# CLINICAL STUDY PROTOCOL

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|---|---|
| **Protocol Title:** | A Phase 1 Multicenter Study of KITE-585, an Autologous Anti-BCMA CAR T-Cell Therapy, in Subjects with Relapsed/Refractory Multiple Myeloma |
| **Protocol Number:** | KITE-585-501 |
| **USAN/INN** | Not applicable |
| **Company Code** | KITE-585 |
| **IND Number:** | 17619 |
| **Clinical Study Sponsor:** | Kite Pharma, Inc.<br>2225 Colorado Avenue<br>Santa Monica, CA 90404 |
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| **Amendment Number and Date:** | **2.0, 11 September 2017** |
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**INVESTIGATORS AGREEMENT**

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

Protocol Date: **11 September 2017**

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations and guidelines and agree to abide by all provisions set forth therein.

I agree and will ensure that financial disclosure statements will be completed by:

- Me (including, if applicable, my spouse, legal partner, and dependent children)
- Sub-investigators (including, if applicable, their spouse, legal partner, and dependent children) at the start of the study and for up to one year after the study is completed

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the clinical investigation without prior written consent from Kite Pharma, Inc.

_____
Signature

_____
Name of investigator

_____
Date

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **Title:** | A Phase 1 Multicenter Study of KITE-585, an Autologous Anti-BCMA CAR T-Cell Therapy, in Subjects with Relapsed/Refractory Multiple Myeloma |
| **Indication:** | The treatment of patients with relapsed/refractory multiple myeloma (MM) that has progressed within 60 days after the last dose of prior therapy and who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are refractory to both a proteasome inhibitor and an immunomodulatory agent (ie, dual-refractory). |
| **Study Design:** | Study KITE-585-501 is a Phase 1, multicenter, open-label study evaluating the safety and efficacy of KITE-585 in subjects with relapsed/refractory multiple myeloma (RRMM).<br><br>Approximately 6 to 24 subjects will be enrolled in a standard 3 + 3 dose escalation to evaluate the safety of KITE-585 regimens. Following enrollment and treatment with cyclophosphamide and fludarabine conditioning chemotherapy, subjects will be assigned to one of the following cohorts at a fixed dose (see Sections 3.1 and 6.5.1). |

| Dose Level | Total Anti-BCMA CAR T-cell Dose[†] |
|---|---|
| -1[*] | [redacted] CCI |
| 1 | $3 \times 10^7$ |
| 2 | [redacted] CCI |
| 3 | [redacted] CCI |
| 4 | [redacted] CCI |

[*]If the incidence of dose-limiting toxicities (DLTs) in Cohort 1 is ≥ 2 of 6 subjects 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 6.5.1 for additional information.

Safety within each cohort will be assessed by the incidence of dose-limiting toxicities (DLTs). Enrollment in each cohort will continue to occur sequentially until a maximum tolerated dose (MTD) is reached (see Section 9.6).

A safety review team (SRT), internal to the study sponsor and including at least 1 study investigator, will review the safety data and make recommendations on further study conduct as outlined in Section 9.6.

The sponsor may, in consultation with the SRT, choose to treat up to 40 additional subjects at any dose deemed safe by the SRT up to, and including, the MTD in Expansion Cohort 1 and Cohort 2 to further characterize benefit/risk. Expansion Cohort 1 will be comprised of approximately 20 subjects who meet all eligibility criteria specified for the dose escalation portion of the study. Expansion Cohort 2 will be comprised of up to approximately 20 subjects who meet all eligibility criteria specified for the dose escalation criteria with the exception that they will have moderate renal impairment (creatinine clearance 30 to 59 mL/min by Cockcroft-Gault estimation [Grade 2 chronic kidney disease]).

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:

- Screening
- Enrollment/leukapheresis
- Bridging therapy (at the discretion of the treating investigator)

| | |
|---|---|
| | • Conditioning chemotherapy<br>• KITE-585 treatment (Day 0 through Week 2)<br>• Post-treatment assessment (Week 2 through Month 3)<br>• Long-term follow-up (Month 3 through Year 15) |
| **Study Objectives:** | **Primary Objective**:<br>The primary objective of this study is to evaluate the safety and tolerability of KITE-585, as measured by the incidence of DLTs, as outlined in Section 9.6.1.<br>**Secondary Objectives**:<br>The secondary objective of this study is to gain insight into additional features of safety, tolerability, and efficacy of KITE-585 in subjects with both intact and moderately impaired renal function, including depth and durability of response, minimal residual disease (MRD), survival, and toxicity of the regimen. |
| **Hypothesis:** | KITE-585 at one of the planned dose levels will be considered safe as determined by the incidence of DLTs. |
| **Primary Endpoint:** | Incidence of adverse events defined as DLTs |
| **Secondary Endpoint(s):** | • Objective response rate (partial response [PR] + very good PR (VGPR) + complete response [CR] + stringent CR [sCR]), as determined by study investigators, according to International Myeloma Working Group (IMWG) Consensus Panel 1 Criteria (see Appendix 1)<br>• Duration of response (DOR)<br>• Progression-free survival (PFS)<br>• Time to next treatment (TTNT)<br>• Overall survival (OS)<br>• Incidence of adverse events and clinically significant changes in laboratory values in subjects treated with KITE-585 |
| **Exploratory Endpoint(s):** | CCI |
| **Sample Size:** | Approximately 6 to 64 subjects overall will be enrolled and treated as follows:<br>• 6 to 24 subjects in the initial dose escalation portion<br>• Up to approximately 20 additional subjects with creatinine clearance ≥ 60 mL/min by Cockcroft-Gault estimation (Expansion Cohort 1)<br>• Up to approximately 20 subjects with moderate renal impairment (creatinine clearance 30 to 59 mL/min by Cockcroft-Gault estimation [Grade 2 chronic kidney disease]) |

| | |
|---|---|
| | (Expansion Cohort 2) |
| **Study Eligibility** | Refer to Section 5 for a complete and detailed list of inclusion and exclusion criteria. |
| **Treatment** | **Bridging Therapy (optional):**<br>CCI [redacted].<br>**Conditioning Chemotherapy Treatment:**<br>KITE-585 is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m$^2$/day and cyclophosphamide 300 mg/m$^2$/day, administered daily for 3 days. Refer to Section 6.4 and Section 7.3.4 for chemotherapy treatment details.<br>**Investigational Product:**<br>KITE-585 treatment consists of a single infusion of autologous anti-BCMA CAR T cells administered intravenously. Refer to Sections 6.5 and 7.3.5 for treatment details. |
| **Procedures:** | At specific time points as outlined in the schedule of assessments, subjects will undergo the following procedures:<br>• Collection of informed consent and general medical history, including previous treatments for MM<br>• Physical exam, including vital signs, weight, and performance status<br>• Neurologic assessment<br>• Baseline electrocardiogram (ECG) and echocardiogram (ECHO)<br>• Brain magnetic resonance imaging (MRI)<br>• Disease staging and assessments by serum and urine biomarkers, bone marrow aspirate, and biopsy and positron emission tomography–computed tomography (PET CT)<br>• CCI [redacted]<br>• Blood draw for local laboratory: complete blood count (CBC), chemistry panels, C-reactive protein (CRP), and serum/urine pregnancy test for women of childbearing potential<br>• Blood draw for central laboratory: serum cytokines, peripheral blood mononuclear cells (PBMCs; lymphocyte subsets, replication-competent lentivirus [RCL], and anti-BCMA CAR T cells), and CCI [redacted]<br>• Bone marrow aspirate and biopsy for evaluation of MRD and other biomarkers<br>• Lumbar puncture (LP) for collection of cerebrospinal fluid (CSF) as applicable<br>• Leukapheresis<br>• Bridging therapy (at discretion of treating investigator)<br>• Conditioning chemotherapy (fludarabine and cyclophosphamide)<br>• Hospitalization for KITE-585 infusion<br>• KITE-585 infusion |

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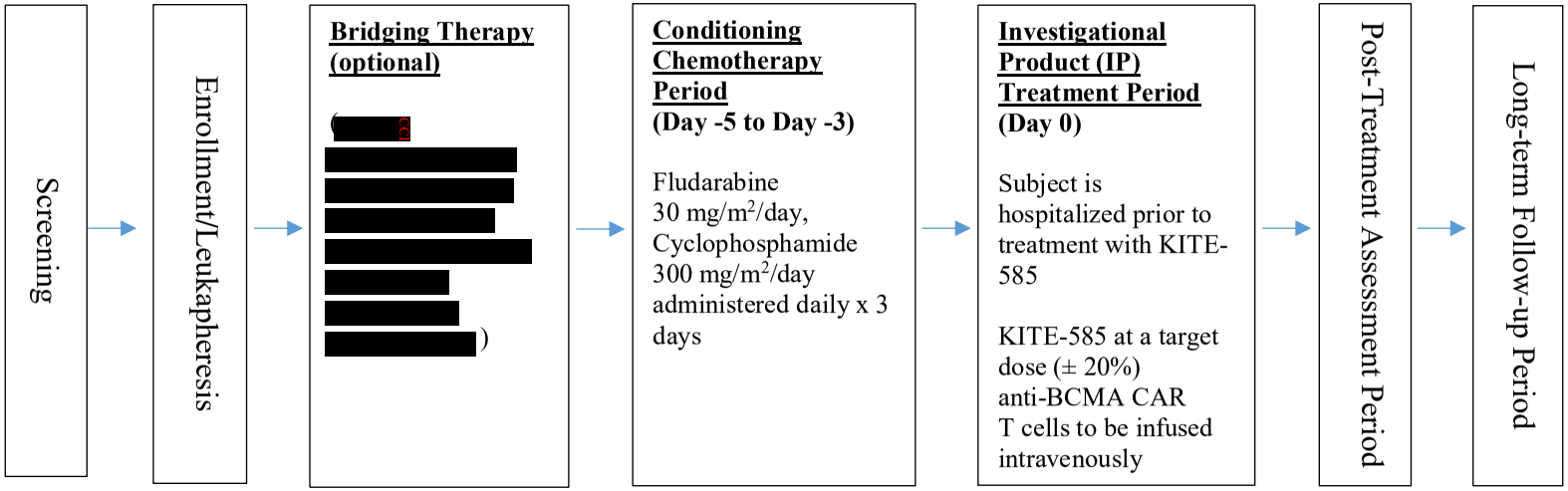
| **Safety Review Team:** | A SRT that is internal to the study sponsor, and including at least 1 study investigator, will review safety data and make recommendations on further study conduct as depicted in Section 3.1, Figure 4, and outlined in Section 9.6. |
| **Statistical Considerations:** | The primary endpoint is the incidence of DLTs.<br>All subjects treated with KITE-585 will be included in the safety analysis. Subject incidence of adverse events and abnormalities in clinical laboratory will be summarized.<br>Demographics, baseline characteristics, pharmacokinetic and pharmacodynamic parameters, and other biomarkers will be analyzed in descriptive statistics. Disease assessments will be evaluated locally per the IMWG Consensus Panel 1 (Rajkumar et al, 2011). MRD will be assessed by IMWG criteria (Kumar et al, 2016). See detailed methods in Section 10.<br>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. |

**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 3.1). **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 3.1, Table 1):

-

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 4, and outlined in Section 9.6.

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.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation/Term | Definition |
|---|---|
| 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 |
| DVT | Deep vein thrombosis |
| ECG | Electrocardiodiogram |
| ECHO | Echocardiodiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |

| Abbreviation/Term | Definition |
|---|---|
| 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 |
| 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 |

| Abbreviation/Term | Definition |
|---|---|
| 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 |
| 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 |

| Abbreviation/Term | Definition |
|---|---|
| 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 9.6.

## 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. DISEASE BACKGROUND AND RATIONALE

Multiple myeloma (MM) is a disease of neoplastic proliferation of antibody-producing plasma cells in the bone marrow. Approximately 86,000 cases of MM occur annually worldwide (Becker 2011), and MM accounts for about 1% of all malignancy and about 10% of hematologic malignancy in the US. Median age of diagnosis is ~70 years (Howlader et al, 2015). Diagnosis of MM is usually made in one of two distinct manners. Subclinical clonal proliferation of plasma cells may precede the formal diagnosis of MM by several years and is usually discovered via the incidental finding of an elevated level of monoclonal antibody concentration in serum, the M-spike, during a workup for unrelated signs or symptoms. This elevation of so-called paraprotein is measured by a serum- or urine protein electrophoresis (SPEP or UPEP, respectively), and represents, in the absence of clinical signs and symptoms of end-organ damage related to MM, a precursor state of either monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM (Landgren 2013). Alternatively, patients may present with full-blown MM, which is characterized by neoplastic plasma cell proliferation in the setting of one of the following clinical hallmarks of MM: hypercalcemia, renal insufficiency, anemia, or pathological bone disease. Formal histopathologic diagnosis is made upon examination of a bone marrow aspirate and core biopsy in which ≥ 10% of cells are clonal plasma cells, which classically contain a nucleus that appears as a "clock face" and contains no nucleoli. Immunophenotypically, the cells will either be kappa or lambda light chain-restricted and display surface expression of CD79a, VS38c, CD138, and CD38 (Swerdlow et al, 2008).

Choices for induction and consolidation strategies are based on both patient-based factors, such as fitness and eligibility for high-dose therapy, followed by autologous stem cell transplantation (ASCT) and disease-based factors, such as tumor cell cytogenetics. Thus, workup for a new case of MM involves an overall health assessment, as well as fluorescent in-situ hybridization (FISH), or conventional cytogenetics. FISH analysis for t(11;14), t(4;14), t(6;14), t(14;16), t(14;20), del17p13, 1q+, and trisomy of odd numbered chromosomes and conventional cytogenetics for del 13, monosomy 13, or hypodiploidy will provide sufficient risk-stratification for clinical decision-making. High-risk disease characteristics include clinical features, such as lactose dehydrogenase (LDH) ≥ 2 times the upper limit of normal (ULN) and the following cytogenetic abnormalities: del 17p, t(14;16), and t(14;20) (Rajkumar 2012).

Initial therapy for MM has changed considerably over the last 15 years. Recent randomized clinical trials have demonstrated that regimens containing novel agents, such as the proteasome inhibitor (PI) bortezomib, and immunomodulatory agents, such as thalidomide or lenalidomide, administered in 2- or 3-drug combinations, have dramatically improved efficacy and safety profiles over older regimens built around cytotoxic chemotherapy backbones (Cavo et al, 2010; Harousseau et al, 2010; Moreau et al, 2011; Kumar et al, 2012; Rosinol et al, 2012; Sonneveld et al, 2013). In the Intergroupe Francophone du Myélome (IFM) cooperative group Phase 3 trial IFM 2005-01, post-induction overall response rates were defined as a very good partial response (VGPR) or better, in subjects treated with bortezomib plus dexamethasone (78.5%) vs vincristine/doxorubicin/dexamethasone (62.8%). Post-induction near-complete responses (nCR), defined as 100% reduction in M-spike, but detectable disease by immunofixation, were seen in 14.8% of subjects treated with bortezomib/dexamethasone vs 6.4% of subjects treated with vincristine/doxorubicin/dexamethasone. Following ASCT and consolidation with cyclophosphamide, etoposide, and cisplatin, progression-free survival (PFS) was improved to 36 months in subjects who received bortezomib vs 29.7 months in those treated in the control arm (Harousseau et al, 2010).

Addition of the immunomodulatory agent thalidomide to bortezomib in the front-line setting led to further improvements in responses. The GIMEMA Italian Multiple Myeloma Network randomized Phase 3 study in nearly 500 patients demonstrated that the combination of bortezomib, thalidomide, and dexamethasone led to a significantly improved objective response rate (ORR) rate vs thalidomide and dexamethasone alone. After post-induction therapy, 62% and 31% of patients treated with the triple therapy achieved a VGPR or nCR or better, respectively, as compared to the thalidomide/dexamethasone only arm in which patients achieved VGPR and nCR rates of 28% and 11%, respectively (Cavo et al, 2010).

More recently, use of the thalidomide analogue lenalidomide in 2- or 3-agent containing regimens with dexamethasone and bortezomib has further improved outcomes. The randomized Phase 2 EVOLUTION trial was designed to evaluate various combinations of bortezomib, lenalidomide, and cyclophosphamide and showed rates of VGPR or better and complete response (CR) (defined as nCR with negative immunofixation) in 51% and 24% of patients, respectively (Kumar et al, 2012). As a result of these and other studies, bortezomib and the immunomodulatory (IMiD) drugs thalidomide and lenalidomide are part of several category 1 recommendations for first-line treatment of newly-diagnosed MM (Kumar et al, 2017).

Unfortunately, in spite of these impressive improvements in durable responses following induction therapy as well as routine use ASCT and prolonged maintenance therapy with either bortezomib or an IMiD in all eligible patients, nearly all patients will eventually relapse. In the first salvage setting, a number of options are available to clinicians and patients, including re-challenge with the original induction regimen, introduction of a different anti-myeloma therapy, ASCT or allogeneic stem cell transplant (SCT), or enrollment in a clinical trial of a novel agent. The original studies of lenalidomide were performed in heavily pretreated patients with MM. Lenalidomide plus dexamethasone received FDA approval for treatment of patients with relapsed MM who had received at least 1 prior therapy, based on 2 randomized studies that enrolled a combined total of 704 subjects. In the MM-009 trial and MM-010 studies, subjects were randomized to receive lenalidomide plus dexamethasone or

dexamethasone alone (Dimopoulos et al, 2007; Weber et al, 2007). The results of these studies were pooled and, at a median follow-up of 48 months, the overall survival (OS) for the lenalidomide/dexamethasone arms was 38 months compared to 31.6 months in the dexamethasone-only arms (p = 0.045) despite crossover after disease progression or unblinding among 47.6% of subjects (Dimopoulos et al, 2009).

Furthermore, combination of lenalidomide with cytotoxic chemotherapy, monoclonal antibodies (eg, elotuzumab and daratumumab), or PI (bortezomib or carfilzomib, a recently FDA-approved second-generation PI) have increased the ORR from 65% to 95% (Baz et al, 2006; Plesner et al, 2012; Richardson et al, 2012; Wang et al, 2013; Richardson et al, 2014; Reece et al, 2015). Carfilzomib and, more recently, ixazomib, an orally-available PI, have produced clinically meaningful responses in patients who have received 1 to 3 prior lines of treatment, including a PI and an IMiD. A randomized Phase 3 trial of carfilzomib, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone in 792 patients (ASPIRE) showed a median PFS (primary endpoint) of 26.3 months and 17.6 months, respectively, and a hazard ratio for progression or death of 0.69 (p = 0.0001) (Stewart et al, 2015).

Next-generation IMiDs like pomalidomide and the orally available PI ixazomib have recently entered clinical usage. Pomalidomide was approved by the FDA in 2013 for use in patients who have received at least 2 prior therapies, including lenalidomide and a PI, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Accelerated approval was based on the results of a randomized open-label study, CC-4047-MM-002, in which 221 subjects were treated with either pomalidomide alone or in combination with low-dose dexamethasone (Richardson et al, 2014). The ORR (including minimal response [MR], partial response [PR], and CR) was 33% in the combination regimen and 18% with pomalidomide monotherapy. The CR rates were 3% and 2%, and the median PFS was 4.2 and 2.7 months, respectively, for the 2 treatment arms. In subjects refractory to both lenalidomide and bortezomib, the CR rates and median PFS for the combination and pomalidomide monotherapy arms were 0% and 1%, respectively, and 3.8 and 2.0 months, respectively (Richardson et al, 2014).

In a randomized study of 722 patients with relapsed MM after 1 to 3 prior therapies, the VGPR rate was 48% in patients treated with the orally available PI ixazomib in combination with lenalidomide and dexamethasone compared with 39% in subjects treated with lenalidomide and dexamethasone alone (Moreau et al, 2016). Rates of serious adverse events (SAEs) were similar, whereas Grade 3 or higher adverse events (AEs) occurred more frequently in the patients randomized to the ixazomib arm (74% vs 69%).

The monoclonal antibodies daratumumab and elotuzumab, which bind CD38 and CS1/SLAMF7, respectively, on the surface of MM cells, have also recently been approved for use in the relapsed MM setting. When it was combined with lenalidomide and dexamethasone in patients with 1 to 3 prior lines of therapy in the randomized Phase 3 study ELOQUENT-2, elotuzumab demonstrated a higher ORR (79%) vs lenalidomide and dexamethasone alone (66%) and improved PFS (19.4 vs 14.9 months; HR 0.70, 95% confidence interval [CI] 0.57 to 0.85) (Lonial et al, 2015). Toxicity was higher in the experimental arm, with higher incidence of Grade 3/4 AEs (65% vs 57%), opportunistic infections (22% vs 13%), and invasive secondary malignancies (9% vs 6%).

The efficacy of daratumumab in patients who have received at least 1 prior line of therapy was demonstrated in 2 randomized Phase 3 studies. First, the POLLUX study randomized 569 subjects to receive lenalidomide and dexamethasone with or without daratumumab (Dimopoulos et al, 2016). ORR was higher in the daratumumab-containing arm (93% vs 76%), with 76% and 25% of subjects attaining a VGPR or CR, respectively, compared to 44% and 12%, respectively, in the control arm. PFS at 12 months was also improved (83% vs 60%, respectively; HR 0.37; 95% CI 0.27 to 0.52, $P < 0.001$). Infusion reactions were observed in 47.7% of subjects in the daratumumab arm and rates of Grade 3 or higher neutropenia (51.9% vs 37.0%) as well as any grade of diarrhea, upper respiratory tract infection, and cough were higher in patients receiving daratumumab than in the control arm.

Daratumumab also became the first FDA-approved treatment for use in patients with relapsed/refractory MM (RRMM) after a minimum of 3 lines of prior therapy or in patients who have documented disease progression following a PI and IMiD-containing regimen (ie, dual-refractory). In 106 subjects treated in the open-label single-arm study SIRIUS, the ORR was 29.2%, with 9.4% and 2.8% achieving a VGPR or stringent CR (sCR), respectively (Lonial et al, 2016). The median PFS was 3.7 months, and the most common Grade 3 or higher AEs were anemia (24%), thrombocytopenia (19%), and neutropenia (12%).

The SIRIUS study is the first pivotal trial to enroll subjects with a minimum of 3 prior lines of treatment that must have included a PI and an IMiD as well as subjects who are dual-refractory to these agents. These are 2 groups where the unmet medical need in MM is highest. However, because of the relative paucity of clinical data in this population, detailed prognostic information on these 2 subgroups of subjects is not yet available. Any potential difference in outcomes in these 2 populations in KITE-585-501 will, therefore, be examined by covariate analysis (see Section 10.2.4).

Similar to patients with other hematologic malignancies, patients with MM typically are treated with novel or more potent agents with each subsequent relapse, and remissions achieved with these agents tend to be more shallow and shorter than the prior remission (Kumar et al, 2012). While the extent to which this observation holds true in the era of novel agents, such as daratumumab, remains uncertain; this pattern of relapsing-remitting disease highlights the lack of curative therapy currently available to patients with multiply relapsed or refractory MM.

## 2.1. Study Rationale

Chimeric antigen receptor (CAR) T cells have recently demonstrated clinically meaningful results in CD19-expressing B-cell malignancies. Academic and industry groups have shown durable remissions in a host of B-cell cancers including non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL) (Porter et al, 2011; Lee et al, 2015; Kochenderfer et al, 2017; Locke et al, 2017). Furthermore, anti-B-cell maturation antigen (BCMA) CAR T-cell therapies have recently entered human testing (Section 2.4; NCT02954445, NCT02546167, NCT02658929, NCT02215967). CAR T-cell therapy, thus, has an established clinical proof of concept in hematologic malignancies. KITE-585-501 is a first-in-human study of an anti-BCMA CAR in patients with MM.

### 2.1.1. Rationale for Treatment of Subjects with Moderate Renal Impairment

Patients with MM are at significant risk of developing acute or chronic renal failure. Myeloma kidney is a frequent complication in which pathological serum light chains are deposited in the renal tubules, causing tubule rupture and interstitial inflammation, ultimately leading to a reduction in glomerular filtration rate. Additionally, the management of MM can lead to further decreases in renal function predominantly via exposure to nephrotoxic agents, such as iodinated contrast, non-steroidal anti-inflammatory drugs, and anti-myeloma therapies, such as lenalidomide (Batts et al, 2008; Lipson et al, 2010). The incidence of renal dysfunction increases with time following an initial MM diagnosis, and subjects who will meet eligibility criteria for this study with respect to prior treatment history commonly have moderate-to-severe renal failure. In the clinical trial that led to FDA approval of daratumumab in subjects with RRMM who had received at least 3 prior lines of therapy, including a PI and an IMiD, or who had disease that was refractory to dual therapy with both a PI an and IMiD, the prior treatment history required in this study, only 57% of subjects had a baseline creatinine clearance of ≥ 60 mL/min; another 40% had a baseline creatinine clearance of 30 to < 60 mL/min.

As discussed above, patients who have multiply-relapsed or refractory disease have few remaining treatment options and are in need of novel and efficacious therapies. Additionally, patients with abnormal kidney function tend to have worse outcomes, representing a significant unmet need in this patient population (Winearls 1995; Blade et al, 1998; Knudsen et al, 2000). However, many patients who receive CAR T cells, including for MM, have experienced cytokine release syndrome (CRS), which may be accompanied by hypotension, vascular leak, and fluid third-spacing, which may exacerbate renal dysfunction at least temporarily and possibly permanently. Therefore, this study will evaluate the safety of KITE-585 in subjects with renal dysfunction cautiously as described in Section 3. If KITE-585 can be delivered safely to subjects with moderately decreased renal function (creatinine clearance of between 30 and 59 mL/min), a substantial additional fraction of patients with RRMM may ultimately benefit from this therapy.

## 2.2. KITE-585 Anti-BCMA CAR T Cells

### 2.2.1. BCMA Background and Tissue Expression

BCMA, the receptor for B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), is a member of the tumor necrosis factor (TNF) receptor superfamily and is also known as TNF superfamily member 17 (TNFRSF17). BCMA is expressed in normal human plasma cells and has limited expression in other tissues. Gene and protein expression profiling has shown that BCMA is broadly expressed in MM cell lines and primary MM cells (Tai and Anderson 2015; Hudecek and Einsele 2016).

In agreement with these published reports of the high prevalence of BCMA expression in MM, a Kite Pharma, Inc., (hereafter referred to as Kite and Kite Pharma) analysis of next-generation sequencing data from the Multiple Myeloma Genomics Portal (Zhan et al, 2006; Keats et al, 2007) found that BCMA RNA was expressed in 91 of 92 MM primary patient samples.

Further, across at least 5 independent studies in the literature, all primary MM cell samples from 114 unique patients tested positive for BCMA cell surface protein or RNA. Three studies of protein

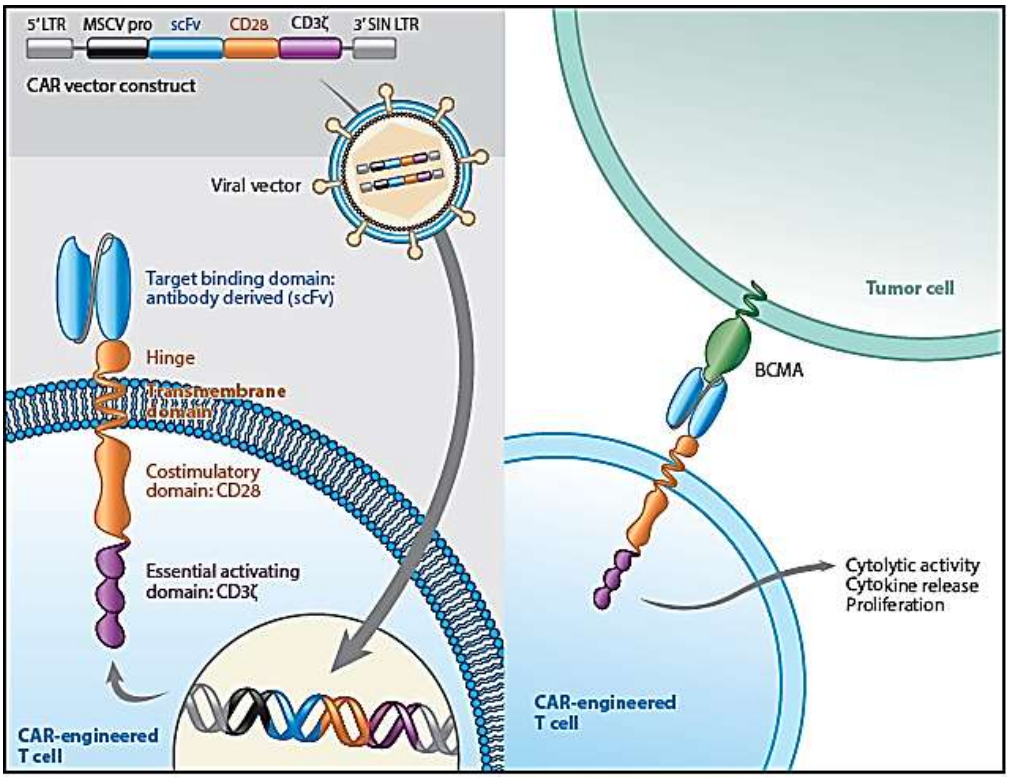
surface expression by flow cytometry or intracellular protein expression by immunohistochemistry, showed that tumor cells from 70 of 70 (100%) patients with MM were positive for BCMA protein expression (Novak et al, 2004; Carpenter et al, 2013; Lee et al, 2016). Forty-four of 44 (100%) patient samples in 2 studies were positive for BCMA RNA expression (Moreaux et al, 2004; Bellucci et al, 2005). BCMA RNA was also found to be maintained in samples tested serially from diagnosis through subsequent relapses in 3 patients with RRMM (Lee et al, 2016).

These analyses and published studies support that BCMA is near universally expressed in MM. Studies of CAR T cells against both CD19 (Neelapu et al, 2016) and BCMA (Cohen et al, 2016) have shown that patients with even low levels of target antigen may experience disease remissions. Therefore, a retrospective analysis of outcomes by BCMA expression levels will be performed to evaluate the relationship between target expression and response.

### 2.2.2. Anti-BCMA CAR T-cell Product

The active moiety for KITE-585 is autologous T cells transduced with a self-inactivating (SIN) lentiviral vector encoding an anti-BCMA CAR construct (Figure 2).

**Figure 2. KITE-585 Construct and Mechanism of Action**




Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD28, cluster of differentiation 28; CD3ζ, cluster of differentiation 3 ζ; LTR, long terminal repeat; [redacted]; scFv, single-chain variable fragment; SIN, self-inactivating.

As shown in Figure 2 and Figure 3, the anti-BCMA CAR comprises 3 regions: 1) a human, anti-BCMA single-chain variable region fragment (scFv) with high specific binding to BCMA expressed on the cell surface; 2) CCI [redacted] CD28; and 3) CD3ζ, the intracellular signaling component of the human T-cell receptor/CD3 complex. CD3ζ provides signals that are essential for T-cell activation (Guy and Vignali 2009), while the CD28 cytoplasmic domain provides important co-stimulatory signals that support T-cell survival and function (Finney et al, 1998; Boomer and Green 2010; Restifo et al, 2012).

**Figure 3. Anti-BCMA CAR Construct**

CCI [redacted]

CCI [redacted]

KITE-585 product is a cryopreserved, autologous, anti-BCMA CAR T-cell product that will be thawed and administered to patients at the bedside. The KITE-585 manufacturing process consists of several distinct processing steps that occur over a period of 6 to10 days. Refer to the KITE-585 Investigator's Brochure (IB) for a detailed discussion of the KITE-585 lentiviral vector, CAR transgene, and manufacturing process.

## 2.3. Nonclinical Experience

### 2.3.1. Safety

Details of the assay methodology and additional results and discussion of nonclinical studies are provided in the KITE-585 IB. Briefly, nonclinical safety studies of KITE-585 were not performed due to the unavailability of suitable murine models. Rather, the potential for off-target toxicities was addressed by 2 in vitro specificity studies.

The first study tested binding of the anti-BCMA CAR T cells to an array of 4,542 human plasma membrane proteins comprising approximately 70% of human plasma membrane proteins. Both a primary screen and a confirmatory assay were performed. Results showed that 19 gene products bound to anti-BCMA CAR T cells in both the primary and confirmation assays. However, 16 of the gene products also bound to non-transduced control T cells, suggesting binding unrelated to the anti-BCMA CAR scFv. The 3 remaining gene products that selectively bound to anti-BCMA CAR T cells, but not control T cells, were tumor necrosis factor RSF17 (TNFRSF17; another name for BCMA), Kit ligand (KITLG), and retinoic acid early transcript 1L (RAET1L; also known as ULBP6). The positive results for KITLG had very weak fluorescence intensity. Further, KITLG had been identified in previous studies as a CAR-independent T-cell binding protein (data not shown). These observations suggest that KITLG is unlikely to be a relevant target for anti-BCMA CAR T cells.

The remaining gene product that bound to anti-BCMA CAR T cells, RAET1L (also known as ULBP6), encodes a glycophosphatidylinositol (GPI)-anchored cell membrane protein that has a limited expression profile in primary human tissues (Eagle et al, 2009). Importantly, the RAET1L receptor, NKG2D, is expressed on almost all T cells (Antoun et al, 2012). Because of its weak binding in the in vitro assay and its known ability to bind T cells through the NKG2D receptor, RAET1L was considered an assay artifact.

To confirm that RAETIL binding was nonspecific, co-culture cytotoxicity assays were performed using a Jurkat cell line known to be positive for RAET1L, but negative for BCMA. This pattern was determined by flow cytometric analysis of surface BCMA and RAET1L expression. Results showed that the anti-BCMA CAR was not cytotoxic against Jurkat cells, while potent cytotoxic activity was seen against 2 BCMA-expressing cell lines, confirming that RAET1L is not a binding target of anti-BCMA CAR T cells. An additional confirmatory test was performed using RD-1, the monoclonal antibody from which the anti-BCMA scFv was derived. In these studies, RD-1 was applied to slides containing the HEK293 cells expressing the 19 different cell surface proteins identified in the primary screen. Only HEK293 cells expressing BCMA, and not those that expressed KITLG or RAET1L, bound to RD-1, providing confirmation that the scFv is selective for BCMA.

Tissue cross-reactivity of RD-1 was also assessed. Sections from frozen tissue microarrays prepared from duplicate 1.5 mm cores of 36 human tissue types from 3 donors were examined by immunohistochemistry (IHC). IHC staining by antibody RD-1 was not suggestive of target expression across 36 human tissues from all 3 donors. Positive signals were observed in colon, placenta, and spleen, but are likely due to the presence of plasma cells in those tissues (Carpenter et al, 2013). Weak, inconsistent signal was seen in brain cortex (1 of 5 duplicate samples), lung parenchyma (1 of 6 duplicate samples), and perineurium of a peripheral nerve (2 of 4 duplicate samples). Weak RD-1 cytoplasmic staining was observed within the liver in 2 of 3 donors. RD-1 staining was also observed in kidney tubule epithelium in 1 of 3 donors.

A repeat study of RD-1 staining in whole sections of liver and kidney from 3 different donors showed no binding to hepatocytes or bile duct epithelium and weak, patchy, and inconsistent cytoplasmic immunoreactivity in kidney tubule epithelium. Similar kidney tubule cytoplasmic staining was seen with an antibody included as a control that was derived from the scFv used in the CAR currently in clinical testing at the National Cancer Institute (NCI) (see Section 2.4). In contrast, staining of the human MM cell line, MM.1s, with both RD-1 and the NCI clone, showed strong immunoreactivity on the cell membrane. Although the inconsistent and weak staining seen in tubules is likely non-specific, that it is restricted to the cytoplasm provides further assurance that it would not be bound by a CAR, which is only able to bind extracellular targets. Additionally, there have been no renal AEs reported from the ongoing NCI study that would suggest tubule-specific CAR T-cell-mediated toxicity.

Additional details on the preclinical in vitro safety studies can be found in the IB.

### 2.3.2. Efficacy

A xenograft mouse model of human MM was used to evaluate anti-BCMA CAR T cells in mice. Briefly, NSG mice (NOD-*scid* IL2Rg$^{null}$) were given intravenous injections of the human MM cell line MM.1S, which has high BCMA expression and contains a luciferase-expressing plasmid (pMMP-Luc-Neo), to

facilitate non-invasive tumor measurement. Infusion with anti-BCMA CAR T cells caused significant extension of survival compared with untreated control mice. Additionally, all mice treated with anti-BCMA CAR T cells had partial tumor regressions, defined as a 50% decrease in tumor burden relative to size before CAR T-cell infusion. No mice had complete remissions in this study. See the IB for additional detail.

A second xenograft model of MM was also used to evaluate anti-BCMA CAR T cells in vivo. In this model system, NSG mice (NOD-*scid* IL2Rg$^{null}$) were given subcutaneous implants of the RPMI8226 MM cell line. After several days of tumor growth, mice were treated with anti-BCMA CAR T cells or untransduced human T cells. The anti-BCMA CAR T-cell infusion prolonged median survival compared with untransduced T-cell treated mice. Six out of 10 mice treated with anti-BCMA CAR T cells had complete remissions in this study, and an additional 3 out of 10 mice had a partial remission. See the IB for additional detail.

### 2.4. Prior Human Experience

CAR T cells directed against BCMA have been developed and tested in human subjects with RRMM in several ongoing clinical trials (NCT02954445, NCT02546167, NCT02658929, NCT02215967). An additional study is investigating a monoclonal antibody against BCMA conjugated to the antimitotic agent, monomethyl auristatin F, in subjects with MM or other BCMA-expressing malignancies (NCT02064387).

Results from the first 12 subjects treated in a Phase 1 first-in-human, single center, open-label study (NCT02215967) were published in 2016 (Ali et al, 2016). Following treatment with cyclophosphamide and fludarabine (300 mg/m$^2$ and 30 mg/m$^2$, respectively, each given daily for 3 days) subjects were treated in a 3 + 3 dose-escalation schema with increasing doses of anti-BCMA CAR T cells (0.3 x 10$^6$, 1.0 x 10$^7$, 3.0 x 10$^7$, and 9.0 x 10$^7$ CAR T cells/kg).

All subjects experienced at least 1 treatment-emergent adverse event (TEAE), most of which were expected cytopenias and laboratory abnormalities attributable to the conditioning chemotherapy regimen, and were generally self-limited and reversible. With respect to anti-BCMA CAR T-cell-related AEs, there were several events consistent with CRS, which has been observed in clinical trials of anti-CD19 CAR T cells. One of 4 (25%) subjects developed significant fever, tachycardia, and hypotension within 1 day of receiving a single, 3 x 10$^6$ anti-BCMA CAR T-cell infusion. The AEs resolved by Day 6 after infusion.

Both subjects treated with 9 x 10$^6$ cells/kg developed significant toxicity attributable to CRS. One subject developed fever and tachycardia 4 hours after receiving the CAR T-cell infusion. The subject went on to develop a prolonged fever lasting 7 days that reached 41°C as well as elevated C-reactive protein (CRP), hypotension requiring vasopressors, elevated serum creatine phosphokinase (CPK; measured > 20000 U/L, normal 39 to 308 U/L), and muscle weakness. The subject was treated with tocilizumab on Day 3 and Day 4. All toxicities except cytopenias resolved by Day 15.

The second subject treated at this dose level also developed fever 4 hours after CAR T-cell infusion. The subject developed elevated CRP, sustained fever, hypoxemia, and Grade 3 delirium. Tocilizumab was

given at 25 hours and 5 days after infusion. Corticosteroids were also administered for 13 days although the patient had known adrenal insufficiency prior to enrollment in the study. Less than 8 weeks after infusion, all toxicities had resolved to Grade 1 or less except lymphopenia.

Evidence of anti-myeloma CAR T-cell activity was observed. Serum paraprotein, free light-chains, and bone marrow myeloma cell populations all reflected anti-tumor efficacy, and clinical response was observed, particularly at the 3 x $10^6$ and 9 x $10^6$ antiBCMA- CAR T cells/kg dose levels. The ORR across all dosing groups was 4 of 12 (33%) and 3 of 6 (50%) in subjects who received 3 x $10^6$ or 9 x $10^6$ anti-BCMA CAR T cells per kg.

Two additional Phase 1, first-in-human trials, NCT02546167 and NCT02658929, have also recently reported results at international congresses. Both therapies appear to be active, with evidence of both toxicity, including CRS and neurological toxicity, as well as disease control and durable responses (Cohen et al, 2016; Berdeja et al, 2017). Additional details are provided in the IB.

KITE-585 has not yet been tested in human subjects, and KITE-585-501 is a first-in-human study.

## 3. STUDY DESIGN

### 3.1. 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 9.6).

**Table 1. Dosing Cohorts**

| Dose Level | Total Anti-BCMA CAR T-Cell Dose† |
|---|---|
| -1* | [redacted] CCI |
| 1 | 3 x $10^7$ |
| 2 | [redacted] CCI |
| 3 | [redacted] CCI |
| 4 | [redacted] CCI |

*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 6.5.1 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 9.6.

After a dose level has been determined by the SRT to be tolerable based on the incidence of DLTs (see Section 9.6.1), 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.

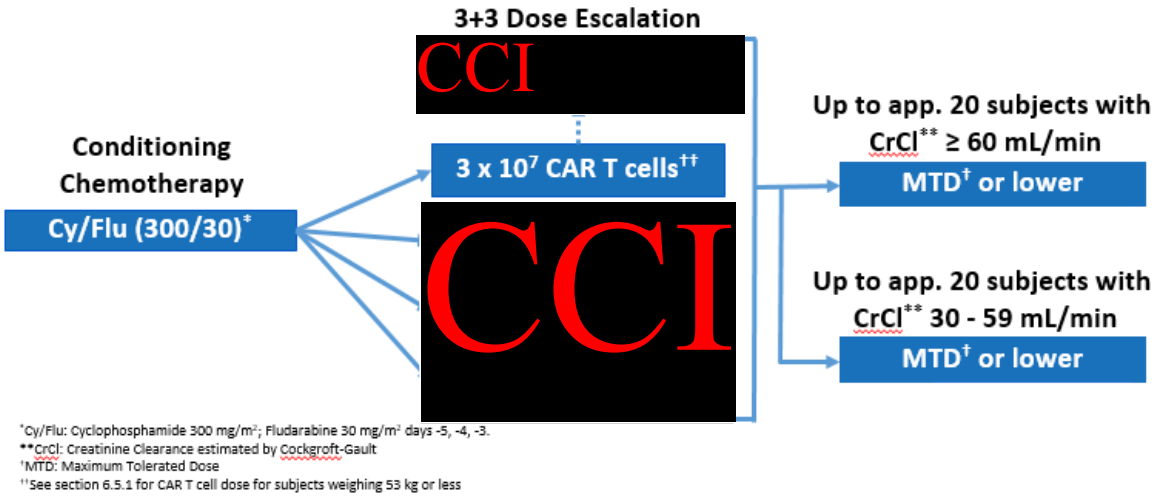
- Expansion Cohort 1: Up to approximately 20 additional subjects with creatinine clearance ≥ 60 mL/min by Cockcroft-Gault estimation
- Expansion Cohort 2: Up to approximately 20 subjects with moderate renal impairment (creatinine clearance 30 to 59 mL/min [Grade 2 chronic kidney disease]). The first 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 4 and outlined in Section 9.6.

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 4. 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 7 for details.

A study schema is provided in the protocol synopsis.

### 3.2. 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.

### 3.3. 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.

### 3.4. Replacement of Subjects

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

### 3.5. Study Duration

#### 3.5.1. 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.

#### 3.5.2. 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).

## 4. 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 7 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).

## 5. SUBJECT ELIGIBILITY

### 5.1. 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 ≥ 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) ≥ 1,000/µL
    - Platelet count ≥ 75,000/µL
    - Absolute lymphocyte count ≥ 100/µL
    - 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 ≤ 3.0 x ULN may be enrolled)
    - Cardiac left ventricular ejection fraction ≥ 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).

### 5.2. Exclusion Criteria

201. Presence of ≥ 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.

# 6. 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 7.3.2.1, 7.3.4.1, and 7.3.5.1, 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.

## 6.1. 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.

### 6.2. Leukapheresis

Subjects will undergo leukapheresis to obtain T cells for the manufacturing of KITE-585 as described in Section 2.2.2 and 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 6.7 for excluded medications prior to leukapheresis.

Before leukapheresis commences, the criteria outlined in Section 7.3.2.1 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 6.5).

### 6.3. Bridging Therapy

CCI

**conditioning chemotherapy to ensure cardiac inclusion/exclusion criteria continue to be met.**

- The following therapies are not allowed for bridging therapy:


See Section 7.3.3 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.

### 6.4. 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.

#### 6.4.1. 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 $mg/m^2$) and fludarabine (30 $mg/m^2$) both given for 3 concurrent days. Cyclophosphamide (500 $mg/m^2$) and fludarabine (30 $mg/m^2$) 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.

### 6.5. 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.

### 6.5.1. 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 4, and further discussed in Sections 3.1 and 9.6.

Given the absence of suitable animal toxicology models as discussed in Section 2.3, 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 $10^5$ CAR T cells/kg (1.6 to 4.0 x $10^7$ 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 $10^6$ or 2 x $10^6$ 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 $10^7$ total CAR T cells in a 50 kg subject to 1 to 2 x $10^8$ 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 $10^6$ CAR T cells/kg dose level. At the 1 x $10^6$ 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 $10^6$ 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 $10^7$ CAR T cells) and 1/3 (33%) of subjects treated with dose level 4 (80 x $10^7$ CAR T cells, Table 2 [Berdeja et al, 2017]). The planned starting dose of KITE-585 of 3 x $10^7$ 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 Two Anti-BCMA CAR T-cell Studies**

| | Target Cell Dose | Cell Dose in 80 kg Subject | Grade ≥ 3 CRS (%) |
|---|---|---|---|
| Study # 1<br>Ali et al.<br>(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%) |
| | 5 x $10^7$ | 5 x $10^7$ | 0/3 (0%) |
| | 15 x $10^7$ | 15 x $10^7$ | 0/3 (0%) |

| | | | |
|---|---|---|---|
| Study #2 Berdeja et al. (NCT# 02658929) | 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 4 calls for a CCI 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 3.1 for dose details). **Finally, subject weight at leukapheresis will be examined as a covariate of safety and efficacy outcomes.**

### 6.6. 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 6.7.

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 9.4 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 9.2 and 9.4)
- 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.

### 6.7. 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.

### 6.8. 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).

### 6.9. 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.**

## 7. 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 7.3.

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

### 7.1. 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** | |
| • Sodium<br>• Potassium<br>• Chloride<br>• Total $CO_2$ (bicarbonate)<br>• Creatinine<br>• Glucose<br>• Calcium total<br>• Total bilirubin<br>• ALT/GPT<br>• AST/GOT | Complete blood count with differential (differentials include neutrophils, monocytes, lymphocytes) | • C-reactive protein (CRP)<br>• Urine or serum β-HCG pregnancy test (for women of childbearing potential)<br>• Serum:<br>  ○ Serum quantitative immunoglobulins<br>  ○ Serum free light chains (FLC)<br>  ○ Serum protein electrophoresis (SPEP)<br>  ○ Serum protein immunofixation electrophoresis (SIFE) | • PBMC, including lymphocyte subsets, RCL, and anti-BCMA CAR T-cell levels<br>• Cytokine levels<br>• CCI [redacted]<br>• Tumor tissue from bone marrow aspirate and biopsy<br>• Soluble BCMA<br>• CSF |

| Local Laboratory Samples and Analysis | | | Central Laboratory Samples and Analysis |
|---|---|---|---|
| **Chemistry** | **Hematology** | **Other** | |
| Recommended:<br>• Blood urea nitrogen (BUN)<br>• Magnesium total<br>• Alkaline phosphatase<br>• Direct bilirubin<br>• LDH<br>• Uric acid<br>• Inorganic phosphorus<br>• Albumin | | • Urine (based on a 24-hour collection):<br>o Total protein<br>o Urine protein electrophoresis (UPEP)<br>o Urine protein immunofixation electrophoresis (UIFE)<br>• CSF<br>• Recommended, see Section 7.3.5.5:<br>o Ferritin<br>o 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.

## 7.2. Baseline Disease and Treatment Response Assessments

### 7.2.1. 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.

### 7.2.2. 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)

### 7.2.3. Bone Marrow Evaluations

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

#### 7.2.3.1. 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.

#### 7.2.3.2. 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.

#### 7.2.3.3. 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 7.4 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.

### 7.2.4. 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. CCI [redacted]
- 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.

## 7.3. 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.

### 7.3.1. 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 5 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 9.2 and 9.4) 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 7.2.2)
  - Local and central bone marrow aspirate and biopsy (see Section 7.2.3)
  - Imaging Studies – PET-CT and brain MRI (see Section 7.2.4)
  - CCI [redacted].
- MRI brain (see Section 7.2.4)
- 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 9 for safety reporting guidelines)
- Concomitant medications documentation (see Section 6.6) and previous cancer treatment history

### 7.3.2. Enrollment/Leukapheresis

#### 7.3.2.1. 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 5), 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.

#### 7.3.2.2. 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 panel
  - CBC with differential
  - CRP
- Central labs (to be drawn prior to leukapheresis**)**
  - CCI [redacted]
  - PBMCs
  - Cytokine levels

- Leukapheresis (see Section 6.2 and 7.3.2)
  - After the pre-leukapheresis criteria are met (see Section 7.3.2.1), mononuclear cells will be obtained by leukapheresis (12 to 15 liter apheresis with a goal to target approximately 5 to 10 x $10^9$ 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 9)
- Concomitant medications documentation (see Section 6.6)

### 7.3.3. Bridging Therapy

Subjects may receive bridging therapy at the discretion of the treating investigator (see Section 6.3 for details).

#### 7.3.3.1. Bridging Therapy Administration

CCI [redacted]

#### 7.3.3.2. Bridging Therapy Procedures

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

CCI [redacted]

### 7.3.4. Conditioning Chemotherapy

#### 7.3.4.1. 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 5)
- No acute neurological toxicity > Grade 1 (with the exception of peripheral neuropathy)
- CCI [redacted].

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 ≥ 20,000/μL within 48 hours prior to conditioning chemotherapy
- CRP is ≥ 100 mg/L
- Temperature is ≥ 38.0°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 5)

#### 7.3.4.2. 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 7.3.4.1 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/m$^2$ IV CCI [redacted]
  - **An additional 1 L of isotonic crystalloid at the completion of the cyclophosphamide infusion**
  - **Add mesna per institutional guidelines**
- Fludarabine 30 mg/m$^2$ IV (or, in the case of subjects with moderate renal impairment, 24 mg/m$^2$; see Section 7.3.4.2.1) CCI [redacted]

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.

#### 7.3.4.2.1. 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/m$^2$ IV CCI
  - **An additional 1 L of isotonic crystalloid at the completion of the cyclophosphamide infusion**
  - **Add mesna per institutional guidelines**
- Fludarabine 24 mg/m$^2$ IV CCI

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

### 7.3.4.3. 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 6.4 and 7.3.4)
  - After the pre-conditioning chemotherapy are met (see Section 7.3.4.1), 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 7.3.4.2), and KITE-585 on Day 0 (see Section 7.3.5).
- AE/SAE reporting (see Section 9)
- Concomitant medications documentation (see Section 6.6)

### 7.3.5. KITE-585 Treatment

#### 7.3.5.1. 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 5)
- 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 ≥ 20,000/μL within 48 hours prior to KITE-585 infusion
- CRP is ≥ 100 mg/L
- Temperature is ≥ 38.0°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 5; 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.

#### 7.3.5.2. 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 ≤ 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/μL) 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.

#### 7.3.5.3. 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

#### 7.3.5.4. 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 non-filtered tubing as follows.

Refer to Sections 3.1 and 9.6 for dose cohort details.

#### 7.3.5.5. 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 (≥ 38.3°C) or other vital sign abnormality
- Neurological exam if applicable (see Sections 7.3.1)
- Disease assessment:
  - CCI [redacted]
- 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 ≥ 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 7.4.

- KITE-585 pre-medication (see Section 7.3.5.3)
- KITE-585 infusion (see Section 7.3.5)
  - After the pre-KITE-585 criteria are met (see Section 7.3.5.1), KITE-585 will be administered (see Section 7.3.5.4 and the IPM).
- AE/SAE reporting (see Section 9)
- Concomitant medications documentation (see Section 6.6)
- 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 7.3.5.2 and the SOA)

### 7.3.6. 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 7.3.1)
- Disease assessment, including serum and urine markers, bone marrow aspirate and biopsy, and, if applicable, imaging (see Section 7.2)
- 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
  - CCI [redacted])

- *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 7.3.5 for details)
- CCI [redacted]
- AE/SAE reporting (see Section 9)
- Concomitant medications documentation (see Section 6.6)

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.

### 7.3.7. 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 7.2)
- CCI [redacted]
- Survival status
- Local labs
  - Chemistry panel
  - CBC with differential
- Central labs
  - CCI [redacted]

        - CCI [redacted].
    - 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 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 7.3.5 for details)
- AE/SAE reporting (see Section 9)
- Concomitant medications documentation (see Section 6.6)
- Subsequent therapy for MM reporting (see Section 6.8)

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 9)
- Targeted concomitant medications (see Section 6.6)

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 9)

### 7.4. 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 KITE-585, 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-2Rα); and chemokines IL-8, MIP-1α, MIP-1β, 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. CCI [redacted]

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 | CCI | Treatment Period | | | | | | | Post-treatment Follow-up (Calculated from Day 0) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Conditioning Chemotherapy | | | | | IP [B, N, O] | | | | | |
| **Timeframe** (d=day, w=week, m=month) | ≤ 28 d | ≤ 14 d | | | D-5 | D-4 | D-3 | D-2 | D-1 | D0 (-1d) | D1 – 10[R] | W2 (± 2 d) | W4 (± 3 d) | M2 (± 1 w) | M 3 (± 1 w) |
| 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 [B] | X [B, R] | X | X | X | X |
| ECOG performance status | | X | | | | | | | | | | | | | |
| Neurological exam[C] | | X | | | | | | | | At time of neurological symptoms [I] (see Section 6.9) | | | | | |
| ECG | | X | | | | | | | | | | | | | |
| ECHO [T] | X | | | | | | | | | | | | | | |
| **Brain MRI** [D, I] | X | | | | | | | | | | | | | | |
| **Disease Assessments** | | | | | | | | | | | | | | | |
| Local serum and 24h urine [E] | X | | | | | | | | | | | | X | X | X |
| Local and central BM aspirate and biopsy [F] | | X | | | | | | | | | | X | X | | X |
| PET CT (neck, chest, abdomen, pelvis) [G] | | X | | | | | | | | | | | 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 [R] | X | X | X | X |
| CBC w/differential | | 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 ≥ 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) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Timeframe (month)** | **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] | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | |
| PET CT (neck, chest, abdomen, pelvis) [G] | For subjects with extramedullary disease at baseline: At time of suspected CR and suspected PD<br>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; $O_2$ 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 6.9). 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 7.2.4):** A baseline brain MRI will be performed. On-study brain MRIs should be considered for subjects with ≥ Grade 2 neurological events (see Section 6.9).

[E] **Local Serum and 24-hour Urine (Section 7.2.2):** 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 7.2.3):** 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 7.2.3**.

- 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.
- CCI [redacted]
- 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 7.2.4):** All subjects will have a baseline PET CT after the last therapy 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. 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] CCI [redacted]

[I] **Lumbar puncture for collection of CSF (Sections 7.3):** 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 ≥ 2 neurological symptoms are present (see Section 6.9). 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 7.3.7):** 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 re-admitted 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 ≥ 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 7.3.5.3):** Acetaminophen and diphenhydramine will be administered approximately 1 hour prior to KITE-585 infusion.

[N] **KITE-585 Administration (Section 7.3.5):** Subjects will be hospitalized on Day 0 through Day 5 to received KITE-585 infusion. See Section 7.3.5 for additional details.

[O] **Additional Labs Recommended (Section 7.1):** 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 9):** 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 ≥ 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 9 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:** CCI [redacted].

[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.**

# 8. 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.

## 8.1. 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

### 8.2. 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

## 9. SAFETY REPORTING

### 9.1. 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 9.2. 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.

### 9.2. 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 9.1 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 9.4).

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.

### 9.3. 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."

### 9.4. Reporting of Serious Adverse Events and Non-serious ≥ 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 9.1 for definition of targeted adverse event) 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 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 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: PPD

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 ≥ 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.

### 9.5. 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: PPD

### 9.6. 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.

#### 9.6.1. 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 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 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<br>Grade<br>(CTCAE 4.03 unless otherwise indicated) | Duration | Exceptions |
|---|---|---|
| Grade 3 CRS<br>(Lee et al, 2014) | ≥ 72 hours | n/a |
| Grade 4 CRS<br>(Lee et al, 2014) | Any | n/a |
| Grade 3 non-hematologic AE | ≥ 72 hours | • Fever<br>• Nausea<br>• Hepatic toxicity that resolves to Grade 2 or better in ≤ 14 days<br>• Hypogammaglobulinemia<br>• Tumor lysis syndrome |
| Grade 4 non-hematologic AE | Any | • Fever<br>• Nausea<br>• Hepatic toxicity that resolves to Grade 3 or better in ≤ 72 hours<br>• Hypogammaglobulinemia<br>• Tumor lysis syndrome<br>• Acute renal toxicity requiring dialysis for ≤ 7 days<br>• Intubation for airway protection for ≤ 7 days<br>• AE resolves to ≤ Grade 1 within 2 weeks and baseline within 4 weeks |
| Grade 4 hematologic AE | ≥ 30 days | 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 3.1 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 10.5. 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 x $10^7$ anti-BCMA CAR T cells is ≥ 2/6, the sponsor may, in consultation with the SRT, choose to decrease the dose to 1 x $10^7$ 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.

### 9.6.2. 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 ≥ 33% Grade 4 non-hematological AEs (irrespective if related to the KITE-585 or at least possibly related) that do not decrease to Grade 2 within 7 days

- Subject incidence of ≥ 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 ≥ 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.

## 10. STATISTICAL CONSIDERATIONS

### 10.1. Hypothesis

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

### 10.2. Study Endpoints

#### 10.2.1. Primary

Incidence of AEs defined as DLTs.

#### 10.2.2. 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 non-responders.
- 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 KITE-585 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

### 10.2.3. Exploratory


### 10.2.4. 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 (≤ 50% vs ≥ 50% clonal plasma cells on bone marrow aspirate or biopsy)
- Disease risk stratification (≥ 1 FISH abnormalities listed in Section 7.2.3.1 vs 0 abnormalities)
- Dual-refractory disease (yes vs no)
- BCMA expression on pretreatment MM cells
- **Subject body weight at time of leukapheresis**

## 10.3. Handling of Missing Data

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

## 10.4. 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)

### 10.5. 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 (± 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.

### 10.6. 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.

### 10.7. Interim Analysis

Safety data will be reviewed by the SRT as detailed in Section 9.6 and Section 10.7.1. Exploratory analysis may be performed given the study data are accumulated and reviewed.

#### 10.7.1. 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 9.6) 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.

## 10.8. 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.

### 10.8.1. Clinical Response Rate

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

### 10.8.2. 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.

### 10.8.3. 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.

### 10.8.4. 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.

### 10.8.5. 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.

### 10.8.6. 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.

## 11. REGULATORY OBLIGATIONS

This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

### 11.1. Independent Review Board/Independent Ethics Committee

A copy of the protocol, ICF, and any additional subject or trial information, such as subject recruitment materials, must be submitted to each site's respective IRB/IEC for approval. After approval is obtained from the IRB/IEC, all documents must be provided to the key sponsor contact before subject recruitment can begin.

The investigator must also receive IRB/IEC approval for all protocol and ICF changes or amendments. Investigators must ensure that ongoing/continuous IRB/IEC approval (ie, annual approval) is provided throughout the conduct of the study. Copies of IRB/IEC approval are to be forwarded to the key sponsor contact for archiving.

During the course of the study, investigators are to submit site-specific and study SAEs (provided to the site by the key sponsor contact), along with any protocol deviations, to their IRB/IEC in accordance with their respective IRB/IEC policies.

### 11.2. Subject Confidentiality

Subject confidentiality must be contained at all material submitted to the key sponsor contact. The following rules are to be applied.

- Subjects will be identified by a unique identification number.
- Date of birth or year of birth/age at time of enrollment will be reported according with local laws and regulations.

For reporting of SAEs, subjects will be identified by their respective subject identification number, initials, and data of birth or year of birth (as per their local reporting requirements for both initials and date of birth).

Per country-specific regulations and ICH/GCP guidelines, investigators and institutions are required to permit authorization to the sponsor, Contract Research Organization (CRO), IRB/IEC, and regulatory agencies to subject's original source documents for verification of study data. The investigator is responsible for informing potential subjects that such individuals will have access to their medical records, which includes personal information.

### 11.3. Investigator Signatory Obligations

Each CSR will be signed by the coordinating investigator. The coordinating investigator will be identified by Kite Pharma under the following criteria:

- A recognized expert in the disease setting
- Provided significant contributions to the design or analysis of study data
- Participated in the study and enrolled a high number of eligible subjects

## 12. PROTOCOL AMENDMENTS AND TERMINATION

If the protocol is amended, the Investigator's Agreement with the amendment and the IRB/IEC approval of the amendment must be obtained. Documentation acknowledging approval from both parties are to be submitted to the key sponsor contact.

Both Kite Pharma and the investigator reserve the right to terminate the investigator's ability to enroll additional subjects or general participation in the study as per the terms of the agreement in the study contract. The investigator is to provide written communication to the IRB/IEC of the trial completion, early termination of enrollment, or termination of study participation and provide the CRO with a copy of the correspondence.

Kite Pharma reserves the unilateral right, at its sole discretion, to determine whether to manufacture CAR T cells and provide them to sites and subjects after the completion of the study and before treatment becomes commercially available.

## 13. STUDY DOCUMENTATION AND ARCHIVE

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfil these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data, and records for which the study data are collected and verified. Examples of such source documents may include, but are not limited to, hospital records and patient charts; laboratory, pharmacy, and radiology records; subject diaries; microfiches; correspondence; and death registries. CRF entries may be considered as source data if the site of the original data collection is not available. However, use of the CRFs as source documentation as a routine practice is not recommended.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all subject records that are readily retrieved to be monitored and/or audited at any time by the key sponsor contact, regulatory authorities, and IRB/IECs. The filing system will include at minimum:

- Subject content, including ICFs and subject identification lists
- Protocols and protocol amendments, IB, copies of pre-study documentation, and all IRB/IEC and sponsor communication
- Proof of receipt, experimental treatment flow records, and experimental product-related correspondence

Original source documents supporting entries into CRFs must be maintained at the site and readily available upon request. No study documents should be discarded without prior written agreement between Kite Pharma and the investigator. If storage is no longer be available to archive source documents or must be moved to an alternative location, the research staff should notify the key sponsor contact prior to the shipping the documents.

## 14. STUDY MONITORING AND DATA COLLECTION

The key sponsor contacts, monitors, auditors, or regulatory inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and verifying source documents and records assuring that subject confidentially is respected.

The monitor is responsible for source document verification of CRF data at regular intervals during the study. Protocol adherence, accuracy, and consistency of study conduct and data collection with respect to local regulations will be confirmed. Monitors will have access to subject records.

By signing the Investigator's Agreement, the investigator agrees to cooperate with the monitor to address and resolve issues identified during monitoring visits.

In accordance with ICH/GCP and the audit plan, a site may be chosen for a site audit. A site audit would include, but is not limited to, an inspection of the facility(ies), review of subject- and study-related records for compliance with protocol requirements as well as ICH/GCP and applicable regulatory policies.

All data will be collected in an eCRF system. All entries must be completed in English, and concomitant medications should be identified by tradenames. For additional details about completing CRFs, refer to the CRF completion guidelines.

## 15. PUBLICATION

Authorship of publications from data generated in the Study KITE-585-501 will be determined based on the uniform requirements for manuscripts submitted to biomedical journals (as outlined in the International Committee of Medical Journal Editors December 2013), which states authorship should be based on:

- Substantial contributions to the conception or design of the work, acquisition of data, analysis, or interpretation of data for the work; and
- Drafting the article or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work re appropriately investigated or resolved

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. This individual should fully meet the criteria for authorship defined above.

Funding, collection of data, or general supervision of the research alone or in combination does not qualify an individual for authorship.

Any publication, in any form, that is derived from this study must be submitted to Kite Pharma for review and approval. The study contract between the institution, principal investigator, and Kite Pharma or its delegate will outline the requirements for publication review.

## 16. COMPENSATION

Kite Pharma will provide compensation for study-related illness or injury pursuant to the information outlined in the injury section of the ICF.

## 17. REFERENCES

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## APPENDIX 1

International Myeloma Working Group (IMWG) Consensus Panel 1 Criteria

| Response | Response Criteria |
|---|---|
| Stringent complete response (sCR) | • Complete response as defined below, *plus*<br>• Normal FLC ratio, *and*<br>• Absence of clonal plasma cells (PCs) by immunohistochemistry or immunofluorescence[1] |
| Complete response (CR)[2] | • Negative immunofixation on the serum and urine, *and*<br>• Disappearance of any soft tissue plasmacytomas, *and*<br>• < 5% PCs in bone marrow aspirates |
| Very good partial response (VGPR)[2] | • Serum and urine M-protein detectable by immunofixation but not on electrophoresis<br>Or<br>• ≥ 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<br>• 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<br>• 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%<br>• 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:<br>• Increase of 25% from lowest response value in any one of the following:<br>  ○ Serum M-component (absolute increase must be ≥ 0.5 g/dL)<br>  ○ Urine M-component (absolute increase must be ≥ 200 mg/24 hours)<br>  ○ 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)<br>  ○ 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%)<br>  ○ 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.