Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 USA
Company Code:	KITE-585
USAN Name:	Not Applicable
Product Name:	KITE-585
Protocol:	A Phase 1 Multicenter Study of KITE-585, an Autologous Anti-BCMA CAR T-Cell Therapy, in Subjects with Relapsed/Refractory Multiple Myeloma
Version Number:	Version 1.0
Release Date:	2/26/2019
Replaces Previous Version(s):	Not Applicable
Date:	26 March 2019

CONFIDENTIALITY NOTICE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADaM	Analysis data model
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
ASCT	Autologous stem cell transplant
CAR	Chimeric antigen receptor
CNS	Central nervous system
CRF	Case report form
CRS	Cytokine release syndrome
CTCAE	Common terminology criteria for adverse event
DMP	Data Management Plan
ECOG	Eastern Cooperative Oncology Group
FLC	Free light chain
HLGT	High-level group term
IL	Interleukin
MA	Marketing application
MM	Multiple Myeloma
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
RCL	Replication-competent lentivirus
R/R	Relapsed/Refractory
RRMM	Relapsed/Refractory Multiple Myeloma
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable disease
SDTM	Study data tabulation model
SMQ	Standardized MedDRA query
SOC	System organ class
SRT	Safety review team
Std Dev	Standard deviation
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides the pre-specification and details for the statistical analyses to support the following study:

- KITE-585-501 Amendment 2 entitled "A Phase 1 Multicenter Study of KITE-585, an Autologous Anti-BCMA CAR T-Cell Therapy, in Subjects with Relapsed/Refractory Multiple Myeloma", dated **11 September 2017.**

2. OBJECTIVES

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). 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, minimal residual disease (MRD), survival, and toxicity of the regimen.

3. STUDY DESIGN

3.1. Overview

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.

Table 1. Dosing Cohorts

Dose Level	Total Anti-BCMA CAR T-Cell Dose†
-1*	CCI
1	3×10^7
2	CCI
3	CCI
4	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 Protocol 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.

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

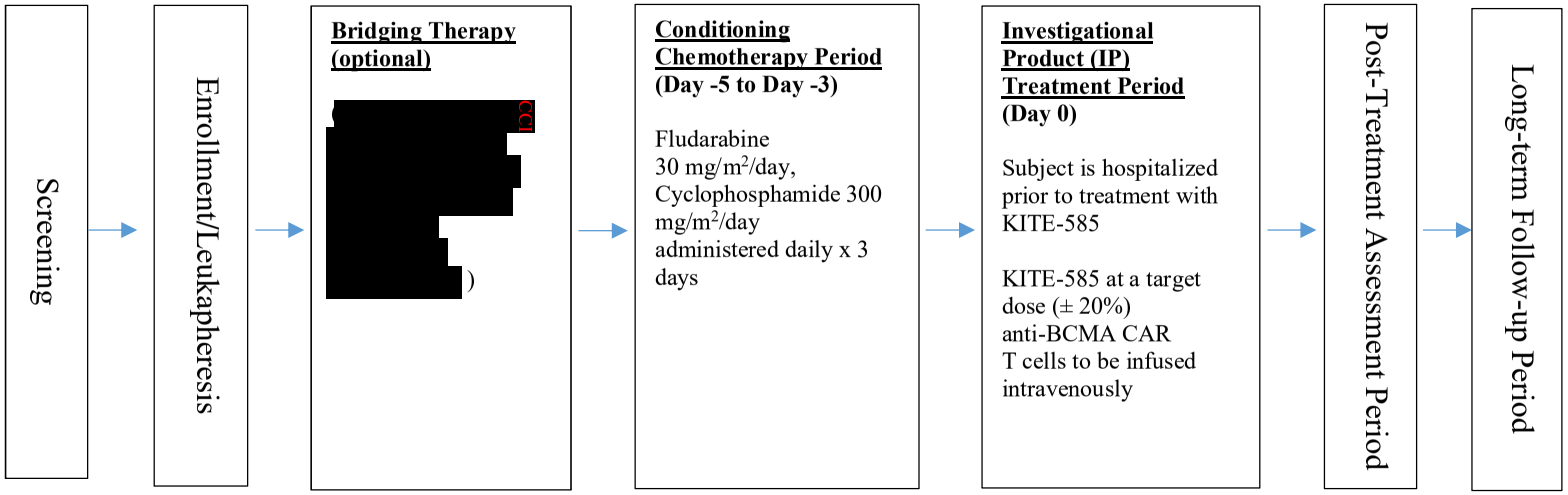
- Expansion Cohort 1: Up to approximately 20 additional subjects with creatinine clearance ≥ 60 mL/min by Cockcroft-Gault estimation may be treated with the MTD or a lower dose.

- Expansion Cohort 2: Up to approximately 20 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. 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.

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, as shown in 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 1. **Study Schema for Study KITE-585-501**



3.2. Hypothesis

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

3.3. Sample Size Consideration

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)

3.4. Statistical Assumptions

There is no plan for formal statistical testing of any safety or efficacy endpoints; no statistical assumptions are made for inference.

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

Primary: Incidence of AEs defined as DLTs.

Secondary:

- Objective response rate (ORR)
- Progression free survival (PFS)
- Duration of response (DOR)
- Time to next treatment (TTNT)
- Overall survival (OS)
- Incidence of AEs and clinically significant changes in laboratory values

Exploratory

4.2. Covariates

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

- Eastern Cooperative Oncology Group (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 vs 0 abnormalities)
- Dual-refractory disease (yes vs no)
- B-cell maturation antigen (BCMA) expression on pretreatment multiple myeloma (MM) cells (%)Subject body weight at time of leukapheresis (<=53 kg vs >53 kg)

Covariate levels that are sparse may be collapsed for purposes of statistical modeling.

Additional associative analyses of covariates with subject outcomes may be explored.

5. DEFINITIONS

5.1. General

Study enrollment: Subject is defined as enrolled as the day of leukapheresis.

Study day 0: Study day 0 is defined as the day the subject received the KITE-585 infusion. The day prior to study day 0 will be day -1. The day of enrollment and any days after enrollment and before study day -1 will be sequential and negative integer valued.

Study day: defined as date of visit/sample/measurement – KITE-585 infusion date.

Baseline: The baseline value is defined as the last value taken prior to conditioning chemotherapy.

Actual follow-up time: Actual follow-up time among all subjects treated with KITE-585 is calculated from KITE-585 infusion date to as death date -1 or last date known alive, whichever is later.

Potential follow-up time: Potential follow-up time is defined for all subjects treated with KITE-585 and is the data cutoff date - KITE-585 infusion date +1.

5.2. Safety

Treatment-emergent adverse event (TEAE): Any adverse event with onset on or after study day 0.

Dose-limiting toxicities (DLT): DLT is defined as the KITE-585-related events with onset within the first 28 days following KITE-585 infusion. Details of the DLT definitions, including duration of event and exceptions, are provided in Protocol Table 6.

Adverse events of interest: Adverse events of interest for KITE-585 treatment includes TEAE of cytokine release syndrome (CRS), neurologic events, infections, cytopenias, and prolonged cytopenia, as described below:

Neurological event: Neurological adverse events are identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy (Topp et al, 2015). The search strategy focuses on central nervous system toxicity, without regard to relatedness, temporal relationship, and concomitant conditions (eg, CRS). Events are identified with a search list of MedDRA preferred terms (PTs).

CRS: CRS will be identified via collection of the syndrome on a case report form (CRF) specifically designed to collect CRS. Specific symptoms of the CRS are collected on the AE log form and are linked to the CRS syndrome. CRS syndrome severity is graded according to a modification of the grading system proposed by Lee and colleagues (Lee et al, 2014). In the modified grading scale, neurologic AEs are not reported as part of the CRS syndrome;

rather, they are reported on the AE log form separately based on specific symptoms per Common Terminology Criteria for Adverse Events (CTCAE).

Cytopenias: Cytopenias (Neutropenia or Thrombocytopenia or Anemia) are identified as:

1) Neutropenia is identified using MST defined by Kite

2) Thrombocytopenia is identified using the SMQ for haematopoietic thrombocytopenia (narrow search)

3) Anemia (**excluding** aplastic anemia) is identified using the SMQ haematopoietic erythropenia (broad search)

Subject incidence of cytopenias will be summarized separately by the 3 blood cell lineages.

Prolonged Cytopenias (Neutropenia or Thrombocytopenia or Anemia)

Subjects with prolonged cytopenias (neutropenia or thrombocytopenia or anemia) will be identified with 2 methods:

- Method 1: Subjects with longest consecutive period with cytopenias (neutropenia or thrombocytopenia or anemia) ≥ 30 days (See Appendix 2 for the definition of longest consecutive period with an AE of interest)

- Method 2: Subjects with cytopenias (neutropenia or thrombocytopenia or anemia) present on or after Day 30 post KITE-585 infusion

Prolonged cytopenias (neutropenia or thrombocytopenia or anemia) will be summarized separately by the 3 blood cell lineages.

Infections: Infections will be identified as AEs within the system organ class (SOC) of infections and infestations that are in MedDRA high level group terms (HLGT) that capture events of:

1) bacterial infection, encompassing preferred terms within the MedDRA HLGT of

   a) bacterial infectious disorders

   b) chlamydial infectious disorders

2) viral infection, encompassing preferred terms within the MedDRA HLGT of viral infectious disorders

3) opportunistic infections, encompassing preferred terms within the MedDRA HLGT of

   a) fungal infectious disorders

   b) mycobacterial infectious disorders

4) Other infections, encompassing preferred terms within the MedDRA HLGT of infections - pathogen unspecified.

Concomitant medication: Concomitant medications are defined as the medications administered to subjects on or after the KITE-585 infusion.

5.3. Efficacy

Objective Response (OR): objective response is defined as either a partial response (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. The derivation of this endpoint will only use response assessments obtained prior to any other anti-cancer therapy (including stem cell transplant or new anti-cancer therapy).

Best overall response (BOR): BOR is defined as the best response recorded from the day of KITE-585 infusion until the end of study, in descending order of precedence by sCR, CR, VGPR, PR, SD, PD or NE. The derivation of this endpoint will only use response assessments obtained prior to any other anti-cancer therapy (e.g. stem cell transplant or new anti-cancer therapy).

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 due to any causeSubjects not meeting the criteria for progression or death due to PD by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Subjects who receive new anti-cancer therapy (including stem cell transplant [SCT]) in the absence of documented progression will be censored at the last evaluable disease assessment prior to the new therapy or SCT.

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 new anti-cancer therapy (including SCT) in the absence of documented progression will be censored at the last evaluable disease assessment prior to the new 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 or death due to any cause, whichever is earlier. Subject with no new anti-cancer therapy and alive by the time of data cutoff will be censored at the last date known to be alive or cutoff date, whichever is earlier

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 or cutoff date, whichever is earlier. Further details on the derivation of overall survival and the specific data modules that will be used to derive the last date known to be alive are provided in Appendix 3.

6. ANALYSIS SUBSETS

6.1. DLT evaluable set:

The DLT evaluable set is used to evaluate the primary endpoint (DLT) and 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.

6.2. Full Analysis Set (FAS)

The full analysis set is defined as all subjects who were enrolled. The FAS will be used for summary of subject disposition, subject listing of deaths and other analyses as specified.

6.3. Safety Analyses Set

The safety analyses 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 except for the primary endpoint (DLT).

6.4. Per protocol analysis set (PPAS)

PPAS includes subjects in the safety analysis set 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.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

7.1. Interim 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 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. Exploratory analysis may be performed given the study data are accumulated and reviewed. SRT will also assess criteria to pause enrollment. For details, refer to protocol section 9.6.2. This is a Phase 1, dose escalation, open-label study, and subjects, study sponsor and investigators will be aware of treatment received.

8. DATA SCREENING AND ACCEPTANCE

8.1. General Principles

The database will be subject to the edit checks outlined in the Data Management Plan and additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analyses and the final database lock. For interim analyses, snapshots may include data that has not passed all data cleaning procedures at the time the data are extracted for snapshot.

8.2. Electronic Transfer and Archiving of Data

The Medidata Rave system will be used to collect the data in this study. Raw data extracted from Medidata Rave will be archived prior to further dataset creation, maintenance, and analysis. Datasets (raw data, study data tabulation model [SDTM] data, and / or analysis data model [ADaM] data) for planned analyses will be archived. Any additional unplanned analyses that occur after the primary analysis and prior to the final analysis will also be archived. Key data external to the clinical study database (see below) will be included in the relevant SDTM and ADaM modules when the external data are available.

8.3. Handling of Missing and Incomplete Data

8.3.1. Efficacy

The method for handling missing data is described in the definition for each efficacy endpoint. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date and the corresponding censoring date for survival, the algorithm in Appendix 1 will be used.

8.3.2. Safety

Partial adverse event start dates will be imputed. If dates are missing or incomplete for adverse event start dates, the algorithm defined in Appendix 1 will be used.

8.4. Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will be summarized. Lack of protocol compliance will be evaluated by summarizing the subject incidence of important protocol deviations. High rates of important protocol deviations may indicate bias.

8.5. Outliers

Descriptive statistics will be used to identify potential outliers in any key variables analyzed. Suspected outliers will be included in all analyses unless there is sufficient scientific justification to exclude them.

8.6. Distributional Characteristics

The exact 95% confidence intervals will be generated for the response rate. The Clopper-Pearson method will be used to generate this interval. While the Clopper-Pearson interval provides adequate coverage probability, it is commonly wider than necessary (Brown et al, 2002), leading to overly conservative estimates of the lower bound of objective response rate.

8.7. Validation and Configuration Management

Programs for the development of the SDTM and ADaM datasets and the generation of the tables, figures, and listings will be developed and maintained according to Kite Pharma Standard Operating Procedures. The software and version used to generate analyses will be indicated in the archived documentation.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

Descriptive statistics will be provided for all endpoints. Continuous measurements will be summarized using the following summary descriptive statistics: number of subjects, mean, median, standard deviation (Std Dev), Q1, Q3, 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. Unless otherwise specified, analyses will be done by dose level. Expansion cohort may be tabulated separately.

The goal of the primary analysis is to find the maximum tolerable dose (MTD) of KITE-585 as determined by subject incidence of DLT in each dose escalation cohort. The analysis of DLTs will be based on the DLT evaluable set. Unless otherwise stated, safety and efficacy analysis will be conducted on the safety analysis set. The per protocol analysis set or other identified subgroups may be used to evaluate safety or efficacy endpoints as additional analyses.

The timing of the interim and primary analyses will be based on subject accrual and disease assessment milestones. The primary analysis 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.

9.2. Subject Accountability

The number of subjects screened, enrolled (leukapheresed), treated with bridging therapy, treated with conditioning chemotherapy, and treated with KITE-585 will be summarized. The reasons for discontinuing KITE-585 treatment and discontinuing study will be summarized.

Summaries of actual and potential follow-up time will be provided.

The number of subjects in each analysis set along with reasons for exclusion will be provided.

9.3. Important Protocol Deviations

The clinical study team will define important protocol deviation categories and review all potential important protocol deviations prior to the database snapshot for the primary efficacy analysis, at a minimum. Important protocol deviations will be categorized by deviation type (eg, entry/eligibility, use of excluded medication). The subject incidence of important protocol deviations will be summarized overall and by deviation category.

9.4. Demographic and Baseline Characteristics

Summary statistics and frequencies for the following demographic and baseline characteristics will be tabulated:

- ECOG performance status at baseline

- Sex (male, female)
- Subject body weight at time of leukapheresis and at baseline
- Age at enrollment and its categories (< 65, ≥ 65)
- Race: white, Asian, other (categories may be collapsed or expanded based on accrual)
- Ethnicity
- Number of prior lines of therapies
- 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 vs 0 abnormalities)
- High cytogenetic risk (yes vs no)
- Dual-refractory disease (yes vs no)
- BCMA expression on pretreatment MM cells
- Disease stage (I or II vs III)
- Creatinine clearance (<30, <60, ≥60)

9.5. Efficacy Analyses

Efficacy analyses will be conducted on the safety analysis set. For the primary analysis, the investigator's read of disease status per IMWG Consensus Panel 1 Criteria (Rajkumar et al, 2011) will be used (Protocol Appendix 1). The investigator will provide the determination of disease status: Stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Not Evaluable (NE) at each time point.

In the event any subject undergoes a stem cell transplant (SCT) or any new anti-cancer therapy while on study, the subject's best response will be derived only based on disease outcomes assessed prior to SCT or initiation of new therapy. For subjects without documentation of disease progression prior to initiation of new therapy (including SCT), PFS/DOR will be censored at their last evaluable disease assessment date prior to the initiation of new therapy (including SCT). Further details are discussed in Appendix 3.

9.5.1. Objective Response Rate (ORR) and Best Response

The subject incidence of objective response per investigator reviewer will be calculated. The subject incidence of best response (sCR, CR, VGPR, PR, SD, PD, or NE) will also be calculated. Confidence intervals will be provided for the ORR and best response rates, calculated with the Clopper-Pearson method. The primary analysis of objective response and best response will include subjects from the safety analyses set.

ORR and its 95% confidence interval will be generated for subgroups of the safety analyses defined by each of the categorical variables in Section 4.2. Subgroup analyses with additional covariate may also be explored.

A forest plot of the ORR for each of these subgroups will be generated.

9.5.2. Progression Free Survival (PFS)

The number of subjects censored or having events, and the reasons for censoring and type of events will be summarized. Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for 25%, 50%, and 75% of progression-free survival (PFS). Kaplan-Meier estimates and 95% confidence intervals of the proportion of subjects alive and progression-free at selected time points will be provided.

Subgroup analyses of the PFS rate may be generated in subgroups defined by the covariates in Section 4.2.

9.5.3. Duration of Response (DOR)

The number of subjects censored or having events, the reasons for censoring, and type of events, will be summarized. Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for 25%, 50% and 75% of DOR. Kaplan-Meier estimates and 95% confidence intervals of the proportion of subjects that are still in response at selected time points after first objective response will be provided.

Primary analysis of DOR will be conducted in the safety analyses set

9.5.4. Overall Survival (OS)

The analysis of OS will use the same methods as the analysis of progression-free survival.

OS may be summarized in subgroups defined by the best response attained on study.

9.5.5. Time to next Treatment (TTNT)

The analysis of time-to-next-treatment (TTNT) will use the same methods as the analysis of progression-free survival. Estimates of the proportion of subjects who have not required additional treatment for progressive MM at selected time points will be provided.

9.5.6. Disease burden

The change in disease burden, as measured by the level of serum and urine M protein, difference between involved and uninvolved free light chain (FLC) levels, percentage of clonal plasma cells on bone marrow aspirate or biopsy and plasmacytoma diameters (only in bone and soft-tissue separately) from baseline to post-baseline nadir will be summarized in absolute numbers and percentage. A graphical summary of this change will be presented in a vertical bar chart with each subject's change from baseline to nadir displayed as a vertical bar, with color coding that indicates best response attained ("waterfall" plot). Summary statistics will be provided for this change. Additionally, plots over time of the percent change in disease burden for each subject (superimposed on one graph) will be presented. Data collected after new anticancer therapy or SCT will not be included for the analyses.

9.5.7. Minimal residual disease (MRD)

The subject incidence of presence of MRD will be provided at selected time points.

9.6. Safety Analyses

A listing of DLTs with additional information on the cohort (eg, number of subjects in each cohort) in the DLT evaluable analysis set will be generated.

All the other safety analyses will be conducted on the safety analyses set. The primary analysis of safety data will summarize all TEAEs and laboratory values. Additional summary tables will present all adverse events with onset time categorized by study treatment period (refer to definition section). Adverse events will be summarized by SOC and PT.

Adverse events will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Cytokine release syndrome (CRS) will be graded using a revised CRS grading scale developed by Lee et al (Lee et al, 2014). The incidence and severity of CRS will be reported as a syndrome with severity per Lee et al (Lee et al, 2014). Individual symptoms associated with CRS will be graded per CTCAE version 4.03.

Subjects enrolled but not dosed with KITE-585 will be followed for adverse events for 30 days after the last study procedure. Adverse events reported in these subjects will be archived in the study database and available in SDTM and ADaM datasets, but will not be tabulated in adverse event summaries.

Safety summaries will be presented by dose and by cohort when applicable.

9.6.1. Adverse Events

The subject incidence of the following adverse events will be tabulated:

- Overall summary of treatment emergent adverse events (eg, any, worst severity, serious, KTE-585 related)
- All treatment emergent adverse events
- All serious treatment emergent adverse events
- All leukapheresis-related adverse events
- All bridging therapy-related adverse events
- All conditioning-chemotherapy-related adverse events
- All KITE-585-related treatment emergent adverse events
- All conditioning chemotherapy-related serious adverse events
- All KITE-585-related serious treatment emergent adverse events
- All grade 3 or higher treatment emergent adverse events
- All grade 3 or higher conditioning chemotherapy-related adverse events
- All grade 3 or higher KITE-585-related treatment emergent adverse events
- Fatal treatment emergent adverse events
- Treatment emergent adverse events of interest

Summary statistics for the onset time and duration of adverse events of interest will be provided.

Death time and reason will be listed and summarized for all the enrolled subjects.

Subgroup analyses of adverse events may be generated for the covariates listed in Section 4.2.

9.6.2. Exposure to Concomitant Medications and Procedures

Concomitant medication drug basket of interest for systemic steroids, vasopressors, nonsteroidal immunosuppressants other than tocilizumab, and IV immunoglobulins are defined by Kite and are documented separately.

The subject incidence of concomitant medications will be provided and summarized. The subject incidence of procedures will also be tabulated.

In addition, the subject incidence of concomitant medications and procedures used to manage adverse events will be tabulated.

9.6.3. Laboratory Test Results

Laboratory results will be graded according to NCI CTCAE (version 4.03). The incidence of post-infusion worst-grade laboratory toxicities for all analytes will be summarized. Additional summaries for the shift from baseline to the worst toxicity grade after KITE-585 infusion may also be generated.

9.6.4. Vital Signs

Vital Sign data will be summarized at selected time points by descriptive statistics. Subject listings may also be provided.

CCI [redacted]

[redacted]

9.6.6. Replication Competent Lentivirus

The subject incidence of replication-competent lentivirus (RCL) detected in blood samples will be tabulated overall and by assessment time. The persistence of RCL over time will be summarized.

9.6.7. Exposure to Study Treatment

Summary statistics and subject listings will be provided for the following:

- Total BSA-adjusted dose of cyclophosphamide
- Total BSA-adjusted dose of fludarabine
- Total anti-BCMA CAR T cells of the KITE-585 infusion
- Total T cells of the KITE-585 infusion
- Transduction ratio
- Percentages of CD4 and CD8 cells and ratio
- Percentages of T-cell memory phenotypes
- Interferon-gamma production in co-cultures of KITE-585 product and anti-BCMA target cells
- Vector copy number of KITE-585 CAR product

Summaries may also be provided by demographics and baseline characteristics as appropriate.

9.7. Pharmacokinetics

Analysis of biomarker and PK parameters will be provided in a separate SAP.

9.8. Pharmacodynamics

Analysis of biomarker and pharmacodynamic parameters will be provided in separate SAP.

9.9. Subsequent Anti-Cancer Therapy

The incidence and type (by WHO Drug coded term and categories) of subsequent anticancer therapy and stem cell transplant by treatment period will be summarized.

9.10. Duration Metrics

Summary statistics will be provided for the following durations:

- Days from leukapheresis to product release
- Days from leukapheresis to product received at the site
- Days from leukapheresis to commencement of bridging therapy
- Days from bridging therapy to commencement of conditioning chemotherapy
- Days from leukapheresis to commencement of conditioning chemotherapy
- Days from leukapheresis to KITE-585 infusion
- Days from conditioning chemotherapy to KITE-585 infusion
- Duration of hospitalization for the KITE-585 infusion

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

The full analyses set in this document refers to all enrolled subjects, while the full analyses set in the protocol has been renamed as the safety analyses set in this document.

11. REFERENCES

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12. APPENDICES

Appendix 1. Conventions for Clinical Data that Require Imputation for Partial or Missing Dates
Appendix 2. Definitions related to Prolonged Cytopenias
Appendix 3. Derivation of Time to Event Endpoints and Last Date Known to Be Alive

Appendix 1. Conventions for Clinical Data that Require Imputation for Partial or Missing Dates

The following data will be imputed using the following algorithm:

- Adverse event start dates
- Deaths (please see exceptions below)
- Concomitant medication start dates
- Subsequent anti-cancer therapy start dates

Table 2. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		**Missing**
		< day 0	**≥ day 0**	**< day 0 *yyyymm***	**≥ day 0 *yyyymm***	**< day 0 *yyyy***	**≥ day 0 *yyyy***	
Partial *yyyymm*	= day 0 *yyyymm*	2	1	2	1	n/a	1	1
	≠ day 0 *yyyymm*		2		2	2	2	2
Partial *yyyy*	=1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = impute the date of day 0
2 = impute the first of the month
3 = impute January 1 of the year
4 = impute January 1 of the stop year
Note: if the start date imputation leads to a start date that is after the stop date, then do not impute the start date.
Imputation rules for partial or missing death dates:

1. If death year and month are available but day is missing:
   - If mmyyyy for the last contact date = mmyyyy for death date, set death date to the day after the last date known to be alive.
   - If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.
   - If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.
2. If both month and day are missing for death date or a death date is completely missing, do not impute and censor the subject survival time at the last date known to be alive.

Appendix 2. Definitions related to Prolonged Cytopenias

1. Longest Consecutive Period with an AE of interest

Longest consecutive period with an AE of interest is calculated as the greatest number of consecutive days (without gaps between events) that subjects experience the AE of interest without gaps between events.

For subjects who have AEs without reported ending dates, the longest consecutive period will be calculated with the ending dates of such AEs imputed using the earliest date of the data extraction date (or the data cutoff date, if applicable), study discontinuation date, and the death date (if applicable). Longest consecutive period will be used for deriving prolonged neutropenia, prolonged thrombocytopenia, or prolonged anemia as described in Section 5.2.

Appendix 3. Derivation of Time to Event Endpoints and Last Date Known to Be Alive

Additional detail on the derivations of Duration of Response (DOR), Progression-free Survival (PFS), and Overall Survival (OS) is provided below.

1) **Duration of Response (DOR)**: DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or death due to disease progression, whichever comes first. Subjects who undergo non-disease-related death (due to reasons other than disease progression) without documented disease progression will be censored at the last evaluable disease assessment before the death date. Subjects not meeting the criteria for progression or death due to disease progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. Duration of response will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy (including SCT). Subjects who undergo new anticancer therapy (including SCT) in the absence of documented disease progression will be censored at the last evaluable disease assessment prior to the new anticancer therapy.

Primary analysis of DOR:

Circumstance	Event / Censored (Short Description)	Date of Event / Censoring
Disease progression prior to initiation of new anticancer therapy (including SCT)	Event (Disease progression)	Progression date
Death due to PD without documented disease progression and without any new anti-cancer therapy (including SCT)	Event (Death due to PD)	Death date
Non-disease related death without disease progression and without any new anti-cancer therapy (including SCT)	Censored (Death due to reasons other than PD)	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including SCT) prior to documented progression and death due to any cause	Censored (Initiated new anti-cancer therapy/SCT)	Last evaluable disease assessment date prior to initiation of new therapy (including SCT)
Remain in response by cut-off date without initiation of new anti-cancer therapy (including SCT)	Censored (Response ongoing)	Last evaluable disease assessment date

Abbreviations: DOR, duration of response; PD, progressive disease; SCT, stem cell transplant.

2) **Progression-free Survival (PFS):** PFS is defined as the time from the KITE-585 infusion date to the date of disease progression or death from any cause, whichever comes first. Subjects alive and not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. PFS will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (including SCT). PFS for subjects who undergo any new anticancer therapy (including SCT) will be censored at the time of last evaluable disease assessment date prior to the new anticancer therapy (including SCT).

Primary analysis of PFS:

Circumstance	Event / Censored (Short description)	Date of Event / Censoring
Disease progression prior to initiation of new anticancer therapy (including SCT)	Event (Disease progression)	Progression date
Death due to any cause without disease progression and without any new anti-cancer therapy (including SCT)	Event (Death due to any cause)	Death date
Alive without PD by cut-off date without initiation of new anti-cancer therapy (including SCT)	Censored (Alive without PD)	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including SCT) prior to documented disease progression or death due to any cause	Censored (Initiated new anti-cancer therapy (including SCT))	Date of last evaluable disease assessment prior to initiation of new therapy (including SCT).

Abbreviations: PD, progressive disease; PFS, progression-free survival; SCT, stem cell transplant. If no disease assessment available before censoring date, the PFS will be censored at KITE-585 infusion date.

3) **Overall Survival (OS):** OS is defined as the time from the KITE-585 infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive or analysis cutoff date, whichever is earlier.

Circumstance	Event/Censored (Short description)	Date of Event/Censoring
Death before data cutoff date for analysis	Event (Death)	Date of death
Death after data cutoff date for analysis	Censored (Alive)	Data cutoff date
Known to be alive after data cutoff date for analysis	Censored (Alive)	Data cutoff date
Alive up to data cutoff date and no further information available after data cutoff date	Censored (Alive)	Last date known to be alive
Early termination due to Full Withdrawal of consent, lost to follow up prior to data cutoff date	Censored (Alive)	Last date known to be alive

4) Last date known to be alive

The last date known to be alive with be derived by obtaining the maximum complete date among the following data modules:

- Start date of AE
- Leukapheresis dates
- Bridging therapy dates

- Conditioning chemotherapy administration dates
- KITE-585 infusion dates
- Serum/Urine/FLC sample date for assessment of disease status
- Bone marrow aspirate/biopsy sample date
- Image sample date (PET/CT)
- Optional plasmacytoma sample date
- Lumbar puncture sample date for CSF
- Plasmacytoma/new plasmacytoma assessment date
- Disease response assessment date
- Start date of new anticancer therapy/transplant date
- Long term follow up subject status date where status = “alive”
- End-of-treatment disposition where status is not equal to death, lost to follow up
- End–of-study data where end–of-study reason is not equal to death, lost to follow up