8-alpha molecule, the signaling moiety of CD28, and the signaling domains of CD3-zeta. T-cells virally transduced with the anti-BCMA CAR produced large amounts of IFN-γ when cultured overnight with the BCMA-expressing cell lines BCMA-K562 and RPMI8226. Furthermore, when one dose of anti-BCMA CAR T-cells was administered to immunodeficient mice implanted with the human myeloma cell line RPMI8226, tumor eradication was evident in 10/10 animals. Following these remarkable preclinical results, a Phase I single ascending dose trial was initiated at NCI. The trial enrolled MM patients who had relapsed or remained refractory after 3 or more lines of therapy.[15] The results of the trial were updated recently, and at the maximum tolerated dose (MTD) of $9x10^6$ cells/kg, 63% of the patients achieved very good partial response (VGPR) or better. [16]

Given the promising efficacy of the virally transduced anti-BCMA CAR T-cells, several other groups created anti-BCMA CAR T-cells now in clinical testing. Bluebird Bio's anti-BCMA-CAR T-cell construct is currently in Phase II clinical trials, with approximately 45% of the patients achieving complete response (CR).[17,18] The CAR developed by the University of Pennsylvania has published results of their first cohort that received $1\text{-}5x10^8$ cells without any chemotherapy and 2 out of 6 patients achieved VPGR or better.[19] Poseida developed an anti-BCMA CAR T-cell product, which expresses a non-antibody based target binding domain in a highly enriched stem cell memory T-cell population and 83% of the patients treated above Dose Level 1 achieved a clinically meaningful result.[20] Finally, LCAR-38M from Nanjing Legend Biotech resulted in VGPR or better response rate in 88% of the patients tested.[21] In addition to these reported phase I

trials, several other anti-BCMA CAR constructs have been synthesized and are undergoing human testing in the United States (NCT03549442, NCT03338972, NCT03288493, NCT03070327, NCT03502577, NCT03602612, NCT03287804, NCT03548207, NCT03318861, NCT03274219) as well as several more in China. To our knowledge, all of these trials use permanently modified CAR T-cell products that are engineered by gene transfer, usually through viral transduction. The published results of the permanently modified CAR T-cell products demonstrate their effectiveness as an anti-myeloma therapy; however, the therapies show significant toxicity (summarized in Section 1.2.5), which unfortunately appears to correlate with antitumor response.

1.2.5 Summary of CAR T-cell Related Adverse Events

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.

1.2.5.1 Cytokine Release Syndrome

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."[22] 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.[23-32] The proliferation of CAR T-cells upon engagement with target antigen drives them to secrete cytokines that initiates a cascade of systemic inflammatory events. It has been shown that severe CRS (requiring vasopressors) was associated with elevated C-reactive protein, ferritin, interleukin-6 (IL-6), interferon gamma (IFN-γ) and soluble interleukin-2 (IL-2) receptor. [25,26,33-35] and an on-going research effort is to design a panel of cytokines that can predict severe CRS before it occurs. [33] 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. [25,26,28,36] 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 [15,16] and addition of preconditioning chemotherapy.[25,28,32,37] As there is gradual progression of signs and symptoms, prompt diagnosis and supportive treatment together with close monitoring are key steps in the management of CRS. Tocilizumab is an anti-IL6 antibody that is approved for the treatment of CRS.[38] Upon administration, in many cases hemodynamic instability resolves rapidly and patients recover within 24-48 hours. Thus, it is important to administer it before patient requires mechanical

ventilation for best outcome. See Section 3.3.6.4 for more details of management of CRS. While Tocilizumab became an important medication to reverse CRS, there are some reservations against its use as tocilizumab has been to shown to increase risk of cytopenia and infection [39] and a small theoretical risk of inhibiting CAR T-cell function exists. Thus, its use should be limited only to patients with severe CRS. Taken together, CRS is the main toxicity of CAR T-cell treatment and its management requires inpatient monitoring, limiting the scope of clinics that are equipped to administer a CAR T-cell based product.

1.2.5.2 Neurotoxicity

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 [25,26,29,30,34,35,37,40,41]. 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[27,42]. However, it has not been reported as frequently in anti-BCMA CAR T-cell trials[16,43]. Factors that underlie CRS like peak CAR T-cell levels[25,27,28,44] or cytokine levels[29,30,37,45] are also associated with neurotoxicity. See Section 3.3.6.5 for management of neurotoxicity.

1.2.5.3 CAR T-cell related CRS grading

Several grading systems have been developed for CAR T-cell-related CRS and this protocol uses grading developed by Lee et al.[46] In the clinical study report, CRS and neurotoxicity will also be analyzed retrospectively by ASBMT consensus criteria.[22]

Table 1. CRS Grading Scale

Grade	Toxicity
Grade 1	Symptoms are not life threatening and require symptomatic treatment only. e.g., fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement less than 40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement equal or more than 40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

The definition of high dose vasopressors is:

- Norepinephrine monotherapy≥20 mcg/min
- Dopamine monotherapy≥10 mcg/kg/min
- Phenylephrine monotherapy≥200 mcg/min
- Epinephrine monotherapy≥10 mcg/min
- If on vasopressin≥ 10 mcg/min norepinephrine equivalent *[norepinephrine (mcg/min)+dopamine (mcg/kg/min)/2]+[epinephrine (mcg/min)]+[phenylephrine (mcg/min)/10]*
  If on combination vasopressors without vasopressin then norepinephrine≥20 mcg/min

1.2.6 Rationale for Current Protocol

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 need for a repeat infusion. While this may provide long-time control of the disease, the sudden, exponential 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. In theory, this should limit the potential for severe CRS and neurotoxicity. Furthermore, because the 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 respect to predictable pharmacokinetics (PK) and pharmacodynamics (PD), properties that would be difficult or impossible to obtain with genomically modified CAR T-cells.[47] 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[48], AML[49], breast cancer[50], neuroblastoma[51], mesothelin-expressing cancers[52] and EGFR-expressing cancers.[53]

Cartesian is currently conducting a Phase I/IIa clinical trial for Descartes-08, an mRNA-transfected CAR T-cell product targeting BCMA, in patients with relapsed/refractory multiple myeloma. The product is currently enrolling patients in a classic 3+3 dose-escalation design. In that protocol, Descartes-08 is infused on Days 0, 3 and 7 to obtain about 2 weeks of CAR T-cell exposure, which was shown to be an adequate time for eliminating myeloma cells using the same CAR protein in the original NCI trial[16] To date, Descartes-08 has been well tolerated.

The current protocol is designed to test a derivative of Descartes-08, named Descartes-11, where the scFv of the CAR has been humanized to display low immunogenicity.[54] Descartes-11 will be administered for up to three 21-day Cycles. Each Cycle will start with preconditioning chemotherapy (except for Dose Level 4C). This will be followed by a dose of Descartes-11 (administered as a split dose, in 2 to 6 equal infusions, according the schedule shown in Section 3.2). After Cycle 1, if a patient does not meet removal from treatment criteria as set forth in Section 4.5.1, he/she may receive up to two more cycles of treatment.

1.2.7 Rationale Behind Preconditioning Chemotherapy

The use of non-myeloablative conditioning to support adoptive cell therapies was developed in the studies using tumor-infiltrating lymphocytes (TILs) in the late 1980s[55] Cytotoxic chemotherapy

prior to cell infusion enhances anti-tumor T-cell responses by eradicating regulatory T-cells, eliminating other immune cells that may compete for homeostatic cytokines, and enhancing antigen-presenting cell activation.[56-58] Since the anti-tumor activity of CAR T-cells also depend on T-cell activity, similar to TILs, preconditioning chemotherapy was used in almost all of the pivotal CAR T-cell studies.[23-26,30,31,34,35,40,59-62] Preclinical studies showed the importance of cyclophosphamide for CD-19 CAR T-cell engraftment,[63] and in a different study this benefit was enhanced by addition of fludarabine to preconditioning regimen.[64] The clinical proof of this concept was shown in an anti-CD19 [59] as well as an anti-BCMA CAR T-cell study.[19] In other anti-BCMA CAR T-cell trials, a combination of fludarabine and cyclophosphamide regimen was given as preconditioning regimen over 2-4 days. [15-17,20,65-69]

Since the benefit of preconditioning chemotherapy regimen for CAR T-cell activity includes enhancing survival of infused T-cells, this protocol will also use a fludarabine/cyclophosphamide combination (25mg/m^2 fludarabine and 250mg/m^2 cyclophosphamide), except for Dose Level 4C, which will test Descartes-11 without preconditioning chemotherapy.

1.2.8 Preface to Protocol Version 1.5

This latest amendment of the protocol subdivides Dose Level 4 into three treatment groups: Dose Levels 4A, 4B, and 4C. Dose levels 4A, 4B, and 4C each administer a total target dose of 150x10^6 cells/kg but differ with respect to the administration schedule (see Table 2). Furthermore, in the case of Dose Level 4C, preconditioning chemotherapy is omitted. The amendment contains various other changes, which are mostly administrative in nature.

1.2.9 Preface to Protocol Version 1.6

To date, no Descartes-11-related adverse events have been observed in patients treated with Dose Level 4A, 4B or 4C. Two new subcohorts (4D and 4E) will be added to Dose Level 4 to test the safety of administering Descartes-11 in patients on a concurrent Immunomodulatory Imide Drug (IMiD), such as lenalidomide and pomalidomide. The rationale for this is that IMiDs potentiate the activity of CAR T-cells, including mRNA transfected anti-BCMA CAR T-cells (Descartes-08)[70-72]. A third subcohort (4F) will administer Descartes-11 by a femoral artery catheter to determine if bypassing the pulmonary vasculature may reduce cell trapping and improve anti-tumor homing of Descartes-11 as demonstrated in a preclinical mouse model.[73] Administration of tumor-infiltrating T-cells[74], lymphokine-activated killer cells[75,76] or CAR T-cells[77] by intraarterial catheter is safe and may lead to increased penetration of these therapeutic cells into tumor tissue.

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

Descartes-11 is frozen after manufacturing, then thawed at the clinical site immediately prior to infusion. Each dose, provided in one or more vials, will be thawed at 37°C on the day of infusion and must be administered within a fixed time after thawing. Please refer to Section 3.3.3.1 and the

Descartes-11 Clinic Storage, Handling and Administration Manual for detailed instructions on how to prepare and administer the study product.

1.3.3 Preclinical Data

Please refer to Investigator Brochure for a detailed description of nonclinical 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 timepoint is specified:

1. Failure of at least 2 prior lines of therapy. Failure of treatment is defined as:
   a. Progression while on treatment OR
   b. Progression within 60 days after last dose of treatment OR
   c. Intolerability of treatment OR
   d. Increase of 25% from lowest confirmed response value in one or more of the following criteria:
      i. Serum M-protein (absolute increase must be ≥ 0.5 g/dL);
      ii. Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥5 g/dL;
      iii. Urine M-protein (absolute increase must be ≥ 200 mg/24 h);
      iv. 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);
      v. Bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%);
      vi. Appearance of a new plasmacytoma lesion(s), ≥ 50% increase in size (sum of the products of the maximal perpendicular diameters (SPD) of measured lesions) from nadir or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis (Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD).
2. Measurable myeloma defined as:
   a. Serum M-protein > 0.5 g/dL OR
   b. Urine M-protein > 200 mg/24 hours OR
   c. An involved serum free light chain (FLC) > 10 mg/dL (provided FLC ratio is abnormal) OR
   d. A biopsy-proven plasmacytoma OR
   e. Patients must have greater than 5% bone marrow plasma cells.
3. Patients with prior ASCT or allotransplant are eligible but must be >100 days post-transplant at the time of leukapheresis.
4. 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 leukapheresis.
5. Patients must have signed written, informed consent.

6. Patients must be 18 years of age or older at the time of enrollment.
7. Patients must have clinical performance status of ECOG 0-2.
8. Due to potential teratogenicity of preconditioning chemotherapy:
   a. Women of childbearing potential must have a negative pregnancy test at the time of screening.
   b. Patients of both genders must agree to effective contraception from the time of enrollment until four months after receiving the last dose of preconditioning chemotherapy.
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 >30,000 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. Therapeutic doses of corticosteroids (defined as > 40 mg/day prednisone or equivalent) within 7 days prior to leukapheresis; physiologic replacement, topical, and inhaled steroids are allowed.
   b. Standard -of-care anti-myeloma treatment within 7 days of leukapheresis. Patients enrolled in Dose Level 4D and 4E may continue receiving ongoing IMiD therapy.
   c. Experimental agents within 28 days of leukapheresis unless progression is documented on therapy and at least 3 half-lives have elapsed prior to leukapheresis

4. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine or systemic steroids above 40 mg/day prednisone equivalent)). Topical, inhaled, or intranasal corticosteroids are allowed.
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: successfully treated non-metastatic basal cell or squamous cell skin carcinoma, or 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, patient cannot hold the anticoagulation 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)

    NOTE: Subjects who have had a venous thromboembolic event but do not meet any of the above 3 criteria are eligible for participation

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 can be referred any time after they meet the criteria for a failure of at least two lines of therapy. Definition for one line of therapy will be based on the guideline published by Rajkumar *et al*. [78] The screening/consent period allows consenting patients earlier than the intended Descartes-11 infusion day and provides extra time for cell manufacturing and shipment. Therefore, it is recommended that patients be informed of the trial as soon as they meet eligibility to facilitate early enrollment. Bridging therapies to control the disease are allowed during the waiting period after enrollment (See Section 3.3 for details). Patients who are already on or eligible for IMiD therapy may be eligible for subcohorts 4D and 4E. The IMiDs will be continued concurrently with CAR T-cells.

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 (e.g., voluntary withdrawal, toxicity, death) 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.

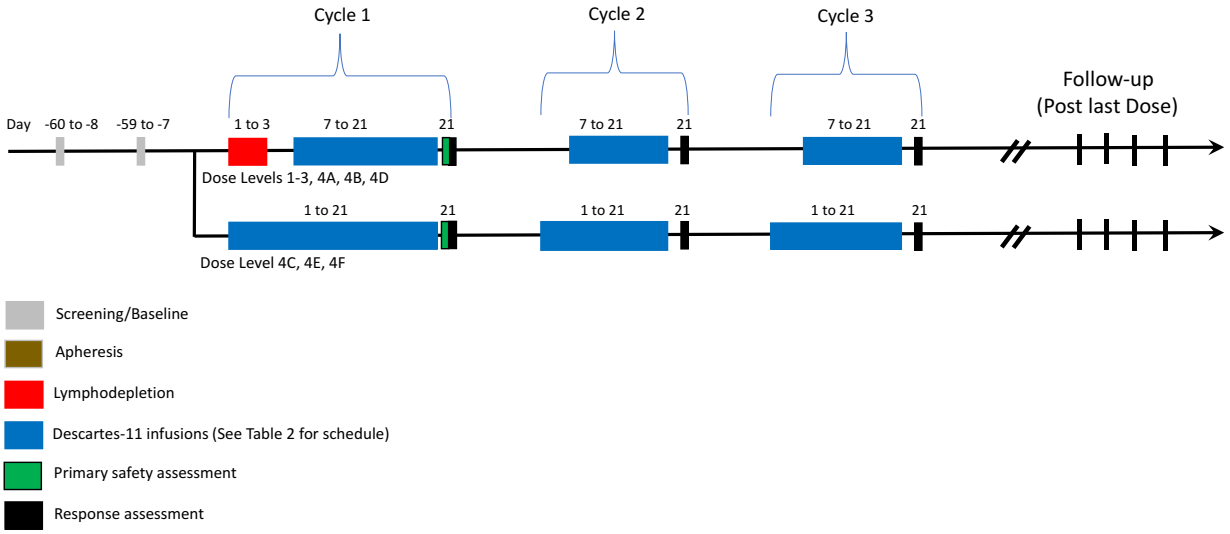
2.2.5 Data Collection and Follow-Up of Early Withdrawals

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 is illustrated in Figure 1.

Patients are enrolled between Day -60 and Day -8, with screening and baseline studies conducted during this time. Enrollment begins with leukapheresis. Patients meeting eligibility criteria are leukapheresed between Day -59 and Day -7.

Eligible patients participate in up to three, 21-Day Cycles of therapy. For all cohorts except 4C, preconditioning chemotherapy is initiated on Day 1 ($\pm$1d) and administered consecutively for 3 Days. Descartes-11 is administered as a split dose (2-6 equal infusions) on designated Days (see Table 2). See Section 3.2.4 for criteria of delaying cell infusion. Safety assessment is on Day 21 (or at least 14 days after first Descartes-11 infusion if cell infusion is delayed). Response assessment is on Day 21 (or at least 14 days after first Descartes-11 infusion if cell infusion is delayed). At least 21 days must elapse between Day 1 of each Cycle of treatment. Start of a cycle can be delayed up to 7 days.

A DLT will preclude the patient from being eligible to receive another Cycle of treatment. Patients who do not experience a DLT during Cycle 1 are eligible for Cycle 2. Patients who do not experience a DLT during Cycle 2 are eligible for Cycle 3. Cycles 2 and 3 are administered on the same 21-Day schedule as Cycle 1 except for lymphodepletion in Dose Levels 4B and 4D, which is not administered in Cycles 2 and 3. Patients are followed up for 12 months after completing their final treatment Cycle.

Once a safe and tolerable dose is identified, up to 12 patients will be enrolled to further characterize the safety and preliminary efficacy of the selected dose.

3.2.2 Dose Levels

Doses are expressed as the number of viable CAR+ cells per kg of patient weight up to 100 kg. The Dose Levels are summarized in Table 2. Dose Level 1 is 10 x 10^6 cells/kg per dose (i.e., 5 x 10^6 cells / kg on Day 7, and 5 x 10^6 cells / kg on Day 14). Dose Level 2 is 32 x 10^6 cells/kg per dose. Dose Level 3 is 100 x 10^6 cells / kg per dose. Dose Level 4 is 150 x 10^6 cells / kg per dose.

The safe and appropriate initial Dose Level 1 (10 x 10^6 cells/kg) was informed by an ongoing clinical trial (NCT 03448978; Descartes-08) for a similar anti-BCMA mRNA CAR T-cell product, manufactured under identical conditions to Descartes-11, to treat the same indication (i.e., relapsed/refractory MM). In the referenced Descartes-08 trial, a dose up to 90 x 10^6 cells / kg has resulted in *no dose-related AEs to date* (please see Descartes-11 Investigator Brochure). Preclinical studies also demonstrated that the two products behave similarly and show similar BCMA binding, tumor cytotoxicity, and in vivo efficacy. For example, similar to Descartes-08, Descartes-11 showed no CAR-specific off-target binding in a panel of 5528 human plasma membrane proteins and human secreted proteins (please see Descartes-11 Investigator Brochure).

Table 2. Dose Levels and Infusion Schedule per Cycle

Dose Level (Cohort)	Total Descartes-11 Dose[a,b]	Flu/Cy Schedule (Only Cycle 1)	Descartes-11 Schedule[c]
Level 1	10 x 10^6 cells / kg	Days 1,2,3	Days 7,14
Level 2	32 x 10^6 cells / kg	Days 1,2,3	Days 7,14
Level 3	100 x 10^6 cells / kg	Days 1,2,3	Days 7,14
Level 4A[d]	150 x 10^6 cells / kg	Days 1,2,3	Days 7,14,21
Level 4B[d]	150 x 10^6 cells / kg	Days 1,2,3	Days 7,10,14,17
Level 4C[d]	150 x 10^6 cells / kg	None	Days 1,4,7,10,14,17
Level 4D[d]	150 x 10^6 cells / kg	Days 1,2,3	Days 7,10,14,17
Level 4E[d]	150 x 10^6 cells / kg	None	Days 1,4,7,10,14,17
Level 4F[d,e]	150 x 10^6 cells / kg	None	Days 1,7,14

[a] For Dose Levels 1-3, each dose is split into 2 equal infusions, administered 7 days apart, per 21-day Cycle. For Dose Level 4A/F, B/D and C/E, each dose is split into 3, 4 or 6 equal infusions, respectively.

[b] Doses are expressed as viable CAR+ cells per kg of patient weight.

[c] ±1 day allowed for each infusion.

[d] DL4 subgroups may enroll in parallel but each subgroup will independently follow the predetermined dose escalation and stopping rules (Section 3.2.2).

[e] Dose is given by intrafemoral catheter

The clinic will contact the Sponsor at the time a patient is determined to be eligible. The Sponsor will then assign the patient to the next cohort where space is available. A dose will be considered acceptable to administer if it is within ±45% of the dose specified for the applicable Dose Level. If it is determined that the patient's CAR T-cells are insufficient for the assigned Dose Level but sufficient for an earlier Dose Level, the Sponsor may (at the discretion of the medical monitor) reassign that patient to a lower Dose Level (even if that Dose Level has been completed) or treat the patient at an intermediate dose between two Dose Levels. Alternatively, at the discretion of the medical monitor, a second attempt may be made to prepare cells for the patient if the patient agrees and if the patient still meets eligibility criteria within the specified assessment windows (repeat assessments are permitted at the discretion of the medical monitor).

3.2.3 Dose Escalation / Stopping Rules

Prior to any dose escalation, a minimum of 3 patients will be dosed at each Dose Level. The first 3 patients from each cohort will be enrolled sequentially. For the first 3 patients enrolled in the study, a minimum of 21 days must elapse between the first dose infusions for successive patients. For all other patients, a minimum of 14 days must elapse between the first dose infusions for successive patients during dose escalation. Selection of Day 14 as a threshold is similar to that in the reference study (NCT 03448978, Descartes-08) and was based on previous CAR-T trials where severe CRS was observed within hours to days after infusion, and mild CRS was observed in the first two weeks[46].

The study will not proceed to a higher Dose Level until: 1) at least 3 patients in the previous Dose Level have been observed through Day 21 study visit, 2) no study stopping rules have been triggered, and 3) the medical monitor has reviewed the cumulative safety data and concluded and documented that the next Dose Level may be initiated.

The medical monitor will apply the following rules to determine if it is safe to proceed to the next Dose Level, or if dose escalation should stop (pre-specified rules for pausing or stopping the whole study are described in Section 5.5; rules for individual patient withdrawal are described in Section 4.5.):

If one of three patients in a Dose Level experiences a DLT within the safety review period AND that DLT is assessed as possibly or probably related to Descartes-11 (i.e., Descartes-11-related), three more patients will be enrolled and treated at that Dose Level. If only 1/6 of patients at that Dose Level has a Descartes-11-related DLT, and if the medical monitor agrees, treatment will proceed to the next higher Dose Level. If two or more out of three to six patients develop a Descartes-11-related DLT, no further patients will be dosed at that Dose Level. If the medical monitor agrees, up to three additional patients will be treated at the previous (lower) Dose Level to provide a total of six patients for that Dose Level and further characterize the safety of the maximum tolerated dose. The maximum tolerated dose (MTD) will be defined as the dose at which a maximum of one of six patients has a DLT. Upon determination of the MTD and documented approval by the medical monitor, an additional 9 more patients may be treated at the MTD; the results of these 9 will not be used to redefine the MTD.

If the patient's CAR T-cells are not sufficient to administer the intended dose, the patient may, at the medical monitor's discretion, receive as many cells as possible up to the intended dose.

If it becomes technically impractical to increase the Dose Level due to cell production constraints and an MTD has not been reached, the maximum Dose Level for which at least three patients have been treated may be declared the maximum feasible dose.

Dose escalation will follow the rules outlined in Table 3. Note that a DLT occurring at given a dose level will be considered a DLT for that dose level regardless of whether it occurs after the first or second infusion.

Table 3. Dose Escalation Rules

Number of patients with DLT at each dose level	Dose escalation rule
0 out of 3	Proceed to next dose level
1 out of 3	Enter up to 3 more patients at this dose level. - If 0 of the added 3 patients experience DLT (1 out of 6 overall), proceed to the next dose level. - Otherwise, see below under "2 or more"
2 or more	Dose escalation will be stopped. Administration to other patients in the same cohort will be stopped, but patients will remain in the study for observation. This dose level will be declared the Maximum Tolerated Dose. Up to 3 additional patients will be treated at the previous (immediately lower) Dose Level to reach enrollment of 6 patients in that Dose Level.
Less than 2 out of 6	This will be the recommended dose for phase 2.

3.2.4 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 it is reasonable to proceed. During this period, patients will be assessed to record adverse events and decide whether the patient meets criteria for cell infusion. Infusions can also be delayed up to 24 hours due to scheduling. Furthermore, prior to study cell infusion, subjects must demonstrate an absence of fever, infection and organ dysfunction since eligibility (See Section 3.3.3.2 for details). If patient does not meet the infusion criteria, the infusion can be delayed up to 2 weeks.

3.3 Drug Administration

3.3.1 Leukapheresis

The patient will undergo leukapheresis at least 14 days prior to cell infusion according to institutional standard operation procedures. A central or peripheral line will be placed prior to leukapheresis. Five to fifteen liters of blood volume will be processed to collect PBMC and plasma that will be used for Descartes-11 manufacturing. The volume of collection will be recommended by Sponsor, in consultation with the investigator, based on Dose Level and target cell

concentration in peripheral blood. Patients will be cared for and discharged as per institution guidelines. Patients are allowed to receive anti-myeloma treatment (excluding proteasome inhibitors and monoclonal antibodies) after enrollment. Bridging therapy should be stopped at least 7 days prior to the start of lymphodepletion chemotherapy. Corticosteroid-based bridging therapy can be stopped up to 3 days prior to the start of lymphodepletion.

3.3.2 Administration of Cyclophosphamide and Fludarabine

On Days 1, 2 and 3 of the first Cycle, patients (except for those in Dose Level 4C) will receive 250 mg/m^2 cyclophosphamide and separately 25 mg/m^2 fludarabine. Infusions can be delayed up to 24 hours based on PI discretion or scheduling. Each infusion bag will be prepared and administered as per institution standards. Dose adjustment is allowed per PI discretion or institution standards. It is recommended to give 1000 mL 0.9% normal saline after completing the infusion of both agents. Patients will receive anti-emetics as per institution guidelines; **however, dexamethasone is not allowed.** Patients should also be provided with anti-emetics to take at home. If the patient is enrolled into Dose Level 4D, IMiD treatment should be paused while patient is cytopenic due to chemotherapy and should be resumed when blood counts permit as per recommendations in the package insert of the drug. See below for further discussion of IMiD therapy in the context of cytopenia.

Dose Levels 4C, 4E and 4F do not administer lymphodepletive chemotherapy.

3.3.3 Preparation and Administration of Study Drug

3.3.3.1 Drug Preparation

Descartes-11 cells will be prepared at a central manufacturing facility and shipped to the clinical site. Cells will be shipped to arrive no later than one day before the start of lymphodepletive chemotherapy. Upon receipt at the clinical site, the cells should be logged in and stored in a secured freezer at -70 to -90 ^{0}C until Day 7. **On the day of infusion, before thawing Descartes-11, study staff must verify that patient identifiers shown on the labels positively match the intended patient.** Detailed instructions for thawing the cells and preparing for administration are written in the Descartes-11 Clinic Storage, Handling and Administration Manual**.**

3.3.3.2 Drug Administration

Refer to Table 2 for schedule of infusions. Prior to each infusion, patients must meet the following criteria:

1. Temperature is less than 37.9^{o}C;
2. There are no signs of an active infection;
3. If patient is taking corticosteroids, the dose has been reduced to 40 mg/day prednisone or equivalent and the dose is held for at least 12 hours prior to infusion;
4. Other than a cytopenia, there are no ongoing Grade 2 toxicities from prior treatment precluding cell infusion;
5. Pre-infusion clinical assessment does not suggest organ dysfunction and/or rapid disease progression since enrollment.

See Section 3.2.4 for conditions to delay cell infusion. 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 is double-checked by two authorized staff (MD or RN), and identification of the product and documentation of administration are 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.

3.3.4 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.

3.3.5 Post-Infusion Observation

Emergency medical equipment (i.e., emergency cart) will be available during the infusion in case the subject has an allergic response, or severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, respiration rate, pulse, blood pressure and oxygen saturation by pulse oximetry) will be measured 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 and 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 should remain within 90 minutes of driving distance for possible daily assessment of toxicities until Primary Safety Review (Day 21, Cycle 1). 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.

3.3.6 Management of Toxicities

For CAR T-cells, significant toxicities, if any, typically occur within one week of administration and include infusion reactions, CRS and neurotoxicity.

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.

3.3.6.1 Febrile Reaction

Between Days 7 and 21 (or 14 days after first Descartes-11 infusion if cell infusion is delayed) of Cycle 1, 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.

3.3.6.2 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.[79] 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.

3.3.6.3 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[80] 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. In addition, serum should be collected in the first 2 hours of the reaction to measure tryptase levels (See Section 4.3.1.3 and Descartes-11 Laboratory Manual for collection details) to confirm diagnosis. A minimum of two, 3 ml aliquots of this serum should be frozen for future analysis.

3.3.6.4 Cytokine Release Syndrome

This protocol has adopted the CRS grading system and management guidelines published by Lee et al.[22] See Table 1 for the grading system and Appendix 1 for a treatment algorithm. See Section 4.3.1.2 for CRS-related blood collection procedures.

3.3.6.5 Neurotoxicity (ICANS)

Management guidelines are summarized in Appendix 1. 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.

3.3.7 Concomitant Medications

3.3.7.1 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.

3.3.7.2 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.

3.3.7.3 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.

3.3.7.4 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 from Cycle 1 Day 1 until cell infusions are completed unless approved by without approval of the Principle Investigator. In addition, corticosteroids should be withheld for 12 hours before and after the Descartes-11 infusion.

3.3.7.5 IMiDs

For patients who are in Dose Levels 4D and 4E, the management of IMiD treatment will be left to PI's discretion. IMiDs should be interrupted when neutrophil and platelet counts are below the levels recommended in the package insert of each drug. Once IMiDs are resumed after cell counts recover, they should be typically resumed at the same dose and further dose titration should be done based on recommendations outlined in the package insert of each drug. Venous thromboembolism prophylaxis is left to the PI's discretion.

4 Protocol Evaluation and Biospecimen Collection

4.1 Study Procedures

4.1.1 Baseline Evaluation (Day -60 to Day -8)

1. Obtain informed consent
2. Review of records for documentation of at least 2 prior lines of therapy and failure of last line of treatment and confirm all other eligibility
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. Anti-HIV 1 and 2 antibody
13. Hepatitis B antigen (HBV DNA if Hepatitis B antigen positive)
14. Anti-HCV (HCV RNA if anti-HCV positive) and anti-HIV antibody
15. Lymphocyte sub-set counts (CD19, CD3, CD4, CD8)
16. Quantitative immunoglobulins (IgG, IgM, IgA, IgE)
17. Serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE)
18. 24-h urine for urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE)
19. Serum free light chain (FLC) assay
20. Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and bone marrow flow cytometry
21. 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.
22. ECG
23. ABO typing
24. Echocardiogram to assess left ventricular function if not performed within the last 6 months

25. 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)).
26. Research blood (See Laboratory Manual for collection details)

4.1.2 Leukapheresis (Day -59 to Day -7)

A central or peripheral line will be placed prior to the procedure. Prior to leukapheresis, following assessments should be completed:

1. Medical history for adverse events
2. Vital signs (should always include pulse oximetry unless stated otherwise) and physical exam including brief neurological exam
3. Concomitant medications
4. ECOG performance status

Leukapheresis and plasma collection will take place as per institutional standards. A sample will be collected from the apheresis product bag to perform CBC analysis that will be reported to the Sponsor prior to shipment of the product. See "Apheresis collection and shipping instructions" for more details.

4.1.3 First day of Pre-conditioning chemotherapy (Day 1 (± 1 d) of Cycle 1)

In patients enrolled into Dose Level 4C, 4E and 4F do not administer lymphodepletive chemotherapy. These patients receive Descartes-11 on Day 1, which is described in Section 4.1.5.

Prior to chemotherapy infusion, the following assessments must be completed (Laboratory tests can be obtained within 48 hours of infusion):

1. Medical history for adverse events
2. Vital signs (should always include pulse oximetry unless stated otherwise), and physical exam including brief neurological exam
3. Concomitant medications
4. ECOG performance status
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. Urine pregnancy test for all women of child-bearing potential
8. Urinalysis (if abnormal then urine culture)
9. Research Blood (See Laboratory Manual for collection details)

4.1.4 Second and Third day of Preconditioning chemotherapy (Day 2 to Day 3 of Cycle 1)

Prior to chemotherapy infusion, the following assessments must be completed:

1. Medical history for adverse events
2. Vital signs (should always include pulse oximetry unless stated otherwise) and physical exam including brief neurological exam
3. Concomitant medications
4. ECOG performance status

Dose Level 4C does not administer lymphodepletive chemotherapy.

4.1.5 Descartes-11 infusion

Please refer to Table 2 for Descartes-11 infusion schedule per Cycle.

Disease reassessment: Within one day of the first Descartes-11 infusion of each cycle, 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. 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. CRP, ferritin

8. Lymphocyte sub-set counts (CD19, CD3, CD4, CD8)
9. Urinalysis
10. Urine pregnancy test for all women of child-bearing potential
11. ECG
12. Research Blood (See Laboratory Manual for collection details)

Within 30±5 min of each infusion:

1. Vital signs – Please see Section 3.3.5 for details.
2. Complete blood count, differential
3. Research blood (See Laboratory Manual for collection details)

4.1.6 Safety Review and Response Assessment Visit (Day 21+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, Alk Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Uric Acid, Cr, ALT, AST, lactate dehydrogenase)
7. Urinalysis
8. Urine pregnancy test for all women of child-bearing potential
9. CRP, ferritin
10. Lymphocyte sub-set counts (CD19, CD3, CD4, CD8)
11. Research blood (See Laboratory Manual for collection details)
12. If present at baseline, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
13. If present at baseline, 24-h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
14. If present at baseline, serum free light chain (FLC) assay
15. β2- microglobulin

16. 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.
17. Imaging of a previously known plasmacytoma if already imaged at baseline visit
18. Quantitative immunoglobulins (IgG, IgM, IgA, IgE)

4.1.7 Follow-up Months 3, 6, 9, 12 (± 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, Alk Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Uric Acid, Cr, ALT, AST, lactate dehydrogenase)
7. Lymphocyte sub-set counts (CD19, CD3, CD4, CD8)
8. Quantitative immunoglobulins (IgG, IgM, IgA, IgE)
9. Urinalysis
10. Urine pregnancy test for all women of child-bearing potential
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

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

Procedures	Screening	LePh[a]	Each Cycle of Treatment									Follow-Up
	Day -60 to Day -8	Day -59 to Day -7	Day 1 ±1d	Day 2	Day 3	Day 4 ± 1d[d]	Day 7 ±1d	Day 10 ±1d[e]	Day 14 ±1d	Day 17 ±1d[e]	Day 21 ±1d	Months 3, 6, 9, 12 ±2 weeks
Informed consent Eligibility Demographics	X											
Medical History	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X
Performance Score	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs, O_2 saturation	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
Weight	X										X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Fludarabine[b]			X[b]	X[b]	X[b]							
Cyclophosphamide[b]			X[b]	X[b]	X[b]							
Descartes-11			X[c,]			X	X	X	X	X	X[f]	
CBC w/ differential	X		X			X	X	X	X	X	X	X
Serum Chemistries[g]	X		X			X	X	X	X	X	X	X
Magnesium, phosphate	X		X				X					
PT/INR, PTT	X		X									
ABO typing	X											
D-Dimer, fibrinogen	X											
CRP, ferritin			X[c]				X	X	X		X	
Urinalysis	X		X				X	X	X		X	X
β-HCG	X											
Urine pregnancy test			X				X	X	X		X	X

Procedures	Screening	LePh[a]	Each Cycle of Treatment									Follow-Up
	Day -60 to Day -8	Day -59 to Day -7	Day 1 ±1d	Day 2	Day 3	Day 4 ± 1d[d]	Day 7 ±1d	Day 10 ±1d[e]	Day 14 ±1d	Day 17 ±1d[e]	Day 21 ±1d	Months 3, 6, 9, 12 ±2 weeks
Lymphocyte counts	X		X[c]				X	X	X		X	X
Quantitative Immunoglobulins	X										X	X
Serum FLC ratio	X		X[c]				X				X[l]	X[l]
Serum electrophoresis and immunofixation	X		X[c]				X				X[l]	X[l]
β_2-microglobulin	X										X	X
24-hour urine for electrophoresis and immunofixation	X		X[c]				X				X[l]	X[l]
Bone marrow biopsy and aspiration	X										X[k]	X[m]
Research Blood	X		X[h]			X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X
Echocardiogram[i]	X											
Central or peripheral venous catheter placement		X										
Imaging	X[j]										X[k,l]	X[l]
Viral serologies	X											

[a] LePh: Leukapheresis
[b] Preconditioning chemotherapy administered in Cycle 1 only.
[c] Only in Dose Level 4C, 4E and 4F. **NOTE:** DL4C, 4E and 4F does not administer preconditioning chemotherapy in any Cycle.
[d] Only in Dose Level 4C and 4E.
[e] Only in Dose Level 4B and 4D.
[f] Only in Dose Level 4A.
[g] Includes Glucose, Ca, Alk Phos, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Uric Acid, Cr, ALT, AST, lactate dehydrogenase.
[h] On days of Descartes-11 infusion, there is 1x pre- and 1x post-infusion collection. See Laboratory Manual for details.
[i] If not done in the previous 6 months.
[j] ONLY if there is known plasmacytoma in medical history.
[k] Procedure should be done only after completing all intended Decartes-11 infusions.
[l] If present at baseline.
[m] Bone marrow aspiration and biopsy tests will be performed ONLY if needed for depth-of-response or relapse evaluation.

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

Pharmacokinetics of circulating Descartes-11 cells will be performed by quantitative PCR or flow cytometry. Blood concentration of Descartes-11 cells will be determined by multiplying the percentage of CAR+CD8+ within the CD3+ population with the absolute number of CD3+ cells obtained from lymphocyte subsets. *Ex vivo* immunological assays will be used to measure the BCMA-specific functional activity of the CAR+ T-cells and will consist of assays such as intracellular cytokine staining, anti-CD107a degranulation assays and killing of BCMA-expressing myeloma cells. Serum BCMA levels will be measured with a validated assay.

4.3.1.2 Serum Biomarkers related to CRS

Monitoring serum biomarkers of inflammation following infusion of CAR-T cells may facilitate identification of factors that are associated with severe CRS and thereby may be used in the future to predict the reaction of a patient to Descartes-11 infusion. Thus, serum at baseline, prior to cell infusion and at Safety Review and Response Assessment visits will be used to monitor the inflammatory markers in the absence of $\geq$ Grade 2 CRS. Following Descartes-11 infusion, if a $\geq$ Grade 2 CRS occurs then serum for research should be collected daily until CRS regresses to Grade 1 or less. Collected serum will be tested for the following cytokines that are associated with severe CRS following CAR-T infusion: C-reactive protein, ferritin, IFNγ, IL-6, soluble gp130, soluble IL-6R, TNFα, IL-2, IL-10, IL-8, IL-5 and fractalkine.[33] Additional cytokines and inflammatory markers including, but not limited to sIL-1Rα, sIL-2Rα, IL-8, IL-12, IL-13, IL-15, MCP1, GM-CSF and MIP1α, will be tested as needed to address changes in standards and/or literature findings.

4.3.1.3 Additional Assays

Patients may be asked to undergo biopsies or additional blood draws for research purposes. Additional blood draws might be necessary to investigate T-cell responses and serum cytokine levels in cases of clinical events such as rapid regressions of malignancy or toxicity. These research biopsies or blood draws are optional and will not impact patient participation in this study. These biopsies will only be performed if minimal morbidity is expected based on the procedure performed and the granulocyte and platelet count.

Immunogenicity will be assessed by a commercially available human anti-mouse antibody ELISA kit.

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 4. IMWG response criteria[82]

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 of serum 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 5. 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:

- DLT as defined in Section 5.1.5 directly attributable to Descartes-11 cells.
- 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.

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 all intended anti-BCMA CAR T-cell 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.

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 Dose Limiting Toxicity (DLT)

DLTs are defined as 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 3 CRS associated with fever, hypotension or hypoxia lasting less than 72 hours (i.e., improves to ≤Grade 2 CRS in less than 72 hours)
- 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
- 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

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.

5.1.6 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 (Descartes-11 vs lymphodepletion): Is there a reasonable possibility that the AE is related to Descartes-11 or lymphodepletion treatment- No (unrelated) or Yes. If yes- is the event definitely, probably, possibly or unlikely related to the investigational treatment (Descartes-11) or the non-investigational treatment (i.e., cyclophosphamide or fludarabine).
- 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 possibly, probably or definitely related to study drug within the first 30 days after first 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

6.1 Primary Endpoints

6.1.1 Safety and Tolerance

Study results will be descriptive. Safety and tolerability endpoints will include descriptive statistics of AEs and SAEs. Patients must be followed until all AEs have resolved to Grade 2 or less except for lymphopenia and alopecia.

6.1.2 Feasibility

The number of manufactured products that do not meet release criteria for potency, T cell purity, viability and sterility will be determined (defined as "manufacturing failures").

6.2 Secondary Endpoints

6.2.1 Efficacy

Efficacy will be assessed by descriptive statistics of treatment response per IMWG criteria.[82]

6.3 Exploratory Endpoints

6.3.1 Descartes-11 Biology

1. Characterize Descartes-11 persistence, homing, phenotype, and function in patients with MM.
2. Determine impact of Descartes-11 on systemic soluble immune factors by cytokine assays.
3. Determine the correlation between serum BCMA levels and response.

6.3.2 Immunogenicity Assessment

Immunogenicity will be assessed by a commercially available human anti-mouse antibody ELISA kit and results will be reported as descriptive.

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 Acetaminophen, Diphenhydramine, Cyclophosphamide, Fludarabine and Tocilizumab, IMiDs (Lenalidomide, Pomalidomide) will be sourced from commercial suppliers of the clinical site. Investigators will be referred to the approved labeling for those products.

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10 Appendix 1 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.[22] 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 37.9^0C 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 0.5-1L 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
    c. 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[22]. 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 0.5-1.0 mg/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).