

Supplemental Materials

A phase 1, multicenter study evaluating the safety and efficacy of KITE-585, an autologous anti-BCMA CAR T-cell therapy, in patients with relapsed/refractory multiple myeloma

Authors: Robert F Cornell¹, Michael R Bishop², Shaji Kumar³, Sergio A Giralt⁴, Ajay K Nooka⁵, Sarah M Larson⁶, Frederick L Locke⁷, Noopur S Raje⁸, Lei Lei⁹, Jinghui Dong⁹, John B Le Gall⁹, John M Rossi⁹, Robert Z Orlowski¹⁰

Table of Contents

1. SUPPLEMENTAL METHODS.....	3
1.1. DEVELOPMENT AND VALIDATION OF BCMA PLASMA CELL PANEL.....	3
1.2. DEVELOPMENT AND VALIDATION OF BCMA IMMUNOHISTOCHEMISTRY (IHC) ASSAY....	3
2. PROTOCOL.....	5

1. Supplemental Methods

1.1. Development and Validation of BCMA Plasma Cell Panel

The purpose of the development of the BCMA plasma cell panel was to determine BCMA expression for immunophenotypic results. To validate the panel, the assay was tested for accuracy, repeatability/reproducibility/inter operator precision, sensitivity/specificity, and linearity. Sensitivity and specificity calculations were as follows:

$$\text{Sensitivity} = \text{True Positive (TP)} / (\text{TP} + \text{False Negative [FN]})$$

$$\text{Specificity} = \text{True Negative (TN)} / (\text{TN} + \text{False Positive [FP]})$$

The results indicated the BCMA plasma cell panel met the criteria for accuracy and the sensitivity and specificity were each 100%. Further, the assay was determined to be repeatable, reproducible, and reproducible between operators. The linearity experiment demonstrated that the assay is linear to 1% for BCMA positive cells. Overall, the BCMA plasma cell panel was determined to be acceptable for use.

1.2. Development and Validation of BCMA Immunohistochemistry (IHC) Assay

The purpose of the development of the BCMA IHC assay was to determine BCMA expression in multiple myeloma clot specimens. Formalin-fixed paraffin-embedded (FFPE) specimens were used for validation to test sensitivity, specificity, and precision. FFPE tissue blocks were sectioned at 4-5 μm and mounted on positively charged slides. BCMA IHC and CD138 stained slides were evaluated by a NeoGenomics pathologist using a brightfield microscope and the percentage of BCMA positive plasma cells out of all plasma cells were determined for each specimen. The approximate plasma cell population and locations were assessed based on CD138 IHC staining on a serial section and the percentage of BCMA positive cells out of all plasma cells were reported. Further, a semi-quantitate H-score assessment of BCMA positive cells was also included in the sensitivity/specificity testing. For optimization of the BCMA IHC assay, 4 commercial antibodies were screened under different conditions. The BioLegend BCMA antibody, clone 19F2, on the Ventana Benchmark Ultra and Dako Link 48 platform was chosen as the best antibody. The optimized conditions for antigen retrieval included using a DIVA buffer in a pressure chamber at 125 °C for 5 minutes and an antibody dilution of 1:50 in Dako Antibody Diluent followed by LINKER amplification. Under these conditions, the specific BCMA IHC signal had little background and was approved by NeoGenomics pathology. Accuracy was not assessed due to limited published literature of BCMA IHC in MM. The sensitivity of the BCMA staining found $\geq 10\%$ of plasma cells being present in 60% of MM specimens and the assay showed a range of 0%-100% BCMA expression in plasma cells, meeting acceptability criteria. The specificity results found that BCMA expression was limited to plasma cell populations and met acceptability criteria. The BCMA IHC repeatability study found an overall percent coefficient of variance of 1% when evaluating total percent positive staining

while the BCMA IHC reproducibility study resulted in an overall percent coefficient of variance of 2% when evaluating total percent positive staining, both meeting acceptability criteria. Overall, the BCMA IHC assay was determined to be acceptable for use.

2. Protocol



Kite, a Gilead Company

Redacted Clinical Trial Protocol for Journal Use

**A Phase 1 Multicenter Study of KITE-585, an Autologous Anti-BCMA
CAR T-Cell Therapy, in Subjects with Relapsed/Refractory Multiple
Myeloma**

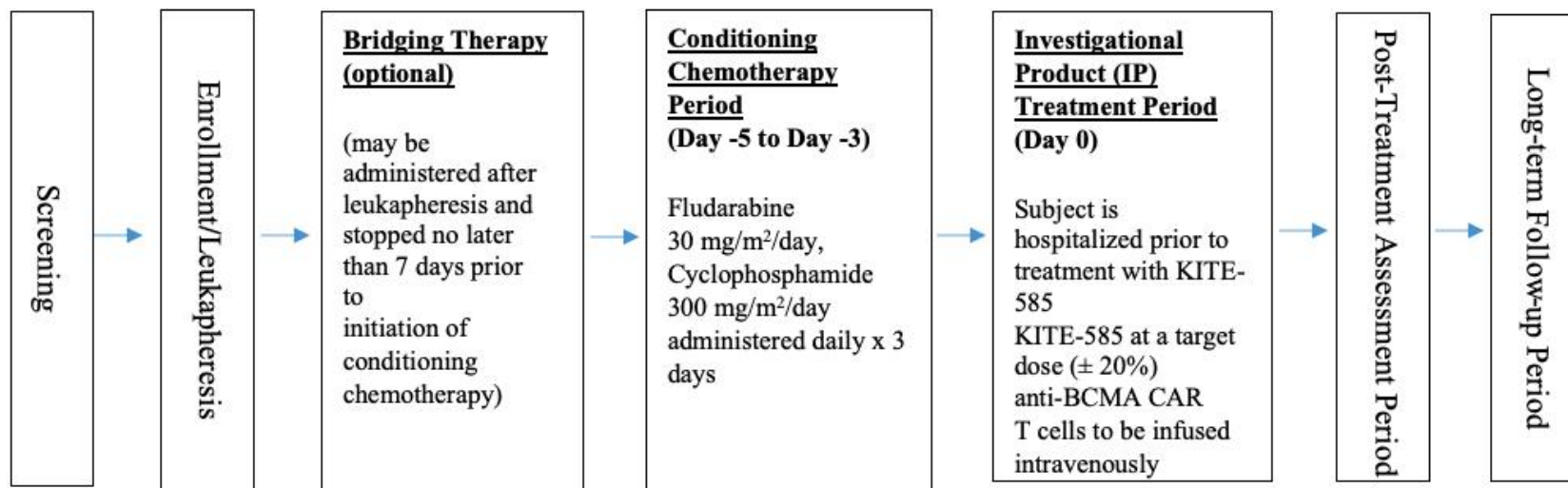
**NCT03318861
IND Number: 17619
Phase 1
FINAL PROTOCOL
KITE-585-501**

Final Protocol Date: 11 September 2017

Original Protocol Date: 27 July 2017

Prepared by: Kite, a Gilead Company, 2225 Colorado Avenue, Santa
Monica, CA 90404

Figure 1. Study Schema



Study KITE-585-501 is a Phase 1, single-arm, open-label, multicenter study evaluating the safety and efficacy of KITE-585, an autologous anti-BCMA CAR T-cell therapy, in subjects with RRMM.

During Phase 1, approximately 6 to 24 subjects with RRMM will be enrolled to evaluate the safety of KITE-585 regimens. Cell dose will be delivered in a single infusion and escalated in a standard 3 + 3 fashion (Section 2.1). **Dose is calculated based on CAR-expressing transduced T cells.** Dosing groups will be as follows with an option to go to a lower dose (Section 2.1, Table 1):

- 3 x 10⁷ anti-BCMA CAR T cells
- 1 x 10⁸ anti-BCMA CAR T cells
- 3 x 10⁸ anti-BCMA CAR T cells
- 1 x 10⁹ anti-BCMA CAR T cells

Upon completion of enrollment and KITE-585 infusion, a safety review team (SRT), internal to the study sponsor and in collaboration with at least 1 study investigator, will review the safety data for each dosing group and will make recommendations on further study conduct as depicted in Table 7, Figure 2, and outlined in Section 8.6. Each subject will follow the same study treatment schedule and procedural requirements. Each subject will follow through the following study periods: a screening period, an enrollment/leukapheresis period, a conditioning chemotherapy period, an IP treatment period, a post-treatment assessment period, and a long-term follow-up period.

Table of Contents

TABLE OF CONTENTS.....	7
LIST OF TABLES.....	10
LIST OF FIGURES.....	11
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS.....	12
1. OBJECTIVES.....	16
1.1. PRIMARY OBJECTIVE.....	16
1.2. SECONDARY OBJECTIVES.....	16
2. STUDY DESIGN.....	16
2.1. GENERAL STUDY DESIGN.....	16
2.2. PARTICIPATING SITES.....	18
2.3. NUMBER OF SUBJECTS.....	18
2.4. REPLACEMENT OF SUBJECTS.....	18
2.5. STUDY DURATION.....	18
2.5.1. STUDY DURATION FOR INDIVIDUAL SUBJECTS.....	18
2.5.2. COMPLETION OF STUDY.....	19
3. SUBJECT SCREENING AND ENROLLMENT.....	19
4. SUBJECT ELIGIBILITY.....	19
4.1. INCLUSION CRITERIA.....	19
4.2. EXCLUSION CRITERIA.....	20
5. PROTOCOL TREATMENT.....	22
5.1. TREATMENT TERMINOLOGY.....	22
5.2. LEUKAPHERESIS.....	23
5.3. BRIDGING THERAPY.....	23
5.4. CONDITIONING CHEMOTHERAPY.....	24
5.4.1. RATIONALE FOR CONDITIONING CHEMOTHERAPY.....	25
5.5. INVESTIGATIONAL PRODUCT KITE-585.....	25
5.5.1. RATIONALE FOR KITE-585 DOSE.....	26
5.6. CONCOMITANT THERAPY.....	27
5.7. EXCLUDED MEDICATIONS.....	28

5.8. SUBSEQUENT THERAPY.....	28
5.9. TOXICITY MANAGEMENT.....	29
6. STUDY PROCEDURES.....	29
6.1. LABORATORY.....	29
6.2. BASELINE DISEASE AND TREATMENT RESPONSE ASSESSMENTS.....	31
6.2.1. DISEASE STAGING.....	31
6.2.2. LOCAL SERUM AND URINE ASSESSMENTS.....	31
6.2.3. BONE MARROW EVALUATIONS.....	31
6.2.4. IMAGING REQUIREMENTS.....	33
6.3. PROCEDURES BY STUDY PERIOD.....	33
6.3.1. SCREENING.....	33
6.3.2. ENROLLMENT/LEUKAPHERESIS.....	36
6.3.3. BRIDGING THERAPY.....	37
6.3.4. CONDITIONING CHEMOTHERAPY.....	38
6.3.5. KITE-585 TREATMENT.....	40
6.3.6. POST-TREATMENT FOLLOW-UP PERIOD.....	44
6.3.7. LONG-TERM FOLLOW-UP PERIOD.....	45
6.4. BIOMARKERS.....	47
7. SUBJECT WITHDRAWAL.....	54
7.1. REASONS FOR REMOVAL FROM TREATMENT.....	54
7.2. REASONS FOR REMOVAL FROM STUDY.....	54
8. SAFETY REPORTING.....	55
8.1. ADVERSE EVENTS.....	55
8.2. REPORTING OF ADVERSE EVENTS.....	56
8.3. DEFINITION OF SERIOUS ADVERSE EVENTS.....	57
8.4. REPORTING OF SERIOUS ADVERSE EVENTS AND NON-SERIOUS \geq GRADE 4 CRS EVENTS, NEUROLOGIC.....	57
8.5. PREGNANCY AND LACTATION.....	58
8.6. SAFETY REVIEW TEAM AND DOSE-LIMITING TOXICITY.....	59
8.6.1. DOSE-LIMITING TOXICITY.....	59
8.6.2. CRITERIA TO PAUSE ENROLLMENT.....	61
9. STATISTICAL CONSIDERATIONS.....	62
9.1. HYPOTHESIS.....	62
9.2. STUDY ENDPOINTS.....	62
9.2.2. SECONDARY.....	62
9.2.3. EXPLORATORY.....	63
9.2.4. COVARIATES.....	63
9.3. HANDLING OF MISSING DATA.....	63
9.4. SAMPLE SIZE CONSIDERATIONS.....	63

9.5. ANALYSIS SUBSETS.....	64
9.6. ACCESS TO INDIVIDUAL SUBJECT TREATMENT ASSIGNMENTS.....	64
9.7. INTERIM ANALYSIS.....	64
9.7.1. SAFETY ANALYSIS.....	64
9.8. PLANNED METHOD OF ANALYSIS.....	64
9.8.1. CLINICAL RESPONSE RATE.....	65
9.8.2. PROGRESSION-FREE SURVIVAL.....	65
9.8.3. OVERALL SURVIVAL.....	65
9.8.4. TIME TO NEXT TREATMENT.....	65
9.8.5. SAFETY ANALYSIS.....	65
9.8.6. LONG-TERM DATA ANALYSIS.....	65
10. REFERENCES.....	66
APPENDIX 1.....	73

LIST OF TABLES

Table 1.	Dosing Cohorts.....	16
Table 2.	Relationship of Cell Dose to Grade ≥ 3 CRS in 2 Anti-BCMA CAR T-cell Studies....	27
Table 3.	Local and Central Laboratory Samples and Analysis.....	30
Table 4.	Schedule of Assessments.....	49
Table 5.	Schedule of Assessment (Long-term Follow-up Period).....	50
Table 6.	Dose-limiting Toxicities.....	59
Table 7.	Recommendations Based on DLTs.....	60

LIST OF FIGURES

Figure 1. Study Schema..... 6
Figure 2. Study Design..... 18

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

<u>Abbreviation/Term</u>	<u>Definition</u>
AE	Adverse event
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BCMA	B-cell maturation antigen
BMMNC	Bone marrow mononuclear cell
KITE-585	Autologous T cells transduced with a lentiviral vector containing anti-BCMA CD28/CD3 zeta chimeric antigen receptor
CAR	Chimeric antigen receptor
CBC	Complete blood count
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of response

<u>Abbreviation/Term</u>	<u>Definition</u>
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
End of study for individual subject	Defined as when the last day that the protocol specified assessments are conducted for an individual subject
End of study (primary completion)	Defined as when the last subject is assessed or received an intervention for the purposes of final collection of data for the primary endpoint at Day 140
End of study (end of trial)	Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments
FAS	Full analysis set
FFPE	Formalin-fixed paraffin embedded block
FISH	Florescent in-situ hybridization
FLC	Free light chain
GCP	Good Clinical Practice
GPI	Glycophosphatidylinositol
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency syndrome
HLH	Hemophagocytic lymphohistiocytosis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IFM	Intergroupe Francophone du Myélome
IFN	Interferon
IHC	Immunohistochemistry
IMiD	Immunomodulatory drug

<u>Abbreviation/Term</u>	<u>Definition</u>
IMWG	International Myeloma Working Group
IP	Investigational product
IPM	Investigational Product Manual
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISS	International Staging System
IV	Intravenous
KITLG	Kit ligand
LDH	Lactate dehydrogenase
LMWH	Low molecular weight heparin
LP	Lumbar puncture
LTFU	Long-term follow-up
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
nCR	Near complete response
NE	Neurologic event
NHL	Non-Hodgkin lymphoma
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET-CT	Positron emission tomography-computed tomography

<u>Abbreviation/Term</u>	<u>Definition</u>
PFS	Progression-free survival
PI	Proteasome inhibitor
PPAS	Per protocol analysis set
PR	Partial response
RCL	Replication-competent lentivirus
RRMM	Relapsed/refractory multiple myeloma
SAE	Serious adverse event
scFv	Single-chain variable fragment
sCR	Stringent complete response
SCT	Stem cell transplant
SIFE	Serum protein immunofixation electrophoresis
SIN	Self-inactivating
SOA	Schedule of assessment
SOC	Standard of care
SPEP	Serum protein electrophoresis
SRT	Safety review team
Study Day 0	Defined as the first day that KITE-585 is administered to the subject
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TTNT	Time to next treatment
UIFE	Urine protein immunofixation electrophoresis
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
WBC	White blood cell

1. OBJECTIVES

1.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of KITE-585 as measured by the incidence of dose-limiting toxicities (DLTs) as outlined in [Section 8.6](#).

1.2. Secondary Objectives

The secondary objective of this study is to gain insight into additional features of safety, tolerability, and efficacy of KITE-585 in subjects with intact (creatinine clearance ≥ 60 mL/min by Cockcroft-Gault estimation) and moderately impaired renal function (creatinine clearance 30-59 mL/min by Cockcroft-Gault), including depth and durability of response, including minimal residual disease (MRD), survival, and toxicity of the regimen.

2. STUDY DESIGN

2.1. General Study Design

KITE-585-501 is a Phase 1, multicenter, open-label study evaluating the safety and tolerability of KITE-585 in subjects with relapsed/refractory multiple myeloma (RRMM).

Approximately 6 to 24 subjects will be enrolled in a standard 3 + 3 dose escalation scheme to evaluate the safety of KITE-585 regimens. Following enrollment and treatment with cyclophosphamide and fludarabine conditioning chemotherapy, subjects will be enrolled into 1 of the following cohorts as outlined in [Table 1](#) at a fixed dose. This dose will be reduced by 33% for subjects weighing ≤ 53 kg. For the first cohort, subjects will be enrolled one by one, with a minimum of 2 weeks between enrollment dates. Safety within each cohort will be assessed for DLTs, and enrollment in each cohort will continue to occur sequentially until a maximum tolerated dose (MTD) is reached (see [Section 8.6](#)).

Table 1. Dosing Cohorts

Dose Level	Total Anti-BCMA CAR T-Cell Dose [†]
-1*	1×10^7
1	3×10^7
2	1×10^8
3	3×10^8
4	1×10^9

*If the incidence of DLTs in Cohort 1 is ≥ 2 of 6 patients treated, the sponsor may, in consultation with the safety review team, choose to decrease to the dose shown for Cohort -1.

[†]Dose is calculated based on CAR-expressing transduced T cells. Subjects weighing less than 53 kg at enrollment will receive a cell dose that is reduced by 33%. See [Section 5.5.1](#) for additional information.

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor.

A safety review team (SRT), internal to the study sponsor and including at least one study investigator, will review the safety data and make recommendations on further study conduct as outlined in [Section 8.6](#).

After a dose level has been determined by the SRT to be tolerable based on the incidence of DLTs (see [Section 8.6.1](#)), the sponsor may, in consultation with the SRT, choose to expand enrollment in the following 2 expansion cohorts to further characterize the risk benefit profile. Enrollment to each cohort may proceed independently of the other.

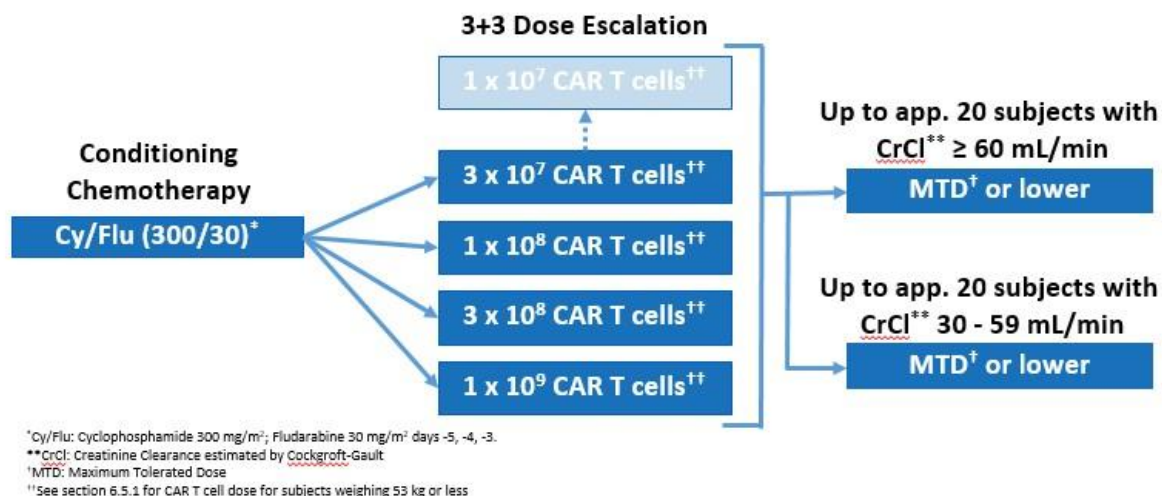
- Expansion Cohort 1: Up to approximately 20 additional subjects with creatinine clearance ≥ 60 mL/min by Cockcroft-Gault estimation.
- Expansion Cohort 2: Up to approximately 20 subjects with moderate renal impairment (creatinine clearance 30 to 59 mL/min [Grade 2 chronic kidney disease]). The first 3 subjects in this expansion cohort will be enrolled with a minimum of 2 weeks between each subject. The SRT will meet to review safety data after the first 6 subjects have been enrolled and have completed the Day 28 visit.

The SRT will review safety data and make recommendations on further study conduct as depicted in [Figure 2](#) and outlined in [Section 8.6](#).

All subjects enrolled in the study will follow the same study treatment schedule and procedural requirements. Each subject will proceed through the following study periods ([Figure 1](#)):

- Screening
- Enrollment/Leukapheresis
- Bridging therapy (at the discretion of the treating investigator)
- Conditioning chemotherapy
- KITE-585 treatment
- Post-treatment assessment
- Long-term follow-up

Figure 2. Study Design



Abbreviations: CAR, chimeric antigen receptor; MTD, maximum tolerated dose. Cell dose is calculated based on CAR-expressing transduced T cells.

For study requirements assigned to each study period, refer to the schedule of assessments (SOAs) and [Section 6](#) for details.

A study schema is provided in the protocol synopsis.

2.2. Participating Sites

Approximately 5 to 15 centers located in North America will participate in this study. During the conduct of the study, additional sites, regions, or countries may be added as necessary.

2.3. Number of Subjects

Participants in this trial will be referred to as “subjects.” It is anticipated that approximately 6 to 64 subjects will be enrolled into this study.

2.4. Replacement of Subjects

Subjects will continue to be enrolled until the specified number of subjects are attained in the DLT evaluable set.

2.5. Study Duration

2.5.1. Study Duration for Individual Subjects

The duration of the study for individual subjects will vary. For a subject who completes the entire protocol from the date of informed consent through the completion of the long-term follow-up period, the duration of the study will take approximately 15 years to complete.

Individual study duration will vary depending on a subject's screening requirements, response to treatment, and survival.

2.5.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or dies (whichever occurs first).

3. SUBJECT SCREENING AND ENROLLMENT

All subjects must sign and date the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved consent form before initiating any study-specific procedures or activities that are not part of a subject's routine care. Refer to [Section 6](#) and the SOA for details.

Each subject who enters the screening period will receive a unique subject identification number before any study-specific procedures or activities are performed. This number will be used to identify the subject throughout the study and must be used on all study documentation related to the subject.

Furthermore, the subject identification number must remain constant throughout the entire clinical study; it must not be changed after enrollment or if the subject is rescreened or retreated. Subjects who fail to meet all eligibility criteria will be allowed to rescreen one time. Only those screening assessments that led to the screen failure need to be repeated, provided that all other screening tests have been completed within the protocol-specified window (eg screening echocardiogram has been performed within 28 days before enrollment).

4. SUBJECT ELIGIBILITY

4.1. Inclusion Criteria

101. Measurable myeloma as defined by the International Myeloma Working Group (IMWG) Consensus Criteria ([Rajkumar et al, 2011](#)), ([Appendix 1](#)):

- Serum and urine markers
 - Serum M-protein ≥ 0.5 g/dL (≥ 5 g/L) or ○ Urine M-protein ≥ 200 mg/24 h
 - or
 - Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal and either:
- Bone marrow aspirate/biopsy demonstrates $\geq 10\%$ clonal plasma cells or
- FDG-avid, biopsy-proven plasmacytoma on positron emission tomography-computed tomography (PET-CT)

102. Progression of multiple myeloma as defined by IMWG Consensus Criteria ([Rajkumar et al, 2011](#)), ([Appendix 1](#)) within 60 days after:

- the last dose of the last line of therapy and following treatment with at least 3 lines of therapy that have included a PI and an IMiD (eg, thalidomide, lenalidomide) at any time during the course of management or
 - the last dose of a regimen that included both a PI and an IMiD, regardless of number of prior lines of therapy
103. Age 18 years or older at the time of informed consent
104. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
105. Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function defined as:
- Absolute neutrophil count (ANC) $\geq 1,000/\mu\text{L}$
 - Platelet count $\geq 75,000/\mu\text{L}$
 - Absolute lymphocyte count $\geq 100/\mu\text{L}$
 - Creatinine clearance (as estimated by Cockcroft-Gault) ≥ 60 mL/min (except in subjects enrolled into the Expansion Cohort 2 evaluating KITE-585 in subjects with moderate renal impairment, in which case the creatinine clearance must be 30 to 59 mL/min)
 - Serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 ULN
 - Total bilirubin ≤ 1.5 mg/dl (subjects with known Gilbert's syndrome who have serum bilirubin $\leq 3.0 \times$ ULN may be enrolled)
 - Cardiac left ventricular ejection fraction $\geq 50\%$ and no evidence of clinically significant pericardial effusion as determined by an echocardiogram (ECHO)
 - No clinically significant electrocardiogram (ECG) findings
 - No clinically significant pleural effusion
 - Baseline oxygen saturation $> 92\%$ on room air
106. Females of childbearing potential must have a negative serum or urine pregnancy test (females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential).

4.2. Exclusion Criteria

201. Presence of $\geq 5\%$ atypical or other cells suspicious for circulating plasma cells detected on screening complete blood count (CBC) with differential that are subsequently confirmed by flow cytometry to be plasma cells
202. Non-secretory multiple myeloma

203. Active or prior history of central nervous system (CNS) or meningeal involvement by malignant plasma cells. (Subjects with calvarial disease that extends intracranially and involves the dura as suggested by magnetic resonance imaging [MRI] will be excluded, even if cerebrospinal fluid [CSF] is negative for myeloma.)
204. Prior BCMA-targeted therapy
205. Prior CAR therapy or other genetically modified T cells
206. Treatment with non-immune directed systemic therapy (eg, PI, IMiD, daratumumab, elotuzumab) within 2 weeks or 5 half-lives, whichever is shorter, before enrollment
207. Treatment with immune-directed systemic therapy (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists) within 3 half-lives before the leukapheresis date
208. Autologous stem cell transplant within 6 weeks before enrollment
209. History of allogeneic stem cell transplantation
210. Treatment with corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs within 7 days before the leukapheresis date
211. Ongoing Grade ≥ 2 toxicities from prior therapies. Subjects with peripheral neuropathy of any grade or clinically non-significant toxicities (eg, alopecia) of any grade may be eligible.
212. History of malignancy other than non-melanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease-free and without anticancer therapy for at least 3 years
213. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides or any other agents used in this study
214. Presence or suspicion of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous (IV) antimicrobials for management
215. Known history of human immunodeficiency syndrome (HIV) infection
216. Known acute or chronic active infection by hepatitis B or hepatitis C virus
217. Active tuberculosis
218. Presence of any indwelling line or drain (eg, percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Dedicated central venous access catheters, such as a Port-a-Cath or Hickman catheter, are permitted.
219. Significant traumatic injury within 3 weeks prior to initiation of conditioning therapy or major surgical procedure within 4 weeks prior to conditioning therapy

220. History or presence of non-malignant CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
221. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac disease within 12 months before enrollment
222. Current or history of clinically significant cardiac amyloid deposition
223. Requirement for urgent therapy due to ongoing or impending oncologic emergency (eg, tumor mass effect, tumor lysis syndrome); focused radiation to prevent or treat pathological fracture is permitted.
224. History of autoimmune disease (eg, Crohn's, rheumatoid arthritis, systemic lupus erythematosus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within 2 years prior to enrollment. Subjects with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and subjects with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.
225. History of symptomatic deep vein thrombosis or pulmonary embolism requiring systemic anticoagulation within 6 months before enrollment
226. Treatment with a live, attenuated vaccine within 6 weeks prior to the planned start of the conditioning chemotherapy or anticipation of need for such a vaccine during the course of the study
227. Women of childbearing potential who are pregnant or breastfeeding
228. Subjects of either sex who are not willing to practice birth control from the time of consent through 6 months following KITE-585 infusion
229. Any medical or psychiatric condition likely to interfere with assessment of safety or efficacy of study treatment
230. In the investigator's judgment, the subject is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.

5. PROTOCOL TREATMENT

If, at any time following screening and before KITE-585 infusion, there is concern for infection or other acute inflammatory process as suggested by the clinical findings detailed in [Sections 6.3.2.1, 6.3.4.1, and 6.3.5.1](#), the Kite medical monitor should be contacted, and treatment may need to be delayed until additional workup can be performed and/or the abnormalities return to normal.

5.1. Treatment Terminology

The following terms will be used to describe and define protocol treatment:

- Leukapheresis refers to the procedure for collection of peripheral blood mononuclear cells (PBMCs) used to manufacture the subject-specific KITE-585 treatment.
- Bridging therapy refers to the treatment used to control the subject's disease after enrollment/leukapheresis and up to 7 days prior to conditioning chemotherapy.
- Conditioning chemotherapy refers to fludarabine and cyclophosphamide used for lymphodepletion prior to administration of KITE-585.
- The investigational product is named KITE-585.
- Concomitant medication refers to treatment that subject receives during the conduct of the study.
- Excluded medications refers to treatment that is not to be administered, unless otherwise specified during the conduct of the study.
- Subsequent therapy refers to treatment administered after KITE-585 or standard of care (SOC) necessary to treat a subject's disease.

5.2. Leukapheresis

Subjects will undergo leukapheresis to obtain T cells for the manufacturing of KITE-585 as described in in the KITE-585 IB. Leukapheresed cells obtained at participating centers will be shipped to the Kite manufacturing facility as described in the Investigational Product Manual (IPM).

See [Section 5.7](#) for excluded medications prior to leukapheresis.

Before leukapheresis commences, the criteria outlined in [Section 6.3.2.1](#) must be met.

After KITE-585 has been manufactured and has passed release criteria, it will be shipped to the treating facility and must be stored per the IPM (see [Section 5.5](#)).

5.3. Bridging Therapy

Subjects may be treated with bridging therapy after leukapheresis and prior to conditioning chemotherapy at the investigator's discretion as follows:

- Priority should be given to the least myelosuppressive regimen deemed appropriate with any necessary dose reductions for baseline cytopenias. Preferred examples include:
 - Single agent dexamethasone
 - Bortezomib/dexamethasone
 - Carfilzomib/dexamethasone
- If a cytotoxic regimen is required, potent myelotoxic regimens or high doses of chemotherapy should be avoided. Examples of low-dose chemotherapy-based regimens include:

- Dexamethasone 6 mg PO every other day (or other equivalent corticosteroid) plus cyclophosphamide 50 mg PO daily
- Bendamustine 60 or 70 mg/m² on days 1 and 2 of a 28 day cycle with or without lenalidomide 15 mg given 21/28 days
- Regardless of the choice of bridging regimen, all organ and marrow functional parameters listed in inclusion criterion 105 must be met prior to conditioning chemotherapy, and all toxicities related to bridging must return to Grade ≤ 1 or baseline prior to initiation of conditioning chemotherapy.

Study subjects who receive bridging therapy and subsequently develop evidence of new onset cardiac dysfunction including chest pain, shortness of breath, peripheral edema, or other signs and symptoms will undergo an echocardiogram prior to initiation of **conditioning chemotherapy to ensure cardiac inclusion/exclusion criteria continue to be met.**

The following therapies are not allowed for bridging therapy:

- Immune checkpoint inhibitors or immune stimulating agents (eg, those listed in exclusion criterion 207)
- Daratumumab or other CD38-directed therapy
- Elotuzumab or other CS1-directed therapy
- Experimental treatments See [Section 5.3.3](#) for details.

Bridging therapy should be administered per institutional guidelines. The current product label should be referenced for guidance on packaging, storage, preparation, administration, including necessary dose reductions for organ dysfunction, and toxicity management associated with the administration of chemotherapy agents.

5.4. Conditioning Chemotherapy

All subjects with significant malignancy burden and without a contraindication such as medication allergy should be started on prophylaxis for tumor lysis syndrome (eg, allopurinol) as per institutional guidelines prior to initiation of condition chemotherapy. Prophylaxis should be discontinued when the risk of tumor lysis has passed.

Conditioning chemotherapy consisting of fludarabine and cyclophosphamide will be supplied by the investigative site unless otherwise noted.

Fludarabine phosphate is a synthetic purine nucleoside that differs from physiologic nucleosides in that the sugar moiety is arabinose instead of ribose or deoxyribose. Fludarabine is a purine antagonist antimetabolite.

Cyclophosphamide is a nitrogen mustard-derivative alkylating agent. Following conversion to active metabolites in the liver, cyclophosphamide functions as an alkylating agent; the drug also possesses potent immunosuppressive activity. The serum half-life after IV administration ranges

from 3 to 12 hours; the drug and/or its metabolites can be detected in the serum for up to 72 hours after administration.

Mesna is a detoxifying agent used to inhibit the hemorrhagic cystitis induced by chemotherapy. The active ingredient mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$. Mesna should be administered to subjects at route, dose, and schedule commensurate with conditioning cyclophosphamide dose per institutional guidelines.

5.4.1. Rationale for Conditioning Chemotherapy

Increasing levels of conditioning chemotherapy correlates with clinical responses to adoptive cell therapy (Dudley et al, 2008). Specifically, there appears to be a link between adequate lymphodepletion and adoptively transferred T-cell expansion and function in preclinical models. The depth and duration of the lymphodepletion in preclinical models correlate with anti-tumor activity of the adoptively transferred tumor-specific CD8⁺ T cells (Gattinoni et al, 2005). Lymphodepletion may function by eradicating cytokine sinks for the transferred cells, eliminating T regulatory cells, or enhancing antigen presenting cell activation (Klebanoff et al, 2005). Cyclophosphamide and fludarabine is a potent lymphodepleting regimen and has been shown to lead to an increase in serum interleukin (IL)-15 concentration, which has been correlated with objective responses following treatment of lymphoma with anti-CD19 CAR T cells (Kochenderfer et al, 2017).

The conditioning chemotherapy dose will be cyclophosphamide (300 mg/m²) and fludarabine (30 mg/m²) both given for 3 concurrent days. Cyclophosphamide (500 mg/m²) and fludarabine (30 mg/m²) both given for 3 concurrent days has been studied and tolerated in subjects with B-cell malignancies (O'Brien et al, 2001). This regimen has been evaluated in the NHL studies at Kite and has not caused undue toxicity in subjects with heavily pretreated and treatment-refractory NHL. See Section 1.1 for dose adjustments in subjects with renal dysfunction. Additional regimens of conditioning chemotherapy may be explored at the recommendation of the SRT.

5.5. Investigational Product KITE-585

This section contains general information and is not intended to provide specific instructions. Refer to the IPM for details and instruction on storage, thawing, and administration of KITE-585. KITE-585 is supplied cryopreserved in cryostorage bags. The product in the bag is clear to opaque, with white to red including shades of white, light yellow, and orange. The cryostorage bag(s) containing KITE-585 arrive cryopreserved in a liquid nitrogen dry shipper. The bag(s) must be stored in the vapor phase of a liquid nitrogen, and the product must remain frozen until the subject is ready for treatment to assure viable autologous cells are administered to the subject. Several inactive ingredients are added to the product to assure viability and stability of the live cells through the freezing, thawing, and infusion process.

KITE-585 is a subject-specific product and the intended subject will be identified by a unique subject ID number. Upon receipt, verification that the product and subject-specific labels match the subject's information (eg, initials, subject ID number) is essential. Do not infuse the product if the information on the subject-specific label does not match the intended subject or if the label is missing or illegible. The volume of KITE-585 infused, the thaw start/stop time, and KITE-

585 administration start/stop time will all be noted in the subject medical record. The product must not be thawed until the subject is ready for the infusion.

In case of accidental overdose, treatment should be supportive. Corticosteroid therapy may be considered if any dose is associated with severe toxicity. Refer to the current KITE-585 IB for details on the management of important risks associated with KITE-585.

If any problems related to the use of KITE-585 or to any products that support the successful delivery and infusion of KITE-585 (eg, cryostorage bags, subject identification labels) in this study are identified, refer to the instructions in the IPM for further information on reporting.

5.5.1. Rationale for KITE-585 Dose

In this first-in-human study, the dose escalation portion of the trial is designed to test different doses of KITE-585 in subjects with RRMM. This will be conducted in a dose-escalating schema as laid out in the protocol synopsis, [Figure 2](#), and further discussed in [Sections 2.1](#) and [8.6](#).

Given the absence of suitable animal toxicology models, the starting dose was selected based on experience with anti-CD19 CAR T cells and publicly available information from other anti-BCMA CAR studies. In the former, activity is observed in subjects as measured by CAR T-cell related toxicity (eg, CRS) and efficacy at CAR T-cell doses as low as 2 to 5 x 10⁵ CAR T cells/kg (1.6 to 4.0 x 10⁷ total CAR T cells for a 80 kg subject) in a variety of malignancies, patient populations, and tumor burdens ([Lee et al, 2015](#); [Turtle et al, 2016](#); [Turtle et al, 2016](#); [Locke et al, 2017](#)). However, in most multicenter studies of anti-CD19 CAR T cells, including in all Kite-sponsored anti-CD19 CAR T-cell studies using a CAR construct with CD28 and CD3ζ signaling domains similar to those used in KITE-585, cell doses of 1 x 10⁶ or 2 x 10⁶ per kg have been carried forward as the target dose. These weight-based cell doses equate to total CAR T-cell doses ranging from 5 to 10 x 10⁷ total CAR T cells in a 50 kg subject to 1 to 2 x 10⁸ total CAR T cells in a 100 kg subject.

In the case of anti-BCMA CAR T cells studied at the NCI, very little toxicity attributable to anti-BCMA CAR T cells was seen in patients treated at the 0.3 x 10⁶ CAR T cells/kg dose level. At the 1 x 10⁶ CAR T cells/kg dose level, 2 of 3 patients treated had mild signs and symptoms of CRS including mild fever and sinus tachycardia. Severe CRS and neurological events (NE) were not observed until dose level 3 (3 x 10⁶ CAR T cells/kg; [Table 2](#); [Ali et al, 2016](#)).

Moreover, in another study of anti-BMCA CAR T cells, Grade ≥ 3 CRS was observed in 1/9 (11%) of subjects treated with dose level 3 (45 x 10⁷ CAR T cells) and 1/3 (33%) of subjects treated with dose level 4 (80 x 10⁷ CAR T cells, [Table 2](#) [[Berdeja et al, 2017](#)]). The planned starting dose of KITE-585 of 3 x 10⁷ anti-BCMA CAR T cells is, therefore, > 20-fold lower than the dose at which either Ali, et al., or Berdeja et al., observed ≥ 33% Grade 3 or higher CRS and, thus, is unlikely to cause severe toxicity.

Table 2. Relationship of Cell Dose to Grade ≥ 3 CRS in 2 Anti-BCMA CAR T-cell Studies

	Target Cell Dose	Cell Dose in 80 kg Subject	Grade ≥ 3 CRS (%)
Study # 1 Ali et al. (NCT# 02215967)	0.3 x 10 ⁶ /kg	2.4 x 10 ⁷	0/3 (0%)
	1 x 10 ⁶ /kg	8 x 10 ⁷	0/3 (0%)
	3 x 10 ⁶ /kg	2.4 x 10 ⁸	1/4 (25%)
	9 x 10 ⁶ /kg	7.2 x 10 ⁸	2/2 (100%)
Study #2 Berdeja et al. (NCT# 02658929)	5 x 10 ⁷	5 x 10 ⁷	0/3 (0%)
	15 x 10 ⁷	15 x 10 ⁷	0/3 (0%)
	45 x 10 ⁷	45 x 10 ⁷	1/9 (11%)
	80 x 10 ⁷	80 x 10 ⁷	1/3 (33%)

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

The dose escalation schema described in [Figure 2](#) calls for a 3-fold increase between dose cohorts, similar to the dose escalation schema used by Ali and Berdeja ([Ali et al, 2016](#); [Berdeja et al, 2017](#)). As an additional precaution against overdosing subjects of low body weight with a relatively high flat dose of KITE-585, a low-dose tier and escalation schema was created using a cutoff of 150% of the KITE-585 cell dose, normalized to body weight, which corresponds to 50% of the planned dose step-up between cohorts during dose escalation. In the Kite database of subjects treated with refractory aggressive NHL in ZUMA-1, the median subject weight was 80 kg (Kite Pharma data on file). Similarly, in the Phase 1 dose-escalation study of daratumumab in RRMM, the median subject body weight was 80.5 kg ([Lokhorst et al, 2015](#)). Using 80 kg as the assumed body weight of KITE-585-501 participants, a subject weighing 53 kg would receive 150% of the cell dose per kg of body weight compared to a subject who weighs 80 kg. Therefore, to prevent overdose, each cell dose in the escalation schema will be reduced by 33% for subjects weighing less than 53 kg (see [Section 2.1](#) for dose details). **Finally, subject weight at leukapheresis will be examined as a covariate of safety and efficacy outcomes.**

5.6. Concomitant Therapy

Investigators may prescribe any concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support (eg, G-CSF) and routine anti-emetic prophylaxis except those medications listed in the excluded medication [Section 5.7](#). For subjects who received KITE-585, all concurrent therapies, including medications, intubation, dialysis, oxygen, and blood products, should be recorded in the case report form (CRF) as follows:

- At screening (informed consent through enrollment): ongoing concomitant medications (this should include all medications being taken, including prescription and over-the-counter drugs, dietary supplements, and homeopathic or naturopathic remedies) and

concomitant medications associated with any SAEs (see [Section 8.4](#) for SAE reporting requirements)

- Enrollment through Month 3: All concomitant medications
- After Month 3 through 24 months after KITE-585 or progressive disease (PD), whichever occurs first:
 - All targeted concomitant medications in the category of gammaglobulin, immunosuppressive drugs, anti-infective drugs, and vaccinations
 - All concomitant medications associated with targeted AEs and targeted SAEs (see [Sections 8.2](#) and [8.4](#))
- After Month 3 through the end of study: All concomitant medications associated with KITE-585 related Grade 5 AEs

For subjects who are enrolled, but not dosed with KITE-585, concurrent therapies will only be recorded from the date of the informed consent through 30 days after the last study specific procedure (eg, leukapheresis, conditioning chemotherapy).

For subjects who are not enrolled (eg, screen failure or who do not undergo leukapheresis), only concurrent therapies related to any SAE(s) will be recorded.

Specific concomitant medication collection requirements and instructions are included in the CRF completion guidelines.

5.7. Excluded Medications

Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 7 days prior to KITE-585 administration.

Systemic corticosteroids may not be administered as premedication to subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance). Such subjects should undergo non-contrast CT scans instead.

Corticosteroids and other immunosuppressive drugs should also be avoided for 3 months after KITE-585 administration unless used to manage KITE-585 related toxicities. Other medications that might interfere with the evaluation of KITE-585, such as non-steroidal anti-inflammatory agents, should also be avoided for the same period unless medically necessary.

Treatment for MM, such as chemotherapy, immunotherapy, targeted agents, radiation, and high dose corticosteroid, other than defined/allowed in this protocol and other investigational agents are prohibited, except as needed for treatment of disease progression after KITE-585.

If permissibility of a specific medication/treatment is in question, contact the Kite Pharma medical monitor. Refer to the KITE-585 IB for additional information about excluded medications.

5.8. Subsequent Therapy

Subsequent therapy administered after KITE-585 necessary to treat a subject's disease, such as non-study specified chemotherapy, immunotherapy, targeted agents, stem cell transplant, and

radiation therapy will be recorded until the subject completes the long-term follow up period, is considered lost to follow up, withdraws consent, or dies (whichever occurs first).

5.9. Toxicity Management

The following potential risks of KITE-585 are based on observations made in other clinical trials with therapies similar to KITE-585 and in clinical trials with anti-CD19 CAR T cells conducted by Kite Pharma:

- CRS
- Neurologic events
- Infections
- Cytopenias

Details of CRS grading and management are found in Section 6.4, Tables 5 and 6 of the KITE-585 IB, version 2.1. As the safety experience with KITE-585 increases, the management guidance for CRS and other potential risks may be updated. Therefore, it is important that the most current version of the KITE-585 IB is consulted for guidance regarding management of KITE-585-related toxicities.

6. STUDY PROCEDURES

Research staff should refer to the SOAs ([Table 4](#) and [Table 5](#)) for an outline of the procedures required.

The visit schedule is calculated from KITE-585 infusion. The KITE-585 infusion is designated as Day 0.

An overview of study assessments/procedures is outlined below. A description for each period of the study is provided in [Section 6.3](#).

Refer to the CRF completion guidelines for data collection requirements and documentation of study procedures.

6.1. Laboratory

The samples listed in [Table 3](#) will be collected at the time points indicated in the SOA. Additional samples (eg, blood, urine, CSF, tissue) may be collected as needed for further safety testing.

Table 3. Local and Central Laboratory Samples and Analysis

Local Laboratory Samples and Analysis			Central Laboratory Samples and Analysis
Chemistry	Hematology	Other	
<ul style="list-style-type: none"> • Sodium • Potassium • Chloride • Total CO₂ (bicarbonate) • Creatinine • Glucose • Calcium total • Total bilirubin • ALT/GPT • AST/GOT 	Complete blood count with differential (differentials include neutrophils, monocytes, lymphocytes)	<ul style="list-style-type: none"> • C-reactive protein (CRP) • Urine or serum β-HCG pregnancy test (for women of childbearing potential) • Serum: <ul style="list-style-type: none"> ○ Serum quantitative immunoglobulins ○ Serum free light chains (FLC) ○ Serum protein electrophoresis (SPEP) <ul style="list-style-type: none"> ○ Serum protein immunofixation electrophoresis (SIFE) 	<ul style="list-style-type: none"> • PBMC, including lymphocyte subsets, RCL, and antiBCMA CAR T-cell levels • Cytokine levels • Anti-KITE-585 antibodies • Tumor tissue from bone marrow aspirate and biopsy • Soluble BCMA • CSF
Local Laboratory Samples and Analysis			Central Laboratory Samples and Analysis
Chemistry	Hematology	Other	
Recommended: <ul style="list-style-type: none"> • Blood urea nitrogen (BUN) • Magnesium total • Alkaline phosphatase • Direct bilirubin • LDH • Uric acid • Inorganic phosphorus • Albumin 		<ul style="list-style-type: none"> • Urine (based on a 24-hour collection): <ul style="list-style-type: none"> ○ Total protein ○ Urine protein electrophoresis (UPEP) <ul style="list-style-type: none"> ○ Urine protein immunofixation electrophoresis (UIFE) • CSF • Recommended, see Section 6.3.5.5: <ul style="list-style-type: none"> ○ Ferritin ○ Lactate 	

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ALT, alanine aminotransferase; GPT, glutamic pyruvic transaminase; AST, aspartate aminotransferase; GOT, glutamic oxaloacetic transaminase; LDH, lactate dehydrogenase; HCG, human chorionic gonadotropin; RCL, replication-competent lentivirus; CSF, cerebrospinal fluid; PBMC, peripheral blood mononuclear cell.

6.2. Baseline Disease and Treatment Response Assessments

6.2.1. Disease Staging

Disease stage per International Staging System (ISS) will be performed at study entry ([Palumbo et al, 2015](#)). Serum LDH and beta-2 microglobulin will be collected.

6.2.2. Local Serum and Urine Assessments

The following samples will be collected at the time points indicated in the SOA and analyzed locally to measure disease activity. These assessments will continue until the subject has PD, withdraws from the study, is lost to follow up, or dies.

- Serum:
 - Serum quantitative immunoglobulins
 - Serum FLC
 - Serum protein electrophoresis (SPEP)
 - Serum protein immunofixation electrophoresis (SIFE)
- Urine (based on a 24-hour collection):
 - Total protein
 - Urine protein electrophoresis (UPEP)
 - Urine protein immunofixation electrophoresis (UIFE)

6.2.3. Bone Marrow Evaluations

Disease assessments will be evaluated locally per the IMWG Consensus Panel 1 ([Rajkumar et al, 2011](#)).

6.2.3.1. Screening Assessments

For all subjects, a screening bone marrow aspirate and biopsy will be performed within 14 days before enrollment and analyzed locally for:

- the following loci by FISH:
 - t(4;14)
 - t(14;16)
 - del17p13
 - del13q
- % plasma cells by flow cytometry
- MRD by flow cytometry or polymerase chain reaction (PCR) (if performed per SOC)

If enrollment is delayed, then a repeat bone marrow biopsy and aspirate will be required to ensure baseline bone marrow is performed within 14 days before leukapheresis.

6.2.3.2. On-study Assessments

For all subjects, a bone marrow aspirate and biopsy will be performed according to the SOA until PD, withdrawal of consent, lost to follow-up, or death (whichever occurs first):

- Week 2
- Week 4
- Month 3
- After Month 3, per SOC
- If serum/urine biomarkers indicate CR, bone marrow will be collected to confirm CR per the IMWG criteria.
- If serum/urine biomarkers indicate PD, bone marrow will be collected at the time of PD and prior to starting subsequent anticancer therapy.

The bone marrow samples will be analyzed locally for % plasma cells by flow per SOC.

6.2.3.3. Bone Marrow Aspirate and Biopsy Samples for Central Laboratory Analysis

At all bone marrow evaluation time points listed in the SOA, a portion of the bone marrow aspirate and biopsy will be prepared per the central laboratory manual and submitted to the central laboratory for evaluation. MRD and other biomarkers per [Section 6.4](#) will be assessed centrally on these samples.

Below is an example of the sample types that will be required:

- Samples from bone marrow aspirate:
 - MRD
 - Bone marrow mononuclear cells (BMMNC)
 - Bone marrow aspirate clot
- Samples from bone marrow biopsy prepared per your institution's standard practice:
 - Formalin-fixed paraffin embedded block (FFPE) or
 - Core biopsy fixed in formalin or
 - Up to 20 unstained slides

See the central laboratory manual for details regarding sample collection, processing, and shipment requirements.

6.2.4. Imaging Requirements

All subjects will have baseline images performed to establish a baseline for later comparison and/or confirm presence of extramedullary disease (including soft tissue plasmacytomas).

- Screening (all subjects)
 - MRI brain will be performed ≤ 28 days before enrollment to rule out CNS MM and establish a pre-treatment anatomic baseline to be used as a comparison to scans that may be obtained during treatment (eg, during evaluation of neurologic events).
 - PET CT of the neck, chest, abdomen, and pelvis will be performed after the last therapy received for MM and ≤ 14 days before enrollment.
 - If the screening PET-CT was positive or suspicious for extramedullary disease and the scans are ≥ 28 days before start of conditioning chemotherapy, then the PET-CT scans will be repeated ≤ 28 days before start of conditioning chemotherapy. Note: If subject receives bridging therapy, then the PET-CT will be repeated after the end of the bridging therapy and before the start of conditioning chemotherapy.
- On-study
 - For subjects with baseline extramedullary disease, a PET-CT of the neck, chest, abdomen, and pelvis will be performed at the time points indicated in the SOA until PD or start of new anticancer therapy for MM, whichever occurs first.
 - For subjects without baseline extramedullary disease, a PET-CT of the neck, chest, abdomen, and pelvis will be performed if there is suspicion of new extramedullary disease.

6.3. Procedures by Study Period

Investigative sites will maintain a written log of all screened subjects who were reviewed and evaluated for study participation. Information collected on the screening log should include limited information, such as the date of screening, date the subject was enrolled, or the reason for why the subject failed screening.

6.3.1. Screening

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and the potential risks.

The consent process and the subject's agreement or refusal to participate in the study is to be documented in the subject's medical records. If the subject agrees to participate, the informed consent form (ICF) is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF will be retained in

accordance with institution policy and IRB/IEC requirements with a copy of the ICF provided to the subject.

All subjects who are enrolled into the study should be re-consented with any updated version of the IRB/IEC approved ICF if relevant to their participation in the study.

The screening period begins on the date the subject signs the IRB/IEC approved ICF and continues through enrollment, which occurs at the beginning of leukapheresis. Subjects should sign the most current IRB/IEC approved ICF prior to any study-specific activity or procedure is performed. Procedures that are part of SOC are not considered study-specific procedures and may be performed prior to obtaining consent and used to confirm eligibility provided they are performed within the screening windows as indicated in the SOA.

Demographic data will be collected as per country and local regulations and guidelines. Where applicable, demographic data will include sex, date of birth, race, ethnicity, and country of enrollment to study their possible association with subject safety and treatment effectiveness. After written informed consent has been obtained, subjects will be screened to confirm study eligibility and participation. Only subjects who meet the eligibility criteria listed in [Section 4](#) and who commence leukapheresis will be considered enrolled into the study. If, at any time prior to enrollment, the subject fails to meet the eligibility criteria, the subject should be designated as a screen failure on the subject screening log with the reasons for failing screening. The following assessments/procedures are to be completed during the screening period as outlined in the SOA:

- Medical history
 - Relevant medical history prior to the start of AE reporting (see [Section 8.2](#) and [8.4](#)) will be collected. Relevant medical history is defined as data on the subject's concurrent medical condition dating back to the subject's original diagnosis that would typically be shared in a referral letter as well as history related to the subject's disease, treatment, and response to treatment.
 - For subjects who are being referred from another clinic or institution to the participating research center, copies from the subjects chart should be obtained.
 - All findings will be recorded in the CRFs.
- Physical examination including height and weight
- Vital signs, including blood pressure, heart rate, oxygen saturation on room air, and temperature
- ECOG performance status
- Neurological exam: A bedside neurologic examination will be performed with any abnormalities of the following recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion).
- ECG
- ECHO: will be performed following the subject's last chemotherapy treatment and ≤ 28 days prior to signing the consent may be used for confirmation of eligibility.
- Disease assessment:
 - Local serum and 24-hour urine (see [Section 6.2.2](#))
 - Local and central bone marrow aspirate and biopsy (see [Section 6.2.3](#))
 - Imaging Studies – PET-CT and brain MRI (see [Section 6.2.4](#))
 - *Optional*: For subjects who sign the optional portion of the consent, a plasmacytoma biopsy will be taken and sent for central analysis.
- MRI brain (see [Section 6.2.4](#))
- Local labs
 - β -Human chorionic gonadotropin (HCG) pregnancy test (serum or urine) on all women of childbearing potential

- Lumbar puncture for collection of CSF to rule out presence of plasma cells if MRI brain is suspicious for CNS involvement of MM; if a lumbar puncture (LP) is performed for this reason, then opening pressure should also be measured.
- Chemistry panel
- CBC with differential SAE reporting (refer to [Section 8](#) for safety reporting guidelines)
- Concomitant medications documentation (see [Section 5.6](#)) and previous cancer treatment history

6.3.2. Enrollment/Leukapheresis

6.3.2.1. Pre-leukapheresis Criteria

Before leukapheresis commences, the following criteria must be met:

- In general, all eligibility criteria confirmed during screening must not be known to be violated prior to leukapheresis. Additionally, the investigator must review and confirm that the last CBC with differential and chemistry panel drawn prior to the start of leukapheresis must meet the eligibility criteria detailed in Inclusion criterion 105. If any screening assessments or procedures are repeated between screening and the start of leukapheresis and results are outside the eligibility criteria ([Section 4](#)), contact the Kite medical monitor before proceeding with leukapheresis.
- Subjects must have no evidence or suspicion of infection prior to leukapheresis. Should a subject have an infection immediately prior to leukapheresis, cell collection must be delayed until the event resolves. If leukapheresis is delayed beyond 5 days, a CBC with differential and chemistry panel must be repeated to confirm they meet the eligibility criteria detailed in Inclusion criterion 105.
- Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis.

6.3.2.2. Enrollment/Leukapheresis Procedures

The following procedures/requirements will occur on the leukapheresis collection day (enrollment) as outlined in the SOA:

- Weight – this weight is used to determine the KITE-585 dose
- Vital signs, including blood pressure, heart rate, oxygen saturation on room air, and temperature
- Local labs (to be drawn prior to leukapheresis)

- Chemistry
- CBC with differential
- CRP
- Central labs (to be drawn prior to leukapheresis)
 - Anti-KITE-585 antibodies
 - PBMCs
 - Cytokine levels

Leukapheresis (see [Section 5.2](#) and [6.3.2](#))

- After the pre-leukapheresis criteria are met (see [Section 6.3.2.1](#)), mononuclear cells will be obtained by leukapheresis (12 to 15 liter apheresis with a goal to target approximately 5 to 10 x 10⁹ mononuclear cells). The leukapheresed cells are then packaged for expedited shipment to the manufacturing facility as described in the IPM.
- AE/SAE reporting (see [Section 8](#))
- Concomitant medications documentation (see [Section 5.6](#))

6.3.3. Bridging Therapy

Subjects may receive bridging therapy at the discretion of the treating investigator (see [Section 5.3](#) for details).

6.3.3.1. Bridging Therapy Administration

Bridging therapy may be administered after leukapheresis but must be stopped no later than 7 days prior to initiation of conditioning chemotherapy.

6.3.3.2. Bridging Therapy Procedures

The following procedures will occur after the completion of bridging therapy and prior to conditioning chemotherapy as outlined in the SOA.

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- **For subjects with new-onset cardiac symptoms only: Repeat echocardiogram**
- Disease assessment:
 - Local serum and 24-hour urine (see [Section 6.2.2](#))

- Local and central bone marrow aspirate and biopsy (see [Section 6.2.3](#))
- PET-CT if screening PET was positive for extramedullary disease (see [Section 6.2.4](#))
- Local labs
 - Chemistry panel
 - CBC with differential

6.3.4. Conditioning Chemotherapy

6.3.4.1. Pre-conditioning Chemotherapy Administration Criteria

Before conditioning chemotherapy commences, the following criteria must be met. If these criteria are not met, then conditioning chemotherapy must be delayed until these events resolve.

- No evidence or suspicion of infection
- No clinically significant cardiac dysfunction
- Creatinine clearance above limits set in eligibility criteria (see [Section 4](#))
- No acute neurological toxicity > Grade 1 (with the exception of peripheral neuropathy)
- If subject received bridging therapy, all organ and marrow functional parameters listed in inclusion criterion 105 must be met prior to conditioning chemotherapy, and all toxicities related to bridging must return to Grade \leq 1 or baseline prior to initiation of conditioning chemotherapy.

In addition, if any of the following are known to occur, a delay in conditioning chemotherapy may be required. Contact the Kite medical monitor before conditioning chemotherapy commences for guidance.

- White blood cell (WBC) count of $\geq 20,000/\mu\text{L}$ within 48 hours prior to conditioning chemotherapy
- CRP is ≥ 100 mg/L
- Temperature is $\geq 38.0^\circ\text{C}$ within 48 hours prior to conditioning chemotherapy. Unexplained fever requires pan-culture, respiratory viral panel, chest CT, and any additional symptom-directed workup to rule out occult infection.
- If any screening assessments or procedures are repeated between enrollment and the start of conditioning chemotherapy, and results are outside the eligibility criteria ([Section 4](#))

6.3.4.2. Conditioning Chemotherapy Administration (Days -5 through -3 Before Infusion of KITE-585)

Fludarabine and cyclophosphamide should be administered per institutional guidelines. Refer to the current product label for guidance on packaging, storage, preparation, administration, and toxicity management associated with the administration of chemotherapy agents.

Before conditioning chemotherapy commences, the criteria outlined in [Section 6.3.4.1](#) must be met.

Provided the criteria for conditioning chemotherapy are met, the 3-day conditioning regimen of fludarabine and cyclophosphamide will be administered in accordance with the following daily dosing instructions.

- IV hydration with 1 L of isotonic crystalloid given prior to cyclophosphamide on the day of infusion followed by:
- **Cyclophosphamide 300 mg/m² IV over 60 minutes**
 - An additional 1 L of isotonic crystalloid at the completion of the cyclophosphamide infusion
 - Add mesna per institutional guidelines
- Fludarabine 30 mg/m² IV (or, in the case of subjects with moderate renal impairment, 24 mg/m²; see [Section 6.3.4.2.1](#)) over 30 minutes

Subjects should be instructed to drink plenty of liquids during and for 24 hours following the chemotherapy (approximately 2 liters/24 hours). In general, subjects should be kept well hydrated but closely monitored to prevent fluid overload.

6.3.4.2.1. Dose Reduction for Renal Dysfunction

Dose reduction of fludarabine by 20% should be performed in subjects enrolled into Expansion Cohort 2 in accordance with standard practice and the fludarabine product label. Therefore, the 3-day conditioning regimen of fludarabine and cyclophosphamide will be administered to subjects with creatinine clearance between 30 and 59 mL/min in accordance with the following daily dosing instructions.

- IV hydration with 1 L of isotonic crystalloid given prior to cyclophosphamide on the day of infusion followed by:
 - **Cyclophosphamide 300 mg/m² IV over 60 minutes**
 - An additional 1 L of isotonic crystalloid at the completion of the cyclophosphamide infusion
 - Add mesna per institutional guidelines
 - Fludarabine 24 mg/m² IV over 30 minutes

Subjects with renal dysfunction should be adequately hydrated, but should be monitored closely for signs and symptoms of volume overload.

6.3.4.3. Conditioning Chemotherapy Procedures

The following procedures/requirements will occur during the conditioning chemotherapy period as outlined in the SOA:

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Local labs (to be drawn prior to chemotherapy)
 - Chemistry panel
 - CBC with differential
- Fludarabine and cyclophosphamide chemotherapy (see [Section 5.4](#) and [6.3.4](#))
 - After the pre-conditioning chemotherapy are met (see [Section 6.3.4.1](#)), subjects will receive conditioning chemotherapy over 3 days (Day -5 through Day -3) in an outpatient setting, followed by 2 days of rest (see [Section 6.3.4.2](#)), and KITE-585 on Day 0 (see [Section 6.3.5](#)).
- AE/SAE reporting (see [Section 8](#))
- Concomitant medications documentation (see [Section 5.6](#))

6.3.5. KITE-585 Treatment

6.3.5.1. Pre-KITE-585 Administration Criteria

Before KITE-585 infusion commences, the following criteria must be met. If these criteria are not met, then KITE-585 infusion must be delayed until these events resolve.

- No evidence or suspicion of infection. Subject must not be receiving systemic anti-microbials for the treatment of an active infection within 48 hours prior to KITE-585 infusion (prophylactic use of anti-microbials is allowed).
- No clinically significant cardiac dysfunction
- Creatinine clearance above limits set in eligibility criteria (see [Section 4](#))
- No acute neurological toxicity > Grade 1 (with the exception of peripheral neuropathy)
- Corticosteroid therapy at a pharmacologic dose (≥ 5 mg/day of prednisone or equivalent doses of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to KITE-585 administration.

In addition, if any of the following are known to occur, the KITE-585 infusion may need to be delayed. Contact the Kite medical monitor before KITE-585 infusion commences for guidance:

- WBC count of $\geq 20,000/\mu\text{L}$ within 48 hours prior to KITE-585 infusion
- CRP is ≥ 100 mg/L
- Temperature is $\geq 38.0^\circ\text{C}$ within 48 hours prior to KITE-585 infusion. Unexplained fever requires pan-culture, respiratory viral panel, chest CT, and any additional symptom-directed workup to rule out occult infection.
- If any screening assessments or procedures are repeated between conditioning chemotherapy and the KITE-585 infusion and results are outside the eligibility criteria ([Section 4](#); with the exception of conditioning chemotherapy-induced cytopenias)

If the KITE-585 infusion is delayed > 2 weeks, conditioning chemotherapy must be repeated. In all cases of KITE-585 infusion delays, contact the Kite medical monitor for guidance.

6.3.5.2. Hospitalization for KITE-585 Administration

All subjects will be hospitalized to receive treatment with KITE-585 followed by an observation period of at least 5 days.

Due to the potential risk of CRS and neurological events following infusion of KITE-585, a minimum of two doses of tocilizumab should be available for immediate use within a maximum of two hours between the determination of the need for tocilizumab and its administration (See the current KITE-585 IB for additional information on the grading and management of KITE-585 related toxicities).

Subjects should not be discharged from the hospital until at least 5 days have elapsed since the KITE-585 infusion and all KITE-585-related non-hematological toxicities return to \leq Grade 1 or baseline. Subjects may be discharged with non-critical and clinically stable or improving toxicities (eg, renal insufficiency) even if > Grade 1, if deemed appropriate by the investigator. Subjects should remain hospitalized for ongoing KITE-585-related or unexplained fever,

hypotension, hypoxia, or ongoing central neurological toxicity > Grade 1 or if deemed necessary by the treating investigator. If the subject is discharged before Day 10, the subject must return to the clinic daily through Day 10 for a history and physical examination, vital signs, and labs. Deep vein thrombosis (DVT) prophylaxis should be utilized in all subjects with reduced mobility during hospitalization per institutional guidelines. Low molecular weight heparin (LMWH) is encouraged as long as there are no contraindications (eg, renal dysfunction, recent surgery, bleeding diathesis, platelet count < 50,000/ μ L) based on benefit/risk. Unfractionated heparin or non-invasive mechanical intermittent pneumatic compression devices for DVT prophylaxis should be used in those with contraindications to LMWH or those who cannot receive anticoagulants due to increased bleeding risk or other concerns (Lyman et al, 2015). Given the possibility that a subject could develop AEs, including CRS or one or more neurologic events, after discharge from the hospital, subjects and their family members/caregivers should be educated on potential symptoms, such as fever, dyspnea, confusion, aphasia, dysphasia, somnolence, encephalopathy, ataxia, seizure, or tremor. If subjects develop these and/or other symptoms, they should be instructed to immediately contact the principal investigator or to seek immediate medical attention.

6.3.5.3. KITE-585 Premedication Dosing

The following medications should be administered approximately 1 hour prior to infusion of KITE-585.

- Acetaminophen 650 mg PO
- Diphenhydramine 12.5 mg IV or 25 mg PO

6.3.5.4. KITE-585 Administration (Day 0)

Materials and instructions for the thawing, timing, and administering of KITE-585 are outlined in the IPM. The IPM must be reviewed prior to administration of KITE-585.

Central venous access, such as a port or a peripherally inserted central catheter, is required for the administration of KITE-585 and for the hospitalization treatment period. Catheter care, per institutional guidelines, should be followed.

Research sites should follow institutional guidelines for the infusion of cell products. Prior to administration of KITE-585, the product label will be checked by 2 personnel at the research site and asked to complete the Kite Pharma Countersignature Form. Sites may use their own countersignature form, provided that the chosen form collects at minimum the same data as required on the Kite Pharma form.

KITE-585 will be administered intravenously by gravity or IV pump set to 5 to 10 mL/min via nonfiltered tubing as follows.

Refer to [Sections 2.1](#) and [8.6](#) for dose cohort details.

6.3.5.5. Other Procedures During KITE-585 Treatment Period

The following procedures/requirements will occur during the KITE-585 treatment period as outlined in the SOA:

- Physical exam

- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature will be taken:
 - Pre- and post-KITE-585 infusion
 - First morning reading for each day during hospitalization and more frequently as clinically indicated for subjects with fever ($\geq 38.3^{\circ}\text{C}$) or other vital sign abnormality
- Neurological exam if applicable (see [Sections 6.3.1](#))
- Disease assessment:
 - *Optional*: For subjects with confirmed plasmacytoma who sign the optional portion of the consent, a fresh biopsy of the plasmacytoma between Day 7 and Day 14 will be performed. This sample will be submitted to the central lab.
- Local labs (to be drawn prior to KITE-585 infusion)
 - Chemistry panel
 - CBC with differential
 - Recommended: Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regard to CRS/neurologic events. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continuing through hospitalization. In addition, lactate should be monitored as clinically indicated.
- Central labs (to be drawn prior to KITE-585 infusion)
 - PBMCs
 - Cytokine levels
- *If applicable*: Lumbar puncture (including collection of opening pressure) for collection of CSF will be performed at the following time points:
 - Subjects with \geq Grade 2 neurologic events and without medical contraindication
 - Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam, will have lumbar puncture for examination of CSF.
 - CSF samples will be analyzed locally for CNS MM (% plasma cells) and will be submitted to the central laboratory for additional analysis as outlined in [Section 6.4](#).

- KITE-585 pre-medication (see [Section 6.3.5.3](#))
- KITE-585 infusion (see [Section 6.3.5](#))
 - After the pre-KITE-585 criteria are met (see [Section 6.3.5.1](#)), KITE-585 will be administered (see [Section 6.3.5.4](#) and the IPM).
- AE/SAE reporting (see [Section 8](#))
- Concomitant medications documentation (see [Section 5.6](#))
- If the subject is discharged before Day 10, the subject must return to the clinic daily through Day 10 for a history and physical examination, vital signs, and labs (see [Section 6.3.5.2](#) and the SOA)

6.3.6. Post-treatment Follow-up Period

The following procedures/requirements will occur at various time points during the post-treatment follow-up period (Week 2 through Month 3) as outlined in the SOA:

- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Neurological exam if applicable (see [Sections 5.3.1](#))
- Disease assessment, including serum and urine markers, bone marrow aspirate and biopsy, and, if applicable, imaging (see [Section 6.2](#))
- Local labs
 - β -HCG pregnancy test (serum or urine) on all women of childbearing potential
 - Chemistry panel
 - CBC with differential
 - Recommended: Monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels may assist with the diagnosis and define the clinical course in regards to CRS/neurologic events. It is, therefore, recommended that CRP, ferritin, and LDH (if elevated at baseline) be monitored daily starting at Day 0 and continuing through hospitalization. In addition, lactate should be monitored as clinically indicated.
- Central labs
 - PBMCs
 - Cytokine levels
 - Anti-KITE-585 antibodies (see [Section 6.3.7](#) for additional anti-KITE-585 antibody collection requirements)

- *If applicable*: If, following discharge from initial hospitalization for KITE-585 infusion, the subject is subsequently re-admitted to the hospital with any KITE-585 related AEs, a PBMC and cytokine sample will be collected on the day of admission, weekly during hospitalization, and on the day of discharge or at the time of AE resolution.
- *If applicable*, an additional cytokine sample will be collected if the subject experiences a Grade ≥ 3 KITE-585 related event (eg, CRS [per [Lee et al, 2014](#) criteria]) or neurologic event, if not already collected on that day
- *If applicable*: Lumbar puncture (including collection of opening pressure) for collection of CSF (see [Section 6.3.5](#) for details)
- *Optional*: For subjects with confirmed plasmacytoma who sign the optional portion of the consent, a fresh biopsy of a progressing or persistent plasmacytoma will be performed. This sample will be submitted to the central lab.
- AE/SAE reporting (see [Section 8](#))
- Concomitant medications documentation (see [Section 5.6](#))

At any time during the post-treatment assessment period, if a subject did not respond to treatment (ie, did not achieve at least a PR) or experiences disease progression following a response, the subject will proceed directly to the Month 3 visit and be followed for survival, subsequent therapy for MM, and disease outcomes in the long-term follow-up period.

6.3.7. Long-term Follow-up Period

The following procedures/requirements will occur during the long-term follow-up period (Month 4 through Year 15) as outlined in the SOA:

- Physical exam
- Vital signs, including blood pressure, heart rate, oxygen saturation, and temperature
- Disease assessment, including serum and urine markers, bone marrow aspirate and biopsy, and any applicable imaging (see [Section 6.2](#))
- *Optional*: For subjects with confirmed plasmacytoma who sign the optional portion of the consent, a fresh biopsy of a progressing or persistent plasmacytoma will be performed. This sample will be submitted to the central lab.
- Survival status
- Local labs
 - Chemistry panel
 - CBC with differential

- Central labs
 - Anti-KITE-585 antibodies
 - For subjects in whom any post-infusion serum sample demonstrates increased antibodies to KITE-585 over baseline levels, attempts should be made to obtain and test additional serum samples approximately every 3 months until Month 12 or until anti-KITE-585 antibody levels return to baseline or become negative, whichever occurs first.
 - PBMCs
 - PBMC samples will be collected throughout the long-term follow-up (LTFU) period.
 - Replication-competent lentivirus (RCL) testing will occur at baseline, Month 3, Month 6, and Month 12. Thereafter, samples will be collected yearly and held for up to 15 years. If a subject tests positive for RCL at any time point within the first year, samples will continue to be collected and tested yearly for up to 15 years or as clinically indicated.
 - PBMC samples will also be used for continued monitoring of anti-BCMA CAR T-cell persistence at Months 6, 9, 12, 18, and 24.
- *If applicable*: Lumbar puncture (including collection of opening pressure) for collection of CSF (see [Section 6.3.5](#) for details)
- AE/SAE reporting (see [Section 8](#))
- Concomitant medications documentation (see [Section 5.6](#))
- Subsequent therapy for MM reporting (see [Section 5.8](#))

Subjects may also be contacted by telephone to confirm survival status and report targeted concomitant medication use. Should a subject require lab collection, labs may be collected at the clinic or at an outside facility to reduce the subject burden.

If the subject fails to return to the clinic for a scheduled protocol specific visit, sites will need to make 2 attempts by a combination of telephone and mail to contact the subject. Sites must document both attempts to contact the subject. If a subject does not respond within 1 month after the second contact, the subject will be considered lost to follow-up, and no additional contact will be required.

Subjects who received treatment with KITE-585, but who experience disease progression, will be followed in the LTFU period and undergo the following assessments at the time points outlined in the SOA:

- Survival status
- Targeted AE/SAEs (see [Section 8](#))

- Targeted concomitant medications (see [Section 5.6](#))

Subjects who were enrolled, but did not receive treatment with KITE-585, will be followed in the LTFU period and undergo the following assessments at the time points outlined in the SOA:

- Survival status
- AE/SAE reporting (see [Section 8](#))

6.4. Biomarkers

Biomarker analysis will be performed on blood, bone marrow (tumor), and CSF samples to evaluate pharmacokinetic and pharmacodynamic markers related to safety or efficacy.

Prognostic markers specific for aggressive MM, related to the tumor immune environment or the safety and efficacy profile of KITE585, may also be evaluated.

Analysis will include baseline and post-KITE-585 BCMA expression levels and other standard markers used to assess MM presence, burden, or other prognostic factors (CD38, CD138, and disease-related markers, such as del17p). Remaining samples may be stored for future exploratory analysis of tumor specific DNA, RNA, or protein markers to better understand the safety profile of KITE-585.

- Levels of anti-BCMA CAR T cells in blood over time to understand the relationship between expansion and clinical outcome
- Levels of serum cytokines in blood. The following cytokines may be included in the panel: pro-inflammatory and immune modulating cytokines IL-2, IL-6, IL-10, IL-15, IL-17a, TNF- α , interferon (IFN)- γ , CRP, and GM-CSF; immune effector molecules granzyme B and perforin; markers of hemophagocytic lymphohistiocytosis (HLH) (ferritin, sIL-2R α); and chemokines IL-8, MIP-1 α , MIP-1 β , IP-10, and MCP-4.
- Levels of soluble BCMA will be measured to understand relationships with clinical outcome.
- Because KITE-585 comprises lentiviral vector transduced T cells, the presence of RCL in the blood of treated subjects will be monitored.
- Baseline leukapheresis and final KITE-585 product samples will be banked and may be analyzed by immunophenotyping, PCR, and/or gene expression profiling. Remaining samples may be stored for future exploratory analysis of immune-related markers.

On-study paired bone marrow aspirates and biopsies will be performed at baseline and 14 days after KITE-585 when we expect peak expansion and tumor infiltration with anti-BCMA CAR T cells. For subjects with extramedullary disease who sign the optional consent, biopsies of extramedullary disease will take place at screening, between Day 7 through Day 14, and at disease progression. Exploratory analysis of tumor or immune cell markers that correlate with response to KITE-585 or disease prognosis or the safety profile of the treatment will be analyzed. All mentioned samples and any other derivatives from these samples may be stored up to 15 years to address exploratory research or safety-related questions to the treatment or disease under

study. Each subject will have the right to have the sample material returned or destroyed at any time by contacting the investigator who, in turn, can contact the central laboratory. The investigator should provide the sponsor with the study and subject number so that the sample can be located and destroyed.

For subjects who withdraw consent, any samples that were not requested to be returned or destroyed will remain with the sponsor, and any data that may be generated will be entered in the study database.

Table 4. Schedule of Assessments

Procedures	Screening (days before enrollment)		Enrollment/ Leukapheresis	Bridging Therapy (optional) ^s	Treatment Period						Post-treatment Follow-up (Calculated from Day 0)				
	≤ 28 d	≤ 14 d			Conditioning Chemotherapy			IP ^{B, N, O}			W2 (± 2 d)	W4 (± 3 d)	M2 (± 1 w)	M 3 (± 1 w)	
Timeframe (d=day, w=week, m=month)					D-5	D-4	D-3	D-2	D-1	D0 (-1d)	D1 – 10 ^R				
Medical history		X													
Physical exam ^{A, I}		X								X	X	X	X	X	X
Weight (plus height at screening)		X	X												
Vital signs (BP, HR, O ₂ sat, temp)		X	X	X	X	X	X			X ^B	X ^{B, R}	X	X	X	X
ECOG performance status		X													
Neurological exam ^C		X								At time of neurological symptoms ^I (see Section 5.9)					
ECG		X													
ECHO ^T	X			X ^T											
Brain MRI ^{D, I}	X														
Disease Assessments															
Local serum and 24h urine ^E	X			X ^S									X	X	X
Local and central BM aspirate and biopsy ^F		X		X ^F								X	X		X
PET CT (neck, chest, abdomen, pelvis) ^G		X		X ^G									X ^G		
Optional plasmacytoma biopsy ^H	X										Day 7 - 14				
Local Labs															
Pregnancy test (serum or urine)		X													X
Chemistry panel		X	X	X	X	X	X			X	X ^R	X	X	X	X
CBC w/differential		X	X	X	X	X	X			X	X ^R	X	X	X	X
CRP			X												

Central Labs															
Anti-KITE-585 antibody ^J			X										X		X ^J
PBMCs ^K			X						X	Q3D _{K,R}	X ^R	X	X	X	
Cytokines ^{K,L}			X						X	Q3D _{K,L,R}	X ^R	X	X	X	
LP for collection of CSF and opening pressure ^{A,I}	X												At the time of \geq Grade 2 neurological symptoms ^{A,I}		
Leukapheresis			X												
Fludarabine/Cyclophosphamide						X	X	X							
KITE-585 infusion IV ^M										X ^M					
AE/SAE/Concomitant medication	X	X	X												X ^R

Table 5. Schedule of Assessment (Long-term Follow-up Period)

Procedure	Long-term Follow-up Period (Calculated from Day 0)														
	4 ± 1 w	5 ± 1 w	6 ± 1 w	9 ± 2 w	12 ± 2 w	15 ± 2 w	18 ± 2 w	21 ± 2 w	24 ± 2 w	30 ± 1 m	36 ± 1 m	42 ± 1 m	48 ± 1 m	54 ± 1 m	Annually for months 60-180 ± 1 m
Physical exam ^A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals (BP, HR, O ₂ sat, temp)	X	X													
Disease Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local serum and 24h urine ^E	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local and central BM aspirate and biopsy ^F	Month 12 and at the time of suspected CR and PD per serum and/or urine biomarkers ^F														
Optional plasmacytoma biopsy ^H	At time of suspected extramedullary disease progression														
PET CT (neck, chest, abdomen, pelvis) ^G	For subjects with extramedullary disease at baseline: At time of suspected CR and suspected PD For subjects without extramedullary disease at baseline: At time extramedullary disease is suspected														

Survival status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local Labs															
Pregnancy test (serum or urine)															
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Central Labs															
Anti-KITE-585 antibody ^J															
PBMCs			X	X	X		X		X		X		X		X
Targeted AE/SAEs ^P	X	X	X	X	X	X	X	X	X						
All KITE-585-related SAEs and Deaths regardless of relatedness	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted concomitant medication	X	X	X	X	X	X	X	X	X						
Subsequent therapy for MM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CR, complete response; PD, progressive disease; SAE, serious adverse event; BM, bone marrow; BP, blood pressure; CBC, complete blood count; PET-CT, positron emission tomography-computerized tomography; HR, heart rate; MM, multiple myeloma; O₂ sat, oxygen saturation; PBMCs, peripheral blood mononuclear cells; PET, positron emission tomography; SAE, serious adverse event; temp, temperature; ECOG, Eastern Cooperative Oncology Group; ECHO, echocardiogram; MRI, magnetic resonance imaging; CBC, complete blood count; CRP, C-reactive protein; LP, lumbar puncture; CSF, cerebral spinal fluid; IV, intravenous.

Schedule of Assessment Footnotes:

^A **Physical Exam:** See footnote I.

^B **Vital signs:** Vital signs include blood pressure, heart rate, oxygen saturation, and temperature. Vital signs will be taken pre- and post-KITE-585 infusion on Day 0. First morning vital signs will be recorded for each day during hospitalization and more frequently as clinically indicated for subjects with fever (≥ 38.3°C) or other vital sign abnormality.

- C Neurological Exam:** All subjects will have a neurological exam at baseline and any time there are neurological symptoms (Section 5.9). A neurologic examination will be performed with any abnormalities of the following recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion).
- D Brain MRI (Section 6.2.4):** A baseline brain MRI will be performed. On-study brain MRIs should be considered for subjects with \geq Grade 2 neurological events (see Section 5.9).
- E Local Serum and 24-hour Urine (Section 6.2.2):** Serum (quantitative immunoglobulins, free light chains, protein electrophoresis, protein immunofixation electrophoresis), and a 24-hour urine (total protein, urine protein electrophoresis, urine protein immunofixation electrophoresis) will be evaluated at the time points indicated in the SOA until the subject has PD, withdraws from the study, is lost to follow-up, or dies.
- F Local and Central BM aspirate and biopsy (Section 6.2.3):** A bone marrow aspirate and biopsy will be performed at the time points indicated in the SOA. At all time points, bone marrow will be analyzed locally and centrally per Section 6.2.3.
- At screening, bone marrow will be evaluated locally for high risk mutations by FISH, % plasma cells by flow cytometry, and **locally/centrally** for MRD. If enrollment is delayed, then a repeat bone marrow biopsy and aspirate will be required to ensure baseline bone marrow is performed within 14 days before leukapheresis.
 - In subjects who receive bridging therapy (Section 5.3), between bridging chemotherapy and start of conditioning chemotherapy. Bone marrow will be evaluated locally for % plasma cells by flow cytometry
 - At **Week 4** and Month 3, bone marrow will be evaluated locally for % plasma cells by flow cytometry.
 - After Month 3, a bone marrow aspirate and biopsy will be collected at the time of suspected CR and at the time of PD per serum and/or urine biomarkers and analyzed for MRD and other biomarkers. At all bone marrow evaluation time points, a portion of the bone marrow aspirate and biopsy will be processed and submitted to the central laboratory per the central laboratory manual.
- G PET/CT neck, chest, abdomen, pelvis (Section 6.2.4):** All subjects will have a baseline PET CT after the last therapy for MM and \leq 14 days before enrollment. If the screening PET CT was positive or suspicious for extramedullary disease and the scans are \geq 28 days before start of conditioning chemotherapy, then the PET CT scans will be repeated. For subjects with extramedullary disease at baseline, on-study PET CT scans will be performed at the time of suspected CR followed by the time of suspected extramedullary PD or PD per serum and/or urine biomarkers. For subjects who receive bridging therapy, a PET CT must be repeated prior to the initiation of conditioning chemotherapy.
- H Optional plasmacytoma biopsy:** For subjects who sign the optional portion of the consent form, a fresh biopsy of the plasmacytoma will be obtained at screening, between Day 7 and Day 14, and at progression of extramedullary disease. This sample will be submitted to the central lab.
- I Lumbar puncture for collection of CSF (Sections 6.3):** CSF will be evaluated at the following times: 1) If the screening brain MRI is suspicious for CNS involvement, then an LP will be performed during screening, 2) Subjects with symptoms of CNS malignancy, such as new onset severe headaches, neck stiffness, seizures, encephalopathy, cranial nerve deficits, or any focal neurologic findings on physical exam, will have lumbar puncture for examination of cerebral spinal fluid, and 3) any time Grade \geq 2 neurological symptoms are present (see Section 5.9). CSF will be analyzed locally for % plasma cells and centrally. An opening pressure will be measured and recorded with every LP.
- J Anti-KITE-585 antibody (Section 6.3.7):** Baseline antibody sample to be collected **at enrollment** prior to start of **leukapheresis**, at **Week 4** and Month 3. For subjects who test positive, additional antibody samples will be collected approximately every 3 months until Month 12 or until anti-KITE-585 antibody levels return to baseline or become negative, whichever occurs first.
- K PBMCs and Cytokines:** Collected Q3D for the duration of hospitalization. If, following discharge from initial hospitalization for KITE-585 infusion, the subject is subsequently readmitted to the hospital with any KITE-585 related adverse events, a PBMC and cytokine sample will be collected on the day of admission, weekly during hospitalization, and on the day of discharge. A PBMC sample will be collected at the time of PD.
- L Cytokines:** As applicable, an additional cytokine sample will be collected if the subject experiences a \geq Grade 3 KITE-585 related event (eg, CRS [per Lee et al, 2014 criteria] or neurologic event) if not already collected on that day.
- M KITE-585 Premeds (Section 6.3.5.3):** Acetaminophen and diphenhydramine will be administered approximately 1 hour prior to KITE-585 infusion.
- N KITE-585 Administration (Section 6.3.5):** Subjects will be hospitalized on Day 0 through Day 5 to received KITE-585 infusion. See Section 6.3.5 for additional details.
- O Additional Labs Recommended (Section 6.1):** Daily monitoring of CRP, ferritin, and LDH (only if LDH is elevated at baseline) levels is recommended daily starting at Day 0 and continuing through hospitalization to assist with the diagnosis and define the clinical course in regards to CRS/neurologic events. Lactate should be monitored as clinically indicated.

- ^P **Targeted AEs/SAEs (Section 8):** Targeted AE/SAEs are events that occur in the following systems/categories: neurological, hematological, infections, autoimmune disorders, secondary malignancies. Targeted AEs, targeted SAEs, and non-serious CRS events \geq Grade 3 (per Lee et al, 2014 criteria) will be reported from Month 3 or initiation of another anti-cancer therapy (whichever occurs first) through 24 months after treatment with KITE-585 or PD, whichever occurs first.
- ^Q **Targeted concomitant medications:** See [Section 8](#) for details.
- ^R **Procedures during and after hospitalization through day 10:** Daily vital signs, chemistry, and hematology lab panels and Q3D cytokine and PBMC draws will continue through hospitalization regardless of day of discharge. If subject is discharged before Day 10, the subject must return to the clinic daily through Day 10 for history and physical exam, vitals, and chemistry and hematology lab panels.
- ^S **Bridging Therapy:** The procedures listed in the SOA will occur after the completion of bridging therapy and prior to conditioning chemotherapy. Serum and 24-hour urine samples must be completed and collected prior to the initiation of conditioning chemotherapy.
- ^T **ECHO: Repeat echocardiogram required only in study subjects who receive bridging therapy and subsequently develop evidence of new onset cardiac dysfunction including chest pain, shortness of breath, peripheral edema, or other signs and symptoms.**

7. SUBJECT WITHDRAWAL

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects can decline to continue to receive study required treatment and/or other protocol required procedures at any time during the study but continue to participate in the study. This is referred to as partial withdrawal of consent.

If partial withdrawal of consent occurs, the investigator must discuss with the subject the appropriate process for discontinuation from investigational product (IP), study treatment, or other protocol-required therapies and must discuss options for continued participation, completion of procedures, and the associated data collection as outlined in the SOA. The level of follow-up and method of communication should also be discussed between the research staff and the subject and documented in the source documents.

Withdrawal of full consent for a study means that the subject does not wish to receive further protocol required therapy or undergo procedures and the subject does not wish to continue further study follow-up. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study and, where permitted, by local regulations; publicly available data (death records) can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

As part of the study, sites may be asked to conduct searches of public records, such as those establishing survival status, if available, to obtain survival data for any subject for whom the survival status is not known. Sites may also be asked to retrieve autopsy reports to confirm status of disease at the time of death.

The investigator and/or sponsor can also decide to withdraw a subject from the IP and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

7.1. Reasons for Removal from Treatment

Reasons for discontinuation of protocol-required IPs or procedures include any of the following:

- AE
- Subject request/non-compliance
- Product not available
- Lost to follow-up
- Death
- Decision by sponsor

7.2. Reasons for Removal from Study

Reasons for removal of a subject from the study are as follows:

- Subject withdrawal of consent from further follow-up
- Investigator decision

- Lost to follow-up
- Death

8. SAFETY REPORTING

8.1. Adverse Events

The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

AEs are:

- Any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a relationship with study treatment.
- Worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition, such as elective cosmetic surgery or a medical procedure while on study, that has not worsened during the study or involves an intervention is not considered an AE.
- Clinically significant abnormal laboratory values (eg, requires intervention, results in new or worsening clinical sequelae, requires therapy or adjustment of current therapy)
 - Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

AEs that occur within the following systems/categories will be reported per [Section 8.2](#). These are called targeted AEs:

- Neurological
- Hematological
- Infections
- Autoimmune disorders
- Secondary malignancies

The following events are not AEs:

- Interventions for pre-treatment conditions (such as elective cosmetic surgery) or medical procedures that were planned before study participation are not considered AEs.
- Hospitalization for study treatment infusions or precautionary measures per institutional policy are not considered AEs.
- Clinically insignificant abnormal laboratory values as determined by the investigator (eg, does not require intervention, does not result in new or worsening clinical sequelae, does not require therapy or adjustment of current therapy)

The term “disease progression,” as assessed by biopsy or other methods, should not be reported as AEs. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, multiple myeloma).

Signs and symptoms of disease progression may be recorded as AEs or SAEs and as being indicated due to disease progression. Worsening of signs and symptoms of the malignancy under study should also be reported as AEs in the appropriate section of the CRF.

The investigator’s clinical judgment is used to determine whether a subject is to be removed from treatment due to an AE. In the event a subject requests to withdraw from protocol-required therapies or the study due to an AE, the subject should undergo the procedures outlined in the Month 3 visit of the SOA.

8.2. Reporting of Adverse Events

Requirements for subjects who receive treatment with KITE-585:

- AEs that occur from enrollment through 3 months after treatment with KITE-585 or until the initiation of another anti-cancer therapy, whichever occurs first, will be reported in the CRF.
- Thereafter, only targeted AEs (see [Section 8.1](#) for definition of targeted AE) that occur from 3 months after treatment with KITE-585 or initiation of another anti-cancer therapy (whichever occurs first) through 24 months after treatment with KITE-585 or disease progression, whichever occurs first, will be reported in the CRF.

Requirements for subjects who are enrolled but do not receive KITE-585:

- AEs that occur from enrollment through 30 days after the last study-specific procedure (eg, leukapheresis, conditioning chemotherapy) will be reported in the CRF.

Requirements for subjects who are screened, but not enrolled (ie, screen-failed):

- SAEs will be collected for 30 days from the last screening-related procedure (see [Section 8.4](#)).

The investigator must provide the information listed below regarding the AEs being reported:

- AE diagnosis or syndrome (if not known, signs or symptoms)
- Dates of onset and resolution
- Severity
- Assessment of relatedness to IP, conditioning chemotherapy, or study procedures
- Action taken

Adverse event grading scale used will be the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A copy of the grading scale can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). Cytokine release syndrome events will be reported using both CTCAE 4.03 and the modified Lee et al, 2014 criteria grading scale outlined in the Guidelines for Management of Important Risks section of the IB.

In reviewing AEs, investigators must assess whether the AE is possibly related to 1) KITE-585, 2) conditioning chemotherapy, or 3) any protocol-required study procedure. The relationship is indicated by a yes or no response and entered into the CRF. A yes response should indicate that there is evidence to suggest a causal relationship between the study treatment or procedure and the AE. Additional relevant data with respect to describing the AE will be collected in the CRFs. The investigator is expected to follow reported AEs until stabilization or resolution.

8.3. Definition of Serious Adverse Events

An SAE is defined as an AE that meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires in-patient hospitalization, prolongation of existing hospitalization, escalation of care
 - An AE would meet the criterion of “requires hospitalization” if the event necessitated an admission to a healthcare facility (eg, overnight stay).
 - Events that require an escalation of care when the subject is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit (ICU) or if that event resulted in a prolongation of the existing planned hospitalization.
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event
 - If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as an SAE with the criterion of “other medically important serious event.”

8.4. Reporting of Serious Adverse Events and Non-serious \geq Grade 4 CRS Events, Neurologic Events, and Product Infusion Reactions

SAEs will be reported through the electronic data capture (EDC) system. This is called eSAE reporting.

Requirements for subjects who receive treatment with KITE-585:

- SAEs that occur from the date of consent through 3 months after treatment with KITE-585 or until the initiation of another anti-cancer therapy, whichever occurs first, will be reported to Kite within 24 hours using the eSAE.

- Thereafter, only serious targeted adverse events (see [Section 8.1](#) for definition of targeted adverse event) that occur from 3 months after treatment with KITE-585 or initiation of another anticancer therapy (whichever occurs first) through 24 months after treatment with KITE-585 or disease progression, whichever occurs first, will be reported to Kite within 24 hours using the eSAE.
- Serious adverse events, which the investigator assesses as related to KITE-585, that occurs from ICF through end of study will be reported to Kite within 24 hours using the eSAE.
- All deaths that occur from date of informed consent through end of study will be reported in the CRF.

Requirements for subjects (ie, screened) who do not receive treatment with KITE-585 (ie, screen-failed, enrolled, but do not receive KITE-585):

- SAEs will be reported through 30 days after the last study-specific procedure (eg, screen procedure, leukapheresis, conditioning chemotherapy) in the CRF and to Kite within 24 hours using the SAE Report Form.

All SAEs and non-serious Grade \geq 4 CRS events as measured by the modified Lee criteria (Lee et al, 2014), product infusion reactions, and neurologic events, must be submitted to Kite within 24 hours of the investigator's knowledge of the event via the eSAE system. If the eSAE system is unavailable (eg, system outage), then the SAE must be submitted using the SAE Report Form and emailed to the SAE Reporting mailbox: Kite_PV@ubc.com. Subsequently, all SAEs will be reported to the health authorities per local reporting guidelines. In addition to all reports of serious unexpected suspected adverse reactions, reports of deaths within 30 days of KITE-585 infusion, regardless of attribution, and all Grade \geq 4 CRS, neurologic events, and product infusion reactions will be submitted to the FDA as expedited case reports.

If the malignancy has a fatal outcome within 3 months of the last day of the conditioning therapy or KITE-585, then the event malignant neoplasm progression must be recorded as a serious adverse event with the outcome fatal.

8.5. Pregnancy and Lactation

There is no relevant clinical experience with KITE-585 in pregnant or lactating women, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

Female subjects and female partners of male subjects must use highly effective contraception for at least 6 months after KITE-585 dosing. Male subjects must not father a child for 6 months after the KITE-585 dosing. If a pregnancy occurs in a female subject enrolled into the study or a female partner of a male subject within 6 months after completing the KITE-585 infusion, the

pregnancy must be reported to the key sponsor contact. Information regarding the pregnancy and/or the outcome may be requested by the sponsor.

The pregnancy should be reported to the key sponsor contact within 24 hours of the investigator’s knowledge of the pregnancy event.

If a lactation case occurs while the female subject is taking protocol-required therapies, report the lactation case to the key sponsor contact.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 6 months. Any lactation case should be reported to the key sponsor contact within 24 hours of the investigator’s knowledge of the event.

Pregnancy and lactation cases will be reported to Kite using the Pregnancy/Lactation Report Form and emailed to the SAE Reporting mailbox: Kite_PV@ubc.com.

8.6. Safety Review Team and Dose-limiting Toxicity

The SRT will be comprised of clinical development representatives from Kite and at least one Phase 1 study investigator. The SRT will be specifically chartered to review safety data during the study and make recommendations on further study conduct based on the incidence of KITE-585 DLT and review of SAEs.

8.6.1. Dose-limiting Toxicity

Dose-limiting toxicity (DLT) is defined as the KITE-585-related events with onset within the first 28 days following KITE-585 infusion. CRS will be graded according to a revised grading system ([Lee et al, 2014](#)). **Details of CRS grading and management are found in Section 5.4, Tables 5 and 6 of the KITE-585 IB, version 2.1. As the safety experience with KITE-585 increases, the management guidance may be updated. Therefore, it is important that the most current version of the KITE-585 IB is consulted for guidance regarding management of KITE-585-related toxicities.** AEs attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT. Details of the DLT definitions, including duration of event and exceptions, are provided in Table 6.

Table 6. Dose-limiting Toxicities

DLT		
Grade (CTCAE 4.03 unless otherwise indicated)	Duration	Exceptions
Grade 3 CRS (Lee et al, 2014)	≥ 72 hours	n/a
Grade 4 CRS (Lee et al, 2014)	Any	n/a

Grade 3 non-hematologic AE	≥ 72 hours	<ul style="list-style-type: none"> • Fever • Nausea • Hepatic toxicity that resolves to Grade 2 or better in ≤ 14 days • Hypogammaglobulinemia • Tumor lysis syndrome
Grade 4 non-hematologic AE	Any	<ul style="list-style-type: none"> • Fever • Nausea • Hepatic toxicity that resolves to Grade 3 or better in ≤ 72 hours • Hypogammaglobulinemia • Tumor lysis syndrome • Acute renal toxicity requiring dialysis for ≤ 7 days • Intubation for airway protection for ≤ 7 days • AE resolves to ≤ Grade 1 within 2 weeks and baseline within 4 weeks
Grade 4 hematologic AE	≥ 30 days	<ul style="list-style-type: none"> • Cytopenias attributable to ongoing or recurrent MM
KITE-585-related Grade 5 AE	Any	n/a

Abbreviations: AE, adverse event; CRS, cytokine release syndrome; MM, multiple myeloma; n/a, not applicable; CTCAE, Common Terminology Criteria for Adverse Events.

Subjects will be dosed in a standard 3 + 3 dose escalating fashion (see [Section 2.1](#) for overview of dose cohorts). The first 3 subjects enrolled will be dosed with a minimum of 2 weeks between each subject’s infusion. The analysis of DLTs will be based on the DLT evaluable set as defined in [Section 9.5](#). The SRT will make recommendations based on the incidence of DLTs and the overall safety profile of KITE-585 as outlined in [Table 7](#).

Table 7. Recommendations Based on DLTs

# of DLTs	Potential Recommendation
0/3 or 1/6	Dose determined tolerable, go to next higher dose cohort; if highest dose, then the highest dose will be the MTD
1/3	Enroll 3 more subjects at same dose level
2/3 or 2/6	Next lower dose cohort will be established as the MTD*

Abbreviations: #, number; DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

*If the incidence of DLT in the first dose-escalation cohort, dose level 1 of subjects treated the planned dose of 3×10^7 antiBCMA CAR T cells is $\geq 2/6$, the sponsor may, in consultation with the SRT, choose to decrease the dose to 1×10^7 anti-BCMA CAR T cells and open another cohort of 3 to 6 subjects. If the incidence of DLT in this cohort is ≤ 1 , this dose will be established as the MTD.

The sponsor may, in consultation with the SRT, choose to treat up to 20 additional subjects at any dose deemed safe by the SRT up to, and including, the MTD in Expansion Cohort 1 to further characterize benefit risk. Expansion Cohort 1 will be comprised of subjects who meet all eligibility criteria specified for the dose escalation portion of the study. The SRT will review the safety data after the first 10 subjects from Expansion Cohort 1 have been treated and have completed the Day 28 visit.

Separately, subjects with moderate renal impairment (creatinine clearance 30 to 59 ml/min by Cockcroft-Gault estimation) may, in consultation with the SRT, be enrolled and treated at any dose deemed safe by the SRT during the dose escalation phase up to, and including, the MTD established during the initial dose escalation in Expansion Cohort 2. The first 3 subjects will be enrolled with a minimum of 2 weeks between each subject's infusion. The SRT will review safety data after the first 6 subjects have been treated and have completed the Day 28 visit. The SRT may make study recommendations including, for example, treatment of additional subjects at the original dose, that the cell dose be reduced and additional subjects treated, or that the cohort be closed to further enrollment.

8.6.2. Criteria to Pause Enrollment

As part of its oversight of the study, the SRT will assess criteria to pause enrollment after 10, 20, 30, and 50 subjects have been treated with KITE-585 (including all subjects from dose-escalation cohorts, Expansion Cohort 1, and Expansion Cohort 2) and have had the opportunity to be followed for 28 days. Enrollment will be paused if any of the following criteria is met:

- Any subject incidence of Grade 5 AE within 30 days of the KITE-585 infusion regardless of relatedness to treatment
- Subject incidence of $\geq 33\%$ Grade 4 non-hematological AEs (irrespective if related to the KITE585 or at least possibly related) that do not decrease to Grade 2 within 7 days

Subject incidence of $\geq 33\%$ Grade 3 KITE-585 related events of CRS, neurologic events, infection, or other non-hematological SAEs that do not resolve to Grade 2 or better within 72 hours of onset and $\geq 33\%$ Grade 4 of such events regardless of duration

FDA will be notified within applicable safety reporting timelines if any of these pausing rules occur. Accrual will be resumed upon recommendation of the SRT.

9. STATISTICAL CONSIDERATIONS

9.1. Hypothesis

KITE-585 at one of the dose levels planned will be considered safe as determined by the incidence of DLTs.

9.2. Study Endpoints

9.2.1. Primary

Incidence of AEs defined as DLTs.

9.2.2. Secondary

- Objective response rate (ORR): objective response is defined as either a PR or very good PR (VGPR) or as a complete response (CR) or stringent CR, as determined by study investigators according to IMWG Consensus Panel 1 Criteria ([Rajkumar et al, 2011](#)). Subjects who did not meet the criteria for objective response by the analysis cutoff date will be considered nonresponders.
- Progression free survival (PFS): PFS is defined as the time from the KITE-585 infusion date to the date of disease progression per the IMWG Consensus Panel 1 Criteria ([Rajkumar et al, 2011](#)) or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive additional anti-cancer therapy (with the exception of stem cell transplant while in KITE-585 induced response) in the absence of documented progression will be censored at the last evaluable disease assessment prior to the additional therapy. Death that occurs after additional anti-cancer therapy will be considered a PFS event.
- Duration of response (DOR): DOR is defined for subjects who experience an objective response and is defined as the date of their first objective response (which is subsequently confirmed) to disease progression per IMWG Consensus Panel 1 Criteria ([Rajkumar et al, 2011](#)) or death from any cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive additional anti-cancer therapy (with the exception of stem cell transplant) in the absence of documented progression will be censored at the last evaluable disease assessment prior to the additional therapy.

- Time to next treatment (TTNT): TTNT is defined as the length of time between the date of KITE585 infusion to the date of initiation of the next therapy that was started after documented disease progression.
- Overall survival (OS): OS is defined as the time from KITE-585 infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive. Subjects known to be alive or to have died after the data cutoff date will have OS time censored at the data cutoff date.
- Incidence of AEs and clinically significant changes in laboratory values

9.2.3. Exploratory

- Incidence of MRD ([Kumar et al, 2016](#))
- Levels of KITE-585 cells in blood and serum cytokines
- Incidence of anti-KITE-585 antibodies

9.2.4. Covariates

The following covariates may be used in efficacy and safety analyses:

- ECOG status (0 vs. 1)
- Prior daratumumab exposure (yes vs no)
- Prior autologous bone marrow transplant (yes vs no)
- Disease burden ($\leq 50\%$ vs $\geq 50\%$ clonal plasma cells on bone marrow aspirate or biopsy)
- Disease risk stratification (≥ 1 FISH abnormalities listed in [Section 6.2.3.1](#) vs 0 abnormalities)
- Dual-refractory disease (yes vs no)
- BCMA expression on pretreatment MM cells
- Subject body weight at time of leukapheresis

9.3. Handling of Missing Data

Missing dates will not be imputed, unless further specified in the statistical analysis plan.

9.4. Sample Size Considerations

Approximately 6 to 64 subjects overall will be enrolled and treated.

- 6 to 24 subjects in the initial dose escalation portion
- Up to approximately 20 additional subjects with creatinine clearance ≥ 60 mL/min by Cockcroft-Gault estimation may be treated with the MTD or a lower dose to gain additional information about benefit/risk (Expansion Cohort 1)

- Up to approximately 20 additional subjects with moderate renal impairment (creatinine clearance 30 to 59 mL/min [Grade 2 chronic kidney disease]) may be treated with the MTD or a lower dose (Expansion Cohort 2)

9.5. Analysis Subsets

DLT evaluable set: The DLT evaluable set is defined for each dosing cohort in the dose escalation period as a subject who:

- Received the target dose ($\pm 20\%$) and were followed for at least 28 days after the first KITE-585 infusion; or
- Received a dose of KITE-585 lower than 20% below the target dose for that cohort and experienced a DLT during the 28-day post-first-infusion period.

If needed, additional subjects will be enrolled to achieve enough DLT evaluable subjects at the target dose for each cohort to estimate the true DLT rate.

Full analysis set (FAS): The full analysis set is defined as all subjects treated with any dose of KITE-585. If not specified otherwise, this analysis set will be used for evaluation of all endpoints.

Per protocol analysis set (PPAS): The per protocol analysis set includes subjects who have not deviated from the protocol in such a manner that the assessment of efficacy endpoints may be biased. A subject may be excluded from the PPAS due to insufficient exposure to study drug, important protocol deviation, enrollment criteria violation, or any other situation that may affect the assessment of efficacy endpoints.

9.6. Access to Individual Subject Treatment Assignments

This is a Phase 1, single-arm, open-label study, and subjects and investigators will be aware of treatment received. Data handling procedures will be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures will be outlined in the study statistical analysis plan.

9.7. Interim Analysis

Safety data will be reviewed by the SRT as detailed in [Section 8.6](#) and [Section 9.7.1](#).

Exploratory analysis may be performed given the study data are accumulated and reviewed.

9.7.1. Safety Analysis

The SRT will be chartered to review subject-level safety data at defined milestones. During the dose escalation phase, the SRT will review safety data at the completion of enrollment and treatment of each dosing cohort (see [Section 8.6](#)) and before opening the next dose level. During Expansion Cohort 1 and Cohort 2, the SRT will review safety data after 10 and 6 subjects, respectively, have been treated with KITE-585 and followed for 28 days. Additional information about safety monitoring is described in the SRT charter.

9.8. Planned Method of Analysis

Analysis to support the clinical study report (CSR) will occur after all enrolled subjects have had the opportunity to complete 6 months of protocol-specified visits, have died, or have withdrawn from the study.

Descriptive statistics will be provided for all endpoints. Unless otherwise stated, safety and efficacy analysis will be conducted on full analysis set. Per protocol analysis set or other identified subgroups can be used to evaluate safety or efficacy endpoints. Continuous measurements will be summarized using the following summary descriptive statistics: number of subjects, median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical measurements. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

9.8.1. Clinical Response Rate

The incidence of response rates, best response, and their exact 2-sided 95% confidence intervals will be generated.

9.8.2. Progression-free Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for PFS time. Estimates of the proportion of subjects alive and progression-free at selected time points will be provided.

9.8.3. Overall Survival

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for overall survival time. Estimates of the proportion of subjects alive at selected time points will be provided.

9.8.4. Time to Next Treatment

Kaplan-Meier estimates and 2-sided 95% confidence intervals will be generated for time to next treatment survival time. Estimates of the proportion of subjects who have not required additional treatment for progressive MM at selected time points will be provided.

9.8.5. Safety Analysis

Subject incidence rates of AEs, including all, serious, fatal, CTCAE version 4.03 Grade 3 or higher, and treatment-related AEs, and reported throughout the conduct of the study will be tabulated by preferred term and system organ class. Changes in laboratory values and vital signs will be summarized with descriptive statistics. The incidence of concomitant medications will be summarized.

Tables and/or narratives of deaths through the long-term follow-up and treatment-related SAEs will be provided.

9.8.6. Long-term Data Analysis

All subjects will be followed for survival for up to approximately 15 years after the last subject receives KITE-585. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

10. REFERENCES

- Ali SA, Shi V, Maric I, Wang M, Stroncek DF, Rose JJ, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. *Blood*. 2016;128(13):1688-700.
- Antoun A, Vekaria D, Salama RA, Pratt G, Jobson S, Cook M, Briggs D, Moss P. The genotype of RAET1L (ULBP6), a ligand for human NKG2D (KLRK1), markedly influences the clinical outcome of allogeneic stem cell transplantation. *British journal of haematology*. 2012;159(5):589-98.
- Batts ED, Sanchorawala V, Hegerfeldt Y, Lazarus HM. Azotemia associated with use of lenalidomide in plasma cell dyscrasias. *Leuk Lymphoma*. 2008;49(6):1108-15.
- Baz R, Walker E, Karam MA, Choueiri TK, Jawde RA, Bruening K, et al. Lenalidomide and pegylated liposomal doxorubicin-based chemotherapy for relapsed or refractory multiple myeloma: safety and efficacy. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2006;17(12):1766-71.
- Becker N. Epidemiology of multiple myeloma. Recent results in cancer research Fortschritte der Krebsforschung Progres dans les recherches sur le cancer. 2011;183:25-35.
- Bellucci R, Alyea EP, Chiaretti S, Wu CJ, Zorn E, Weller E, et al. Graft-versus-tumor response in patients with multiple myeloma is associated with antibody response to BCMA, a plasma-cell membrane receptor. *Blood*. 2005;105(10):3945-50.
- Berdeja J, Lin Y, Raje N, Siegel S, Munshi N, Liedtke M, et al. First-in-human multicenter study of bb2121 anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: Updated results. *J Clin Oncol*. 2017;35(suppl):Abstract #3010 2017 ASCO.
- Blade J, Fernandez-Llama P, Bosch F, Montoliu J, Lens XM, Montoto S, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. *Arch Intern Med*. 1998;158(17):1889-93.
- Boomer JS, Green JM. An enigmatic tail of CD28 signaling. *Cold Spring Harb Perspect Biol*. 2010;2(8):a002436.
- Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, Yang S, Gress RE, Hakim FT, Kochenderfer JN. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. *Clin Cancer Res*. 2013;19(8):2048-60.

Cavo M, Tacchetti P, Patriarca F, Petrucci MT, Pantani L, Galli M, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet (London, England)*. 2010;376(9758):2075-85.

Cohen A, Garfall AL, Stadtmauer EA, Lacey SF, Lancaster E, Vogl DT, et al. B-Cell Maturation Antigen (BCMA)-Specific Chimeric Antigen Receptor T Cells (CART-BCMA) for Multiple Myeloma (MM): Initial Safety and Efficacy from a Phase I Study. American Society Of Hematology (ASH) Annual Meeting. 2016;Abstract #1147.

Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357(21):2123-32.

Dimopoulos MA, Chen C, Spencer A, Niesvizky R, Attal M, Stadtmauer EA, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. *Leukemia*. 2009;23(11):2147-52.

Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016;375(14):1319-31.

Dudley ME, Yang JC, Sherry R, Hughes MS, Royal R, Kammula U, et al. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. *J Clin Oncol*. 2008;26(32):5233-9.

Eagle RA, Traherne JA, Hair JR, Jafferji I, Trowsdale J. ULBP6/RAET1L is an additional human NKG2D ligand. *Eur J Immunol*. 2009;39(11):3207-16.

Finney HM, Lawson AD, Bebbington CR, Weir AN. Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product. *Journal of immunology (Baltimore, Md : 1950)*. 1998;161(6):2791-7.

Gattinoni L, Finkelstein SE, Klebanoff CA, Antony PA, Palmer DC, Spiess PJ, et al. Removal of homeostatic cytokine sinks by lymphodepletion enhances the efficacy of adoptively transferred tumorspecific CD8+ T cells. *Journal of experimental medicine, The*. 2005;202(7):907-12.

Guy CS, Vignali DA. Organization of proximal signal initiation at the TCR:CD3 complex. *Immunol Rev*. 2009;232(1):7-21.

Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol*. 2010;28(30):4621-9.

Howlander N, Noone A, Krapcho M, Miller D, Bishop K, Altekruse S, et al. SEER Cancer Statistics Review, 1975-2013. National Cancer Institute Bethesda, MD, http://seercancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. 2015.

Hudecek M, Einsele H. Myeloma CARs are rolling into the clinical arena. *Blood*. 2016;128(13):1667-8.

Keats JJ, Fonseca R, Chesi M, Schop R, Baker A, Chng WJ, et al. Promiscuous mutations activate the noncanonical NF-kappaB pathway in multiple myeloma. *Cancer Cell*. 2007;12(2):131-44.

Klebanoff CA, Khong HT, Antony PA, Palmer DC, Restifo NP. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. *Trends in Immunology*. 2005;26(2):111-7.

Knudsen LM, Hjørth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. *Eur J Haematol*. 2000;65(3):175-81.

Kochenderfer JN, Somerville RPT, Lu T, Shi V, Bot A, Rossi J, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. *J Clin Oncol*. 2017;Mar 14: doi: 10.1200/JCO.2016.71.3024.

Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood*. 2012;119(19):4375-82.

Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet Oncology*. 2016;17(8):e328-46.

Kumar SK, Callander NS, Alsina M, Atanackovic D, Biermann JS, Chandler JC, et al. Multiple Myeloma, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2017;15:230-69.

Kumar SK, Lee JH, Lahuerta JJ, Morgan G, Richardson PG, Crowley J, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. *Leukemia*. 2012;26(1):149-57.

Landgren O. Monoclonal gammopathy of undetermined significance and smoldering multiple myeloma: biological insights and early treatment strategies. *Hematology Am Soc Hematol Educ Program*. 2013;2013:478-87.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, Grupp SA, Mackall CL. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-95.

Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet (London, England)*. 2015;385(9967):517-28.

Lee L, Bounds D, Paterson J, Herledan G, Sully K, Seestaller-Wehr LM, et al. Evaluation of B cell maturation antigen as a target for antibody drug conjugate mediated cytotoxicity in multiple myeloma. *British journal of haematology*. 2016;174(6):911-22.

Lipson EJ, Huff CA, Holanda DG, McDevitt MA, Fine DM. Lenalidomide-induced acute interstitial nephritis. *The oncologist*. 2010;15(9):961-4.

Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, et al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. *Molecular therapy : the journal of the American Society of Gene Therapy*. 2017;25(1):28595.

Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. *N Engl J Med*. 2015;373(13):1207-19.

Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *N Engl J Med*. 2015;373(7):621-31.

Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet (London, England)*. 2016;387(10027):1551-60.

Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014. *J Clin Oncol*. 2015;33(6):654-6.

Moreau P, Avet-Loiseau H, Facon T, Attal M, Tiab M, Hulin C, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. *Blood*. 2011;118(22):5752-8; quiz 982.

Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016;374(17):1621-34.

Moreaux J, Legouffe E, Jourdan E, Quittet P, Reme T, Lugagne C, et al. BAFF and APRIL protect myeloma cells from apoptosis induced by interleukin 6 deprivation and dexamethasone. *Blood*. 2004;103(8):3148-57.

Neelapu SS, Locke FL, Bartlett NL, Lekakis L, Miklos D, Jacobson CA, et al. Kte-C19 (anti-CD19 CAR T Cells) Induces Complete Remissions in Patients with Refractory Diffuse Large B-Cell Lymphoma (DLBCL): Results from the Pivotal Phase 2 Zuma-1. *Blood (ASH Annual Meeting Abstracts)*. 2016.

Novak AJ, Darce JR, Arendt BK, Harder B, Henderson K, Kindsvogel W, Gross JA, Greipp PR, Jelinek DF. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. *Blood*. 2004;103(2):689-94.

O'Brien SM, Kantarjian HM, Cortes J, Beran M, Koller CA, Giles FJ, Lerner S, Keating M. Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. *J Clin Oncol*. 2001;19(5):1414-20.

Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-9.

Plesner T, Lokhorst H, Gimsing P, Nahi H, Lisby S, Richardson PG. Daratumumab, a CD38 Monoclonal Antibody in Patients with Multiple Myeloma - Data From a Dose-Escalation Phase I/II Study. *Blood (ASH Annual Meeting Abstracts)*. 2012;120(Abstract 73).

Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia. *New England Journal of Medicine*. The. 2011;365(8):725-33.

Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. *American journal of hematology*. 2012;87(1):78-88.

Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117(18):4691-5.

Reece DE, Masih-Khan E, Atenafu EG, Jimenez-Zepeda VH, Anglin P, Chen C, Kukreti V, Mikhael JR, Trudel S. Phase I-II trial of oral cyclophosphamide, prednisone and lenalidomide for the treatment of patients with relapsed and refractory multiple myeloma. *British journal of haematology*. 2015;168(1):4654.

Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. *Nature reviews Immunology*. 2012;12(4):269-81.

Richardson PG, Jagannath S, Moreau P, Jakubowiak A, Raab MS, Facon T, et al. A Phase 2 Study of Elotuzumab (Elo) in Combination with Lenalidomide and Low-Dose Dexamethasone (Ld) in Patients (pts) with Relapsed/Refractory Multiple Myeloma (R/R MM): Updated Results. *Blood (ASH Annual Meeting Abstracts)*. 2012;120(Abstract 202).

Richardson PG, Siegel DS, Vij R, Hofmeister CC, Baz R, Jagannath S, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood*. 2014;123(12):1826-32.

Richardson PG, Xie W, Jagannath S, Jakubowiak A, Lonial S, Raje NS, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. *Blood*. 2014;123(10):1461-9.

Rosinol L, Oriol A, Teruel AI, Hernandez D, Lopez-Jimenez J, de la Rubia J, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood*. 2012;120(8):1589-96.

Sonneveld P, Goldschmidt H, Rosinol L, Blade J, Lahuerta JJ, Cavo M, et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. *J Clin Oncol*. 2013;31(26):3279-87.

Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-52.

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition. Fourth ed: International Agency for Research on Cancer; 2008. 439 p.

Tai YT, Anderson KC. Targeting B-cell maturation antigen in multiple myeloma. *Immunotherapy*. 2015;7(11):1187-99.

Turtle CJ, Hanafi L-A, Berger C, Hudecek M, Pender B, Robinson E, et al. Immunotherapy of nonHodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor– modified T cells. *Science Translational Medicine*. 2016;8(355):355ra116-355ra116.

Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. *The Journal of clinical investigation*. 2016;126(6):2123-38.

Wang M, Martin T, Bensinger W, Alsina M, Siegel DS, Kavalierchik E, Huang M, Orlowski RZ, Niesvizky R. Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. *Blood*. 2013;122(18):3122-8.

Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357(21):2133-42.

Winearls CG. Acute myeloma kidney. *Kidney Int*. 1995;48(4):1347-61.

Zhan F, Huang Y, Colla S, Stewart JP, Hanamura I, Gupta S, et al. The molecular classification of multiple myeloma. *Blood*. 2006;108(6):2020-8.

APPENDIX 1

International Myeloma Working Group (IMWG) Consensus Panel 1 Criteria

Response	Response Criteria
Stringent complete response (sCR)	Complete response as defined below, <i>plus</i> Normal FLC ratio, <i>and</i> Absence of clonal plasma cells (PCs) by immunohistochemistry or immunofluorescence ¹
Complete response (CR) ²	Negative immunofixation on the serum and urine, <i>and</i> Disappearance of any soft tissue plasmacytomas, <i>and</i> < 5% PCs in bone marrow aspirates
Very good partial response (VGPR) ²	Serum and urine M-protein detectable by immunofixation but not on electrophoresis Or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 hours
Partial response (PR)	≥ 50% reduction of serum M-protein plus reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30% In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD
Progressive disease (PD) ³	Any one or more of the following: Increase of 25% from lowest response value in any one of the following: <ul style="list-style-type: none"> • Serum M-component (absolute increase must be ≥ 0.5 g/dL) • Urine M-component (absolute increase must be ≥ 200 mg/24 hours) • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)

- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
 - Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

Source: Rajkumar et al, 2011 (modified for protocol purposes).

Abbreviations: FLC, free light chain; PC, plasma cell.

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

- ¹ Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.
- ² Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a > 90% decrease in the difference between involved and uninvolved FLC levels.
- ³ Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in subjects without measurable disease by M-protein and by FLC levels; “25% increase” refers to M-protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia, and the “lowest response value” does not need to be a confirmed value. For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.