Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	KTE-X19
Protocol:	A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)
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LIST OF ABBREVIATIONS

ADaM	Analysis data model
AE	Adverse event
Allo-SCT	Allogeneic stem cell transplant
Auto-SCT	Autologous stem cell transplant
CAR	Chimeric antigen receptor
CIF	Cumulative incidence
CR	Complete response
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Event
DOR	Duration of response
DORR	Duration of response to retreatment
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European quality of life-5 dimensions
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FAS	Full analysis set
HLGT	High-level group term
ICANS	Immune effector cell-associated neurotoxicity syndrome
IRRC	Independent Radiology Review Committee
MCL	Mantle cell lymphoma
mITT	Modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not evaluable
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RCR	Replication-competent retrovirus
r/r MCL	Relapsed/refractory mantle cell lymphoma
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Stable disease
SDTM	Study data tabulation model
SMQ	Standardized MedDRA query
s-MIPI	Simplified Mantle Cell Lymphoma International Prognostic Index
SOC	System organ class
SPD	Sum of the product of the diameter
SSC	Scientific steering committee
TEAE	Treatment-emergent adverse event

TLS	Tumor lysis syndrome
VAS	Visual analogue scale

1. INTRODUCTION

This statistical analysis plan provides the pre-specification and details for the statistical analyses outlined within protocol KTE-C19-102, amendment 8.0 (Date: 10 Dec 2021) entitled "A Phase 2 Multicenter Study Evaluating the Efficacy of KTE-X19 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (ZUMA-2)." The scope of this document is to provide details on the planned interim, primary, and final analyses.

2. OBJECTIVES

The primary objective is to evaluate the efficacy of KTE-X19, as measured by objective response rate (ORR), in subjects with relapsed/refractory (r/r) mantle cell lymphoma (MCL). Secondary objectives include assessing the safety and tolerability of KTE-X19 and additional efficacy endpoints including duration of response (DOR). Secondary objectives related to patient-reported outcomes (PROs) in Cohort 1 and Cohort 2 will include change in the European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6. Secondary objectives related to PROs in Cohort 3 will include change in EQ-5D and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) scores from baseline over time.

3. STUDY OVERVIEW

3.1. Study Design

Study KTE-C19-102 is a multicenter, open-label Phase 2 study evaluating the safety and efficacy of KTE-X19 in subjects with r/r MCL.

This study is designed to examine the safety and efficacy of KTE-X19in patients who have r/r MCL that has progressed on prior chemotherapy and anti-CD20 antibody therapy with or without ibrutinib or acalabrutinib. The study will evaluate the ORR and durability of response after treatment with KTE-X19. An open-label, 3-cohort design is used, with the following cohorts:

- Cohort 1 and Cohort 2 will include subjects with r/r MCL who have been treated with up to 5 prior regimens including a BTKi. Prior therapy must have included all of the following: anthracycline or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, and ibrutinib or acalabrutinib.

- Cohort 3 will include subjects with r/r MCL who have been treated with up to 5 prior regimens but have not received prior therapy with a BTKi. Prior therapy must have included anthracycline, bendamustine, or high-dose cytarabine containing chemotherapy and anti-CD20 monoclonal antibody therapy.

Up to approximately 220 subjects with r/r MCL in total will be enrolled and treated to evaluate the efficacy of KTE-X19:

- Cohort 1 will treat up to approximately 90 subjects at a target dose of $2x10^6$ anti-CD19 CAR T cells/kg, including up to approximately 80 KTE-X19 subjects and 10 axicabtagene ciloleucel subjects. The Cohort 1 KTE-X19 subjects will form the basis for statistical hypothesis testing on the primary end point in Cohort 1, with a target ORR in the alternative hypothesis of 50% and a futility criterion that the ORR is no more than 25%. As of 28May2019, Cohort 1 has completed enrollment.
- Cohort 2 will treat up to 40 KTE-X19 subjects at a target dose of 0.5×10^6 anti-CD19 CAR T cells/kg. As of 01May2018, Cohort 2 has completed enrollment.
- Cohort 3 will enroll and treat up to approximately 90 KTE-X19 subjects at a target dose of $2x10^6$ anti-CD19 CAR T cells/kg, forming the basis for statistical hypothesis testing on the primary end point in Cohort 1 with a target ORR in the alternative hypothesis of 75% and a null hypothesis that the ORR is 57% or less.

Each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Bridging therapy, if applicable
- Conditioning chemotherapy
- Investigational product treatment
- Post-treatment assessment
- Long-term follow-up

Additional details on study procedures may be found in the study protocol.

An independent Data Safety Monitoring Board (DSMB) will meet and review safety and/or efficacy data for Cohort 1 and Cohort 2 at 4 times during the study:

For Cohort 1: The DSMB will first meet to review safety data when 10 subjects have been treated with anti-CD19 CAR T cells and have been followed for 30 days. The DSMB will meet for the second time to review both safety and efficacy data after 20 subjects have been treated with anti-CD19 CAR T cells and have had the opportunity to complete the 3-month disease assessment. The DSMB will review safety again after 44 subjects in Cohort 1 have been treated with anti-CD19 CAR T cells and have had opportunity to be followed for at least 30 days after the anti-CD19 CAR T cells infusion, with focus on the safety data from the 6 KTE-X19 subjects treated most recently within this cohort.

For Cohort 2: The DSMB will meet to review both safety and efficacy data after 10 subjects have been treated with KTE-X19 and have had the opportunity to be followed for 30 days.

The DSMB will be chartered to make trial conduct recommendations for Cohort 1 and Cohort 2 based on an analysis of risk vs benefit. The DSMB may meet more often as needed.

For Cohort 3: A Scientific Steering Committee (SSC), comprising the study sponsor and at least 3 study investigators, will be specifically chartered to review the safety data from Cohort 3 and make recommendations on further study conduct. The SSC will meet after 15 subjects in Cohort 3 have been enrolled, treated with KTE-X19, and have had the opportunity to be followed for 30 days, and again after 50 subjects in Cohort 3 have been enrolled, treated with KTE-X19, and have had the opportunity to be followed for 3 months. The SSC may meet more often as needed.

There will be an additional interim analysis for Cohort 1 after 38 subjects treated with anti-CD19 CAR T cells in Cohort 1 have had the opportunity to be evaluated for response 6 months after the anti-CD19 CAR T cells infusion. This interim analysis will be performed for a Kite Pharma,

Inc., (hereafter referred to as Kite or Kite Pharma) internal review of the accumulating data of safety and efficacy.

The primary analysis in Cohort 1 and Cohort 2 will occur after 60 KTE-X19 subjects have been enrolled and treated in Cohort 1 and have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment (see details in Section 3.3).

The primary analysis in Cohort 3 will occur after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier (see details in Section 3.3).

The primary analysis of efficacy endpoints will be based on the Lugano Classification {Cheson 2014} per Independent Radiology Review Committee (IRRC) review for all cohorts. These assessments will be referred to as "Central Read" in this document. Secondary efficacy analyses will be based on investigator review of disease assessments, henceforth referred to as "Investigator Read." For Cohort 1, the Investigator Read will be based on the revised International Working Group Criteria for Malignant Lymphoma {Cheson 2007}; for Cohort 2 and Cohort 3, the Investigator Read will be based on the Lugano Classification {Cheson 2014}.

3.2. Hypothesis

An alternative hypothesis will be tested among Cohort 1 KTE-X19 subjects with a target 50% ORR per independent review against a null hypothesis that the ORR is 25% or less. The hypothesis is that the ORR to KTE-X19 in Cohort 1 KTE-X19 subjects is significantly greater than 25%.

For Cohort 3, an alternative hypothesis will be tested with a target 75% ORR per independent review against a null hypothesis that the ORR is 57% or less. The hypothesis is that the ORR to KTE-X19 per independent review is significantly greater than 57% in Cohort 3 subjects.

3.3. Sample Size Considerations

This study uses an open-label 3-cohort design to test for an improvement in ORR. Up to approximately 220 subjects with r/r MCL will be enrolled and treated with anti-CD19 CAR T cells, including 10 axicabtagene ciloleucel subjects and up to approximately 80 KTE-X19 subjects in Cohort 1, up to approximately 40 KTE-X19 subjects in Cohort 2 and up to approximately 90 KTE-X19 subjects in Cohort 3.

Hypothesis testing of the primary endpoint ORR will be conducted on Cohort 1 inferential analysis set. Primary analysis in Cohort 1 will be conducted after 60 KTE-X19 subjects have been enrolled and treated and have had the opportunity to be assessed for response 6 months after the Week 4 disease assessment. A sample size of 60 KTE-X19 subjects in Cohort 1

provides at least 96% power to distinguish between an active therapy with a 50% true response rate from a therapy with a response rate of 25% or less, with a 1-sided alpha level of 0.025.

The primary analysis in Cohort 3 will be conducted after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier. For the test of efficacy in Cohort 3, a sample size of 86 subjects will provide at least 90% power to distinguish between an active therapy with a 75% true response rate and a therapy with a response rate of 57% or less with a 1-sided alpha level of 0.025.

Four interim analyses in Cohort 1 and one interim analysis in Cohort 2 will be performed:

- Cohort 1 interim analysis 1 will be conducted after 10 subjects have been treated with anti-CD19 CAR T cells and have been followed for 30 days. In this interim analysis, the DSMB will review data for safety only.

- Cohort 1 interim analysis 2 will be conducted after 20 subjects have had the opportunity to be evaluated for response 3 months after treatment with anti-CD19 CAR T cells. In this interim analysis, the DSMB will review data for both safety and efficacy (futility only).

- Cohort 1 interim analysis 3 will occur after all the 38 treated subjects in this cohort have had the opportunity to be evaluated for response 6 months after anti-CD19 CAR T cells infusion. This interim analysis will be performed for a Kite internal review of the accumulating data of safety and efficacy.

- Cohort 1 interim analysis 4 will occur after 44 subjects in Cohort 1 have been treated with anti-CD19 CAR T cells and have had the opportunity to be followed for 30 days after anti-CD19 CAR T cells infusion. In this interim analysis, the DSMB will review data for safety only, with focus on the 6 KTE-X19 subjects treated most recently in this cohort.

- Cohort 2 interim analysis will occur after 10 subjects in this cohort have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days after KTE-X19 infusion. This interim analysis will be for safety and efficacy.

In Cohort 3, two interim analyses will be performed for safety only:

- Cohort 3 interim analysis 1 will be conducted after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days after the KTE-X19 infusion.

- Cohort 3 interim analysis 2 will be conducted after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months after the KTE-X19 infusion.

Accrual to and treatment on the study will continue during all interim analyses.

Two primary analyses for the study will be performed, followed by long-term follow-up analyses as described below:

One primary analysis for Cohort 1 and Cohort 2 will occur after 60 KTE-X19 subjects have been enrolled and treated in Cohort 1 and have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment. Data from both Cohort 1 and Cohort 2 will be analyzed. However, as mentioned above, no statistical hypothesis will be formally tested on Cohort 1 axicabtagene ciloleucel subjects and Cohort 2 subjects, and, thus, no alpha-spending is assigned for the analysis of Cohort 1 axicabtagene ciloleucel subjects and Cohort 2 subjects. The primary analysis on Cohort 1 will use a 1-sided alpha level of 0.025, with one interim efficacy analysis for futility. This procedure preserves the designated overall alpha level (1-sided) of 0.025 and achieves at least 96% power.

For Cohort 1, a rho (parameter = 0.30) beta spending function will be used to allocate the beta level between the futility analysis and the primary efficacy analysis. The non-binding futility boundary for this interim analysis is reached if no more than 5 responders (≤5) out of 20 subjects are observed. EAST version 6.4 was used to evaluate the statistical power and operating characteristics of this design.

A follow-up analysis of subjects treated with KTE-X19 will be performed after all subjects in the mITT set of Cohort 1 have had the opportunity to be assessed for response 18 months after the first objective response. This additional analysis will be descriptive. The final analysis of Cohort 1 and Cohort 2 will occur when all subjects in both cohorts have completed the study.

The primary analysis in Cohort 3 will be conducted after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier. In this analysis, inferential testing on efficacy in Cohort 3 will be performed using a 1-sided alpha level of 0.025. This procedure preserves the designated overall alpha level (1-sided) of 0.025 and has at least 90% power when 86 subjects are included. EAST version 6.5 was used for power calculation and evaluation of the operating characteristics of this design.

A follow-up analysis will be performed after 86 subjects in Cohort 3 have had the opportunity to be assessed for response 18 months after the first objective response to further evaluate the risk-benefit profile of KTE-X19, including the durability of response. This analysis will be descriptive.

Additional descriptive analyses may occur after the primary analysis and follow-up analyses described above have been completed. The final analysis of Cohort 3 will occur when all subjects in Cohort 3 have completed the study.

3.4. Statistical Assumptions

As described in Section 3.3, an open-label 3-cohort design is used for this study. In the Cohort 1 KTE-X19 subjects, a target ORR of 50% and a historical control rate of 25% are assumed for statistical inference. In Cohort 3, a target response rate of 75% and a historical control rate of 57% are assumed for statistical inference. The responses from subjects in the study population are assumed to be independent and follow binomial distribution, and, thus, an exact binomial test will be used to test the statistical hypothesis.

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

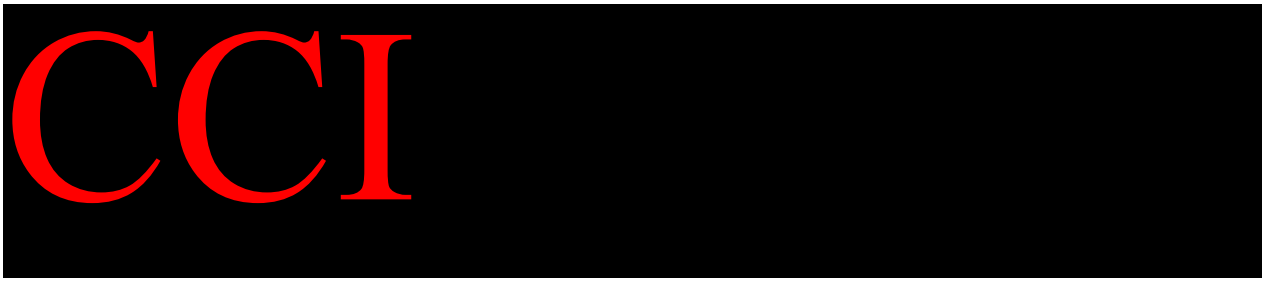
4.1.1. Primary

- ORR, defined as the incidence of complete response (CR) or partial response (PR) per the Lugano Classification {Cheson 2014} as determined by the IRRC review

4.1.2. Secondary

- Duration of response (DOR)
- Best objective response
- ORR per investigator review
- Progression-free survival (PFS)
- Overall survival (OS)
- Incidence of adverse events (AEs) and clinically significant changes in laboratory values
- Incidence of anti-CD19 CAR antibodies
- Levels of anti-CD19 CAR^+ T cells in blood
- Levels of cytokines in serum
- Changes over time in the European quality of life-5 dimensions (EQ-5D) scale score and EQ-5D visual analogue scale (VAS) score
- Changes in the EORTC-QLQ-C30 score from baseline over time (Cohort 3 only)

4.1.3. Exploratory



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4.2. Covariates

4.2.1. Baseline Covariates

The following baseline covariates may be used to examine efficacy and/or safety in subgroups or covariate analyses:

- Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0, 1, 2, 3, 4)
- Age (in years) at baseline (< 65, ≥ 65)
- Sex (male, female)
- Race: white, Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, other (categories may be collapsed or expanded based on accrual)
- Relapsed/Refractory subgroup (relapsed after autologous stem cell transplant [auto-SCT], relapsed after last mantle cell lymphoma [MCL] chemotherapy, refractory to last MCL chemotherapy)
- Morphologic characteristics (blastoid, pleomorphic, diffuse, mantle zone, nodular)
- Ki-67 index (%) (< 30%, ≥ 30%, < 50%, ≥ 50%)
- t(11; 14) (Y/N)
- Cyclin D1 overexpression (Y/N)
- Disease stage (I, II, III, IV) and extent (presence of B symptoms, S [splenic involvement], E [extranodal disease], X [bulky disease], bone marrow involvement) as determined by the investigator at screening
- Simplified Mantle Cell Lymphoma International Prognostic Index (s-MIPI)
- Number of prior regimens
- Prior Bruton tyrosine kinase inhibitors (ibrutinib vs acalabrutinib) for Cohort 1 and Cohort 2

- Prior therapy regimens (anti-CD20 [Y/N], anthracycline [Y/N], bendamustine [Y/N], ibrutinib [Y/N], acalabrutinib [Y/N], lenalidomide [Y/N], bortezomib [Y/N], temsirolimus [Y/N], stem cell transplant [Y/N], platinum [Y/N])

- Tumor burden, as measured by the SPD of selected nodes or lesions at baseline

- Lactate dehydrogenase (LDH), as weighted to upper limit of normal (< 0.67*ULN, >= 0.67*ULN and < ULN, >= ULN and < 1.5*ULN, >=1.5*ULN)

4.2.2. Tocilizumab and Steroid use after Anti-CD19 CAR T Cells Infusion

Post-baseline tocilizumab and steroid use may be used to examine efficacy in subgroups or covariate analyses:

- Tocilizumab use after Anti-CD19 CAR T cells infusion (Y/N)

- Steroids use after Anti-CD19 CAR T cells infusion (Y/N)

- Tocilizumab or steroids use after Anti-CD19 CAR T cells (Y/N)

- Tocilizumab and steroids use after Anti-CD19 CAR T cells (Y/N)

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

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment occurs when a subject commences leukapheresis.

Study Day 0: Day 0 is defined as the day the subject receives the first anti-CD19 CAR T cells infusion. The day prior to Day 0 will be Day –1. Any days after enrollment and prior to Day –1 will be sequential and negative integer-valued.

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

Study therapy: Study therapy includes conditioning chemotherapy and anti-CD19 CAR T cells.

On-study: Time from enrollment to the last date of contact.

End of study: Defined as when the last subject is assessed or received an intervention for evaluation in the study, including survival assessments.

Relapsed/Refractory subgroup: Relapsed/refractory subgroups are defined as below. Subjects meeting both "Relapsed after SCT" and any of the other categories will be categorized as "Relapsed after SCT." Note that bridging therapies should not be included for defining the Relapsed/Refractory subgroups.

- Relapsed after SCT: A subject is considered to be relapsed after SCT if the subject experienced relapse (nonresponse, disease recurrence or disease progression) after SCT.
- Refractory to last MCL therapy: A subject is considered to be refractory to the last MCL therapy if the subject failed to achieve a PR or CR to the last MCL therapy.
- Relapsed after last MCL therapy: A subject is considered to be relapsed after last MCL therapy if the subject responded and subsequently experienced disease progression after the last MCL chemotherapy.

Bulky disease: Bulky disease is defined as the presence of a single lesion with largest diameter being 10 cm or larger or mediastinum wider than 1/3 of the chest on a chest x-ray. The presence of bulky disease will be determined by the investigator when baseline disease extent is evaluated.

Actual follow-up time: Actual follow-up time among all subjects treated with anti-CD19 CAR T cells is calculated as the time from the first dose of anti-CD19 CAR T cells to the date of death, last date known to be alive, lost to follow-up, or full withdrawal of consent, whichever is later.

Potential follow-up time: Potential follow-up time is defined as the time from the anti-CD19 CAR T cells infusion to the data cutoff date for the analysis.

5.2. Safety

Treatment-emergent adverse event (TEAE): Any adverse event with onset on or after the anti-CD19 CAR T cells infusion. All TEAEs will be summarized by preferred term and toxicity grade. AEs occurred within other study periods may be summarized as appropriate. For subjects taking retreatment of KTE-X19/axicabtagene ciloleucel, TEAEs during retreatment period may be summarized separately.

Deaths: All deaths that occur from the beginning of the chemotherapy conditioning period up through the end of study will be summarized. Deaths that occur from the anti-CD19 CAR T cells infusion up through 30 days after the infusion will also be summarized. For subjects taking retreatment of KTE-X19/axicabtagene ciloleucel, deaths occurred during retreatment period may also be summarized separately.

AEs of special interest: Adverse events of special interest for KTE-X19/axicabtagene ciloleucel treatment include identified risks (CRS, neurologic events, cytopenias, infections, and hypogammaglobulinemia) and potential risks (immunogenicity, secondary malignancies, RCR, and tumor lysis syndrome [TLS]).

CRS will be identified via collection of the syndrome on a case report form (CRF) specifically designed to record CRS. Specific individual symptoms of CRS (eg, fever) collected on the AE log will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and linked to the corresponding CRS episode. Individual symptoms of CRS will be graded per Common Terminology Criteria for Adverse Events (CTCAE) v 4.03, and CRS as a syndrome will be graded per modified Lee criteria ((Lee et al, 2014). In the modified grading scale, neurologic AEs are not to be reported as part of the CRS syndrome and will be reported separately and summarized separately.

Neurologic events will be identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy ({Topp 2015}). The search strategy focuses on central nervous system (CNS) toxicity, without regard to relatedness, temporal relationship, or concomitant conditions (eg, CRS). Additionally, the MedDRA system organ classes (SOCs) of Psychiatric Disorders and Nervous System Disorders will be reviewed for additional events; these events will then be evaluated for potential inclusion as neurologic AEs.

Immunogenicity will be identified by the development of antibodies to antibodies against CAR expressing cells by flow cytometry. In addition, a manual review of the AE terms indicative of autoimmunity, inclusive of infusion-related events and anaphylactic reactions among subjects who test positive for anti-CD19 CAR antibodies, will be performed.

For other AEs of special interest, specific adverse events may be mapped to these categories using dictionary coded event term and standardized MedDRA queries (SMQs) or other search strategies. Specific definitions of these events and the coded terms to which they correspond will be provided in the Program Safety Analysis Plan.

Duration of an AE of special interest: The duration of an AE of special interest may be derived only among subjects for whom all events of the class have resolved by the analysis data cutoff date. The duration is defined as the stop day of the last AE in the event class – the start day of the first AE in the event class + 1.

5.3. Efficacy

ORR: ORR is the proportion of subjects with either a CR or PR while on study. All subjects who do not meet the criteria for objective response by the analysis data cutoff date will be considered non-responders, including the subjects with non-evaluable assessment data and those without any assessment. The derivation of this endpoint will only include response assessments obtained prior to any other additional therapy (eg, SCT or subsequent anti-cancer therapy or retreatment with anti-CD19 CAR T cells). Response may be defined per Central Read or Investigator Read.

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. Response and progression may be defined per Central Read or Investigator Read. Data from retreatment period will not be included for analysis. 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. DOR will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy (including SCT). The DOR for subjects who undergo SCT while in remission will be censored at the last evaluable disease assessment date prior to SCT; the DOR for subjects that undergo other new anti-cancer therapies including the retreatment with anti-CD19 CAR T cells in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anti-cancer therapies. A sensitivity analysis will be conducted in which disease assessments obtained after SCT are included in the derivation of DOR. Additional details on the derivation of DOR are provided in Appendix 3. In case that 5% or more subjects with two or more consecutive disease assessments missed prior to receiving SCT or new anti-cancer therapy, another sensitivity analysis will be performed with such subjects being counted as events and their DOR event time imputed based on the first missed scheduled assessment visit prior to the SCT or new anti-cancer therapy.

PFS: PFS is defined as the time from the anti-CD19 CAR T cells infusion date to the date of disease progression or death from any cause. For PFS analysis with the full analysis set (defined in Section 6.4) in which enrolled but not treated subjects are included, the PFS time will be calculated. as the time from the enrollment date to the date of disease progression or death from any cause. Progression may be defined per Central Read or Investigator Read. Data from retreatment period will not be included for analysis. 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). The PFS for subjects who undergo SCT while in remission will be censored at the last evaluable disease assessment date prior to SCT; the PFS for subjects that undergo other new anti-cancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anti-cancer

therapies. A sensitivity analysis will be conducted in which disease assessments obtained after SCT are included in the derivation of PFS. Additional details on the derivation of PFS are provided in Appendix 3.

OS: OS is defined as the time from the anti-CD19 CAR T cells infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at the last date known to be alive or the data cutoff date, whichever is earlier. For OS analysis with the full analysis set, the OS time will be calculated as the time from the enrollment date to the date of death from any cause. Additional 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.

Duration of response to retreatment (DORR): DORR is defined the same as DOR, except that the definition applies to the response after KTE-X19/axicabtagene ciloleucel retreatment.

6. ANALYSIS SETS

Analysis sets are defined within each cohort as follows.

6.1. Modified Intent-to-treat

The mITT analysis set will consist of all subjects enrolled and treated with any dose of anti-CD19 CAR T cells. This analysis set will be used for efficacy analyses for Cohort 1 subjects treated with axicabtagene ciloleucel, Cohort 2 subjects, and Cohort 3 subjects. For Cohort 3, this analysis set will be used for the hypothesis testing of the primary endpoint ORR.

6.2. Inferential Analysis Set

The inferential analysis set will consist of the first 60 treated KTE-X19 subjects in Cohort 1. This analysis set will be used for efficacy analyses in Cohort 1 and also the hypothesis testing of the primary endpoint ORR for Cohort 1 at the time of the primary analysis.

6.3. Safety Analysis Set

The safety analysis set is defined as all subjects treated with any dose of anti-CD19 CAR T cells (same as mITT).

6.4. Full Analysis Set

The full analysis set (FAS) will consist of all enrolled subjects and will be used for the summary of subject disposition. This analysis set will also be used for analyses of objective response rate and other key efficacy endpoints (BOR, DOR, PFS, and OS).

6.5. mITT Retreatment Analysis Set

The mITT retreatment analysis set will consist of all subjects who undergo retreatment with any dose of anti-CD19 CAR T cells. This set will be used for all retreatment efficacy analyses.

6.6. Safety Retreatment Analysis Set

The safety retreatment analysis set will consist of all subjects who undergo retreatment with anti-CD19 CAR T cells.

Note that subjects treated with anti-CD19 CAR T cells to expanded access (ie, “compassionate use” subjects not treated under Protocol KTE-C19-102) will not be included in the safety analysis set or the mITT analysis set.

6.7. Subgroup Analysis Sets

Subgroup analyses of selected efficacy and safety endpoints may be performed for subgroups defined by the baseline covariates defined in Section 4.2.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

7.1. Interim Analysis

In Cohort 1 and Cohort 2, an independent DSMB will be chartered to make recommendations on study conduct. The DSMB will meet 4 times during the study (Cohort 1 interim analysis 1, Cohort 1 interim analysis 2, Cohort 1 interim analysis 4, and Cohort 2 interim analysis 1), as described in Section 3.1 and Section 3.3. The DSMB will review safety and efficacy data and will be chartered to make trial conduct recommendations based on the risk versus benefit of treatment with anti-CD19 CAR T cells. For Cohort 1, a rho (parameter = 0.30) beta spending function will be used to allocate the beta level between the futility analysis at Cohort 1 interim analysis 2 and the primary efficacy analysis. The non-binding futility boundary for this interim analysis is reached if no more than 5 responders (≤ 5) out of 20 subjects are observed.

Details of the DSMB composition and responsibilities may be found in the DSMB charter.

In addition to the 4 interim analyses for Cohort 1 and Cohort 2 to be reviewed by DSMB, an additional interim analysis (Cohort 1 interim analysis 3) will be performed for a Kite internal review of the accumulating data of safety and efficacy (see Section 3.3). After the planned primary analysis of the study, additional efficacy and safety analyses may be performed to support regulatory interaction or publications. These analyses will be descriptive.

In Cohort 3, a SSC, comprising the study sponsor and at least 3 study investigators, will be specifically chartered to review the safety data from Cohort 3 and make recommendations on further study conduct.

The SSC will meet after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days, and again after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months. The SSC may meet more often as needed.

No interim analyses for efficacy will be performed in Cohort 3.

The DSMB and SSC will also monitor safety criteria to pause enrollment in the respective cohorts.

7.2. Assessment of Criteria to Pause Enrollment

As part of its oversight of the study, the DSMB for Cohort 1 and Cohort 2, will also assess criteria to pause enrollment after 10, 20, 30, and 50 subjects treated with anti-CD19 CAR T cells in Cohort 1 have had the opportunity to be followed for 30 days.

The assessments of criteria to pause enrollment will be triggered when 10, 20, 30, and 50 subjects have been treated with anti-CD19 CAR T cells and have had the opportunity to be followed for 30 days. At each assessment, the subject incidence of the events listed in the below criteria will be tabulated for the first treated 10 subjects, 20 subjects, 30 subjects, and 50 subjects, respectively. If either criterion is met (with incidence rates calculated with 10 subjects, 20 subjects, 30 subjects, and 50 subjects as denominators, respectively) prior to an assessment milestone, the DSMB will proceed with the assessment with available data.

For Cohort 3, a SSC will meet after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days, and again after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months. The SSC may review data more often as needed.

As part of its oversight of the study, the SSC will also assess criteria to pause enrollment in Cohort 3 after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days, and again after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months, using the criteria described below. The SSC may request additional analyses of safety data if a safety concern arises during the course of the trial.

Enrollment will be paused if any of the following criteria is met:

- Incidence of Grade 5 KTE-X19/axicabtagene ciloleucel-related adverse events within 30 days is > 10%.
- Incidence of the following Grade 4 KTE-X19/axicabtagene ciloleucel-related adverse events lasting more than 7 days is > 33%:
  - Neurologic toxicities
  - CRS (per Lee 2014 criteria)
  - Other non-hematological serious adverse event (SAE)
  - Infection (treatment-related)

The DSMB and SSC will monitor safety criteria to pause enrollment in the respective cohorts.

7.3. Access to Aggregate and Subject-level Data and Individual Subject Treatment Assignments

This study is open label. Subjects, the study sponsor, and investigators will be aware that each subject is planned to be treated with KTE-X19/axicabtagene ciloleucel. Data handling

procedures designed to maintain the trial credibility and validity in this study are described in the Trial Integrity Document.

For Cohort 1 and Cohort 2, an independent statistician will perform Cohort 1 interim analysis 1, Cohort 1 interim analysis 2, Cohort 1 interim analysis 4, and Cohort 2 interim analysis for the study, as well as the safety assessment to pause enrollment, and provide these reports to the DSMB. Members of the DSMB and independent statistician will not have any direct contact with study center personnel or subjects. The DSMB will communicate recommendations to Kite Pharma in accordance with the DSMB charter. Additional details of the DMSB composition and reviews are described in the DSMB charter.

For Cohort 3, the sponsor will perform Cohort 3 interim analyses for SSC review. More details can be found in the SSC charter.

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 analysis 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 Archival 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.

Data from the central pathology laboratory (including tumor pathology, tumor genetic, and molecular characteristics), the product manufacture (total T cells, CAR T cells [transduction ratio], duration of manufacturing time), central laboratory assessment of subject serum samples (including CAR T cell levels in the peripheral blood, antibody assays, RCR testing), and central radiology review will be generated from contract laboratories and Kite Pharma. These data will be transferred to Kite and held in a peripheral directory and not built into the clinical trial database. At the time when analyses require these data, they may be merged with the SDTM and ADaM datasets.

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 AE 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. Completely missing death dates or death dates with only a year reported will not be imputed.

8.4. Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will include, but not be limited to, violations of eligibility criteria and use of exclusionary medication during the study. 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.

Endpoints derived from investigator assessment of radiologic scans and disease assessments may be subject to bias; the concordance between investigator and central review of radiologic scans and disease assessments will be summarized where appropriate.

8.5. Outliers

Descriptive statistics may 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 primary analysis of the primary endpoint is an exact binomial test used to compare the observed ORR per Central Read to a response rate of 25% in the Cohort 1 inferential analysis set and 57% in the Cohort 3 mITT analysis set. These tests assume the independence of the individual subject responses.

An exact 95% confidence interval will be generated about the ORR. The Clopper-Pearson method will be used to generate this interval.

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 Cytel Inc. Standard Operating Procedures (SOPs) and Kite SOPs if applicable. The software and version used to generate analyses will be indicated in the archived documentation.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

The goal of the primary statistical analysis is to compare the observed ORR per Central Read to a historical control rate of 25% in the Cohort 1 inferential analysis set and 57% in Cohort 3 mITT analysis set, respectively. Hypothesis testing will be one-sided, and all 95% confidence intervals will be 2-sided. At the time of the primary analysis, 95% confidence intervals for ORR will be presented for Cohort 1 inferential analysis set subjects and Cohort 3 mITT analysis set subjects. ORR with 95% confidence intervals may be generated for Cohort 1 axicabtagene ciloleucel subjects, and Cohort 2 subjects, respectively, for descriptive purpose only.

The timing of the interim and primary analyses will be based on subject accrual and safety or disease assessment milestones. The primary analysis Clinical Study Report will be written at the primary analysis of the study. The Clinical Study Report may be amended with additional subject safety and survival follow-up after the planned primary analysis.

9.2. Subject Accountability

The number of subjects screened, enrolled/leukapheresed, treated with bridging therapy, treated with conditioning chemotherapy, treated with anti-CD19 CAR T cells, and retreated with anti-CD19 CAR T cells will be summarized. The reasons for discontinuing treatment and discontinuing study will be summarized.

Summaries of actual and potential follow-up time among all subjects treated with anti-CD19 CAR T cells will be provided.

The number of subjects enrolled by country and site will be summarized.

The number of subjects in each analysis set 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 at minimum, prior to the database snapshot for the primary efficacy analysis. 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 demographic and baseline characteristics as listed in Section 4.2.1 will be tabulated.

9.5. Efficacy Analyses

The hypothesis testing of ORR will be conducted on the inferential analysis set in Cohort 1 and mITT analysis set in Cohort 3, respectively. Other efficacy analyses will also be conducted on the inferential analysis set for Cohort 1 KTE-X19 subjects. Efficacy analyses for Cohort 1 axicabtagene ciloleucel subjects, Cohort 2 subjects and Cohort 3 subjects will be conducted on the mITT analysis set. FAS will also be used for analyses on key efficacy endpoints (ORR, BOR, DOR, PFS, and OS). For the primary analysis, the IRRC assessments based on the Lugano Classification {Cheson 2014}, referred to as "Central Read," will be used. Sensitivity analyses will be conducted based on the investigator assessments. For Cohort 1, the Investigator Read will be based on the revised International Working Group Criteria for Malignant Lymphoma {Cheson 2007}; for Cohort 2 and Cohort 3, the investigator review will be based on the Lugano Classification {Cheson 2014}. The independent radiology reviewers and investigators will provide the determination of disease status (CR, PR, SD, PD, not evaluable [NE]) at each time point. Statistical analysis system (SAS) programs will be used to derive the best overall response, DOR, and PFS based on these assessments. Efficacy analyses of Cohort 1 axicabtagene ciloleucel subjects and Cohort 2 KTE-X19 subjects will be descriptive.

The analysis of objective response rate and DOR will be presented in the following analysis sets:

- Inferential analysis set (Cohort 1 KTE-X19 subjects)
- mITT analysis set
- FAS

Disease assessment obtained after retreatment will not be used in the primary summaries of objective and best response, DOR, and PFS. For such subjects, disease assessments obtained after retreatment will be included in the summaries of objective and best response to retreatment with anti-CD19 CAR T cells and DORR. The subject's OS time will be derived from the last date known to be alive regardless of retreatment time.

In the event any subject undergoes an autologous or allogeneic SCT or any other 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, whichever is earlier. For subjects without documentation of progression prior to initiation of new therapy (including SCT), DOR and PFS time will be censored at the last disease assessment prior to the initiation of new therapy (including SCT). A sensitivity analysis for DOR will be conducted in which disease assessments after SCT are included to derive events and censoring times for subjects who undergo SCT while in KTE-X19/axicabtagene ciloleucel-induced response. (See details in Appendix 3.)

9.5.1. ORR and Best Response

9.5.1.1. Primary Analyses of ORR per Central Read

The subject incidence of objective response per Central Read will be calculated. The subject incidence of best response (CR, PR, SD, PD, NE) per Central Read will be tabulated. Confidence intervals will be provided about the ORR and best response, calculated with the following methods:

- Clopper-Pearson (an exact interval)

An exact binomial test will be used to compare the observed ORR per Central Read to the hypothesized historical control rate specified previously.

The analysis of ORR and best response per Central Read will include subjects from the Inferential analysis set for Cohort 1 and mITT analysis set for Cohort 2 and Cohort 3. Analysis of objective response in Cohort 1 KTE-X19 subjects and Cohort 3 subjects will also be conducted using the FAS.

9.5.1.2. Analyses of Objective Response and Best Response per Investigator Read

The analyses of ORR and best response specified above will be repeated for ORR and best response per Investigator Read.

The concordance of objective response and best response per Central Read and Investigator Read will be evaluated in Cohort 1. A summary table of concordance, concordance rate, a kappa statistic, and a 2-sided 95% confidence interval about the kappa statistic will be provided.

Further analyses comparing the Investigator and Central Reads may be performed as appropriate.

9.5.1.3. Subgroup Analyses of ORR

ORR and 95% confidence intervals will be generated for subgroups defined by each of the categorical covariates in Section 4.2.1 of the inferential analysis set of Cohort 1 KTE-X19 subjects and mITT set of Cohort 3 subjects. Subgroup analysis with additional covariates may also be explored.

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

9.5.2. DOR

The Kaplan-Meier approach will be used to estimate DOR. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for DOR per Central Read, as well as per Investigator Read. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR.

A sensitivity analysis of DOR will be conducted in which disease assessments obtained after SCT (for subjects who undergo SCT while in a KTE-X19/axicabtagene ciloleucel induced

response) are used in the derivation of DOR. In case that 5% or more subjects with two or more consecutive disease assessments missed prior to receiving SCT or new anti-cancer therapy, another sensitivity analysis will be performed with such subjects being counted as events and their DOR event time imputed based on the first missed scheduled assessment visit prior to the SCT or new anti-cancer therapy.

An analysis of DOR will also be conducted in the FAS for Cohort 1 KTE-X19 subjects and Cohort 3 subjects.

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

9.5.3. PFS

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals will be generated for PFS. Estimates of the proportion of subjects alive and progression-free at 3-month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for PFS per Central Read and PFS per Investigator Read.

A sensitivity analysis will be conducted in which disease assessments obtained after SCT (for subjects undergoing SCT while in a KTE-X19/axicabtagene ciloleucel induced response) are included in the derivation of PFS.

A PFS analysis will also be conducted in the FAS.

Subgroup analyses of the PFS rate at 6 months may be generated in subgroups defined by the covariates in Section 4.2.

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

9.5.4. OS

The analysis of OS will use the same methods as the analysis of PFS. An OS analysis will also be conducted in the FAS.

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

9.5.5. Tumor Burden

The change in tumor burden, as measured by the SPD of the selected lesions (reported as target lesions), from baseline to post-baseline nadir will be summarized in absolute numbers (mm^2) and percentage. A graphical summary of this change will be presented in a vertical bar chart with each subject's percent change from baseline to nadir displayed as a vertical bar, with color coding that indicates best response attained ("waterfall" plot). Analyses will be generated for change in tumor burden per Central Read and per Investigator Read. Data collected after new anti-cancer therapy, retreatment of anti-CD19 CAR T cells, or SCT will not be included for the analyses.

9.5.6. Objective Response and Best Response Among Subjects Retreated with Anti-CD19 CAR T Cells

The incidence of subjects retreated with anti-CD19 CAR T cells will be tabulated or listed. ORR and best response (CR, PR, SD, PD, NE) to the retreatment among subjects retreated with anti-CD19 CAR T cells will be calculated. Confidence intervals may be provided about the ORR and best response to the retreatment. Analyses may be conducted per Central Read and Investigator Read.

9.5.7. DORR

The analysis of DORR may be conducted using the same methods as the analysis of DOR and performed using the mITT retreatment analysis set..

9.5.8. Incidence of SCT

The subject incidence of SCT post-treatment with anti-CD19 CAR T cells and prior to disease progression will be tabulated among subjects who undergo SCT while in KTE-X19/axicabtagene ciloleucel induced response.

9.5.9. European Quality of Life-5 Dimensions and Visual Analogue Scale Scores

EQ-5D and VAS scores will be summarized at baseline and post study treatment visits. Changes in the EQ-5D-5L and VAS scores from baseline at each post-study treatment visit will also be summarized with descriptive statistics.

9.5.10. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) scores

For Cohort 3, EORTC-QLQ-C30 scores will be summarized at baseline and post study treatment visits. Changes in the EORTC-QLQ-C30 scores from baseline at each post-study treatment visit will also be summarized with descriptive statistics.

9.6. Safety Analyses

Safety analyses will be conducted on the safety analysis set for Cohort 1 KTE-X19 subjects, Cohort 1 axicabtagene ciloleucel subjects, Cohort 2 subjects, and Cohort 3 subjects, separately. Safety analysis will also be conducted on the treated KTE-X19 subjects combined from Cohort 1 and Cohort 2. The primary analysis of safety data will summarize TEAEs, death, and laboratory values with onset on or after the anti-CD19 CAR T cells infusion date and prior to retreatment period (if applicable). Additional summary tables may be provided to present the AEs that occurred within certain study periods. For subjects who undergo retreatment with anti-CD19 CAR T cells, AEs occurring in the retreatment period may be summarized or listed separately. Sample table layouts are provided in Appendix 2.

AEs will be coded with the 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 AEs will be graded using the National Cancer Institute CTCAE version 4.03.

CRS will be graded using a revised CRS grading scale developed by Lee et al {Lee 2014}. The incidence and severity of CRS will be reported as a syndrome with severity per Lee et al {Lee 2014}. Individual symptoms associated with CRS will be graded per CTCAE version 4.03. The severity of neurologic events in Cohort 3 will be graded using CTCAE version 4.03 and the American Society for Transplantation and Cellular Therapy (ASTCT) immune effector cell-associated neurotoxicity syndrome (ICANS) consensus grading system. In Cohort 3, CRS will also be assessed by ASTCT grading {Lee 2019}. ASTCT grading is collected only for the purposes of comparison and will not be used for toxicity management. Fatal AEs that are attributed to disease progression may be included in the death summary with a primary death reason of "disease progression" regardless of the coded CTCAE version 4.03 preferred term.

Subjects enrolled, but not dosed with anti-CD19 CAR T cells, will be followed for AEs for 30 days after the last study-specific procedure. AEs reported in these subjects will be archived in the study database and available in SDTM and ADaM datasets, but will not be tabulated in AE summaries.

9.6.1. AEs

The subject incidence of the following TEAEs will be tabulated:

- Summary of AEs (any, worst severity, serious, treatment-related)
- All AEs
- All SAEs
- All KTE-X19/axicabtagene ciloleucel-related AEs
- All KTE-X19/axicabtagene ciloleucel-related SAEs
- All Grade 3 or higher AEs
- All Grade 3 or higher KTE-X19/axicabtagene ciloleucel-related AEs
- Fatal AEs
- AEs of special interest, including identified risks and potential risks

The subject incidence of deaths by time periods will be provided.

A subject listing of deaths through 30 days after anti-CD19 CAR T cells infusion will be provided overall and by treatment period.

Subgroup analyses of AEs may be generated for selected covariates from the list in Section 4.2.1.

The time to onset and resolution and the duration of CRS will be summarized. Cardiac arrhythmias and cardiac failure in the context of CRS may be summarized.

The time to onset and resolution and the duration of neurologic events will be summarized. Especially neurologic events will be identified using two methods. One is defined by Topp and colleagues {Topp 2015} and the other one is defined by Kite.

Cytopenias will be summarized by categories of neutropenia, anemia, and thrombocytopenia; cytopenias present after 30 days from anti-CD19 CAR T cells infusion will also be summarized.

Infections will be summarized by categories (bacterial infections, viral infections, opportunistic infections, and other infections).

9.6.2. Procedures and Concomitant Medications

The incidences of procedure and concomitant medications used to manage AEs will be tabulated (see Section 9.6.7).

9.6.3. Laboratory Test Results

Laboratory results will be graded according to National Cancer Institute CTCAE version 4.03. The incidence of post-infusion worst-grade lab toxicities for all analytes will be summarized. Additional summaries for the shift from baseline to the worst toxicity grade after anti-CD19 CAR T cells infusion may also be generated.

9.6.4. Anti-CD19 CAR Antibodies

The subject incidence of any anti-CD19 CAR antibodies will be tabulated. For subjects testing positive for antibodies, the persistence of the antibody over time will be listed and summarized

9.6.5. RCR

The subject incidence of RCR detected in blood samples will be tabulated overall and by assessment time. The persistence of RCR over time will be summarized.

9.6.6. Exposure to Study Treatment

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

- Total body surface area-adjusted dose of cyclophosphamide
- Total body surface area-adjusted dose of fludarabine
- Weight-adjusted dose of KTE-X19/axicabtagene ciloleucel

- Total CAR T cells of the KTE-X19/axicabtagene ciloleucel infusion
- Total T cells of the KTE-X19/axicabtagene ciloleucel infusion
- Transduction ratio
- Percentages of CD4 and CD8 T cells
- Percentages of T cell memory phenotypes
- Interferon (IFN)-gamma production in co-cultures of KTE-X19/axicabtagene ciloleucel product and $CD19^+$ target cells
- Vector copy number of KTE-X19/axicabtagene ciloleucel product

Summaries may also be provided by demographics and baseline characteristics as appropriate. Separate summaries will be presented for the retreatment conditioning chemotherapy and KTE-X19/axicabtagene ciloleucel for subjects in the retreatment analysis set.

9.6.7. Exposure to Concomitant Medications and Procedures

The subject incidence of concomitant medications will be summarized by medication category and WHO Drug coded term. The subject incidence of procedures will be tabulated. The duration and indication of concomitant medications of interest, steroids and tocilizumab for example, may be summarized.

9.6.8. Mini-mental Status Exam or Immune Effector Cell-associated Encephalopathy

Summary statistics for the Mini-Mental Status Exam score and change from baseline in the Mini-Mental Status Exam score over time will be provided for all subjects in the safety analysis set in Cohort 1 and Cohort 2, and may be summarized within groups defined by the occurrence of Grade 3 or higher neurotoxicity.

Summary statistics for the immune effector cell-associated encephalopathy score and change from baseline in the immune effector cell-associated encephalopathy score over time will be provided for all subjects in the safety analysis set in Cohort 3.

9.7. Subsequent Anti-cancer Therapy

The incidence of subsequent anti-cancer therapy (by WHO Drug coded term) will be summarized.

9.8. Schedule of Study Treatment

Summary statistics will be provided for the following durations:

- Days from leukapheresis to KTE-X19 product release

- Days from leukapheresis to receipt of anti-CD19 CAR T cells at the study site
- Days from leukapheresis to administration of anti-CD19 CAR T cells
- Duration of hospitalization for the anti-CD19 CAR T cells infusion

9.9. CAR T Cells Measured in Peripheral Blood

Summary statistics for the level of CAR T cells in serum post KTE-X19/axicabtagene ciloleucel infusion will be provided for CAR T cells measured at Day 7, Week 2, Week 4, Month 3, Month 6, Month 12, and Month 24. The maximum CAR T cell level attained, the time at which the maximum level was attained, and the time at which there were no detectable CAR T cells in the serum will be summarized. The area under the concentration over time curve may be summarized from Day 0 to Day 28.

9.10. B-cell Aplasia

The subject incidence of B-cell aplasia based on B cells measured by flow cytometry and the subject incidence of recovery of B-cells aplasia will be summarized. The use of intravenous immunoglobulin may be summarized.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

None.

11. REFERENCES

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12. HISTORY OF REVISIONS

Version	Date	Protocol	Description of Changes
Original (1.0)	15JUN2017	Original to Amendment 3	N/A
2.0	17NOV2017	Amendment 4	• Added Cohort 2 as pivotal cohort (N=40) and changed Cohort 1 to non-pivotal cohort and decreased Cohort 1 sample size from N=67 to N=40; • Modified the interim and primary analyses accordingly; • Changed the primary efficacy endpoint from objective response rate (ORR) based on investigator read per Cheson 2007 to ORR based on Central Read per Lugano Classification (Cheson 2014); • Changed the hypothesis testing on ORR from 40% vs. 20% to 50% vs. 25%; • Added QoL (EQ-5D and VAS score) and RCR incidence rate as secondary endpoints; • Added prior acalabrutinib to baseline characteristics summary; • Other minor or cosmetic changes.
3.0	23APR2018	Amendment 4	• Removed B-cell aplasia analysis; • Simplified the section of definitions; • Updated the potential risks and the analysis method; • Added language for QoL (EQ-5D and VAS score) summary; • Other minor or cosmetic changes.
4.0	12JUL2018	Amendment 5	• Specified that Cohort 1 KTE-X19 subjects will form the basis for statistical hypothesis testing on the primary endpoint; • Increased the sample size of Cohort 1 from N=40 to N=~90 (with at least 60 XLP subjects); • Specified that no hypothesis will be tested in the Cohort 1 axicabtagene ciloleucel subjects or Cohort 2 subjects; • Added an interim analysis to Cohort 1; • Changed the primary analysis time based on Cohort 1 enrollment (ie, after 60 C1 KTE-X19 subjects have had the opportunity to be evaluated for response 6 months after week 4 disease assessment); • Removed competing-risk analysis on DOR; • Other minor or cosmetic changes.

Version	Date	Protocol	Description of Changes
5.0	22OCT2018	Amendment 6	• Changed investigational product name from KTE-C19 to KTE-X19; • Added a sensitivity analysis on DOR in the event of 5% or more subjects with two or more consecutive disease assessments missed prior to receiving SCT or new anti-cancer therapy; • Indicated that inferential analysis set will be used for all key efficacy analyses; • Indicated that full analysis set will be used for efficacy analysis on ORR and other key efficacy endpoints; • Other minor or cosmetic changes.
6.0	8JUL2019	Amendment 6	• Specified that inferential analysis set and FAS will be used for efficacy analyses in Cohort 1 KTE-X19 subjects while mITT set will be used for Cohort 1 axicabtagene ciloleucel and Cohort 2 efficacy analysis; • Added the PFS and OS definitions for FAS; • Indicated that safety analysis will also be done with all treated KTE-X19 subjects combined from Cohort 1 and Cohort 2; • Added back B-cell aplasia analysis; • Added summary for history of revisions; • Other minor or cosmetic changes.

Version	Date	Protocol	Description of Changes
7.0	09FEB2022	Amendment 7 to Amendment 8	• Addition of Cohort 3 (~90 subjects) with BTKi-naïve subjects • Hypothesis that the ORR to KTE-X19 per independent review is significantly greater than 57% in Cohort 3 subjects • Scientific steering committee (SSC) will review safety data for Cohort 3 to make recommendations on further study conduct • Safety interim analysis will be conducted after 15 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 30 days after infusion • Cohort 3 interim analysis 2 will be conducted after 50 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be followed for 3 months after the KTE-X19 infusion • The primary analysis in Cohort 3 will occur after 86 subjects in Cohort 3 have been enrolled and treated with KTE-X19 and have had the opportunity to be assessed for response 6 months after the first objective response or 9 months after the KTE-X19 infusion, whichever is earlier • Updated the section 3.1 of Study Design based on protocol amendment 8. • Added Cohort 3 in section 9.5 of the efficacy analysis. • Added ICANS in section 9.6 for Cohort 3 subjects. • Added immune effector cell-associated encephalopathy score analysis in section 9.6.8 for Cohort 3 subjects.

13. APPENDICES

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 (AE) start dates
- Deaths (see exceptions below)
- Concomitant medication start dates
- Subsequent anti-cancer therapy start dates

Table 1. 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*	= Day 0 *yyyy*	3	1	3	1	n/a	1	1
	≠ Day 0 *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

Abbreviation: n/a, not applicable.
Note: If the start date imputation leads to a start date that is after the stop date, then do not impute the start date.
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.

Imputation rules for partial or missing death dates:

- If death year and month are available, but day is missing:
  - If mmyyyy for the last date known to be alive = 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.
- 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 analysis data cutoff date or the last date known to be alive, whichever is later.

Appendix 2. Sample Adverse Event Table Layouts

Sample Adverse Event (AE) Summary Layout 1: All AE summaries listed in Section 9.6.1 will be provided in format 1 ("Gr 1" and "Gr 2" columns are not needed for "Grade 3 or higher" summary tables). The preferred terms will be sorted by descending order of frequency of the "Any" column.

Table 2. Subject Incidence of <AE Descriptor> AEs by Preferred Term (Worst Grade)

	Any	Gr 1	Gr2	Gr 3	Gr 4	Gr 5
Any <AE descriptor> adverse event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred term 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred term 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)

Abbreviations: AE, adverse event; Gr, Grade.

Sample Adverse Event Summary Layout 2: AE summaries may also be provided in format 2 ("Gr 1" and "Gr 2" columns are not needed for "Grade 3 or higher" summary tables). The system organ classes and preferred terms will be sorted by alphabetical order of system organ class and descending incidence of preferred term within each system organ class.

Table 3. Subject Incidence of <AE Descriptor> AEs by System Organ Class and Preferred Term (Worst Grade)

	Any	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
Any <AE descriptor> adverse event – n(%)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred term 1	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
Preferred term 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 2	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)	XX (X)
…						

Abbreviations: AE, adverse event; Gr, Grade.

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), duration of response to retreatment (DORR), progression-free survival (PFS), and overall survival (OS) is provided below.

1) DOR

DOR is defined only for subjects who experience an objective response (CR or PR) and is the time from the first objective response to disease progression or death. Response and progression may be defined per Central Read or Investigator Read. Data from retreatment period will not be included for analysis. 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. DOR will be derived using disease assessments obtained on study prior to initiation of new anti-cancer therapy. The DOR for subjects who undergo stem cell transplant (SCT) while in remission will be censored at the last evaluable disease assessment date prior to SCT; the DOR for subjects that undergo other new anti-cancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anti-cancer therapies. A sensitivity analysis will be conducted in which disease assessments and death information obtained after SCT are included in the derivation of duration of response.

Table 4. Primary Analysis of DOR

Circumstance	Event/Censored	Date of Event/Censoring
Disease progression prior to initiation of new anti-cancer therapy (including SCT)	Event	Progression date
Death without documented disease progression and without new anti-cancer therapy (including SCT)	Event	Death date
Remain in response without new anti-cancer therapy (including SCT)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including SCT) prior to documented progression or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including SCT
Remain in response without new anti-cancer therapy (including SCT) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date

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

Table 5. Sensitivity Analysis of DOR (to include data after SCT post study treatment)

Circumstance	Event/Censored	Date of Event/Censoring
Disease progression after SCT, but prior to other new anti-cancer therapy	Event	Progression date
Death after SCT without documented progression and other new anti-cancer therapy	Event	Death date
Remain in response after SCT without other new anti-cancer therapy	Censored	Last evaluable disease assessment date after SCT
Remain in response after SCT prior to other initiated new anti-cancer therapy	Censored	Last evaluable disease assessment date after SCT but prior to other initiated new anti-cancer therapy
For subjects without SCT and all the other circumstances, follow the same as the "Primary Analysis of DOR."		

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

2) DORR

DORR is defined the same as DOR, except that the definition applies to the response after KTE-X19/axicabtagene ciloleucel retreatment.

3) PFS

PFS is defined as the time from the anti-CD19 CAR T cells infusion date to the date of disease progression or death from any cause. Progression may be defined per Central Read or Investigator Read. For PFS analysis with the full analysis set in which enrolled but not treated subjects are included, the PFS time will be calculated as the time from the enrollment date to the date of disease progression or death from any cause. Data from retreatment period will not be included for analysis. 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). The PFS for subjects who undergo SCT while in remission will be censored at the last evaluable disease assessment date prior to SCT; the PFS for subjects that undergo other new anti-cancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anti-cancer therapies. A sensitivity analysis will be conducted in which disease assessments and death information obtained after SCT are included in the derivation of PFS.

Table 6. Primary Analysis of PFS

Circumstance	Event/Censored	Date of Event/Censoring
Disease progression prior to initiation of new anti-cancer therapy (including SCT)	Event	Progression date
Death without documented disease progression and without new anti-cancer therapy (including SCT)	Event	Death date
Remain in response and alive without new anti-cancer therapy (including SCT)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including SCT) prior to documented progression or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including SCT. If no evaluable disease assessment is available, then censor at anti-CD19 CAR T cells infusion date
Remained in response without new anti-cancer therapy (including SCT) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date. If no evaluable disease assessment is available, then censor at anti-CD19 CAR T cells infusion date
Subject enrolled and treated with anti-CD19 CAR T cells but the disease assessment has not been done	Censored	Anti-CD19 CAR T cells infusion date

Abbreviations: PFS, progression-free survival; SCT, stem cell transplant.

Table 7. Sensitivity Analysis of PFS

Circumstance	Event/Censored	Date of Event/Censoring
Disease progression after SCT, but prior to other new anti-cancer therapy	Event	Progression date
Death after SCT without documented progression and other new anti-cancer therapy	Event	Death date
Remain in response after SCT without other new anti-cancer therapy	Censored	Last evaluable disease assessment date after SCT
Remain in response after SCT prior to other initiated new anti-cancer therapy	Censored	Last evaluable disease assessment date after SCT but prior to other initiated new anti-cancer therapy
For subjects without SCT and all the other circumstances, follow the same derivation rule as the "Primary Analysis of PFS."		

Abbreviations: PFS, progression-free survival; SCT, stem cell transplant.

4) OS

OS is defined as the time from the anti-CD19 CAR T cells infusion to the date of death from any cause. For OS analysis with the full analysis set, the OS time will be calculated as the time from the enrollment date to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at the last date known to be alive or the data cutoff date, whichever is earlier.

Table 8. Analysis of OS

Circumstance	Event/Censored	Date of Event/Censoring
Death before data cutoff date for analysis	Event	Date of death
Death after data cutoff date for analysis	Censored	Data cutoff date
Known to be alive after data cutoff date for analysis	Censored	Data cutoff date
Alive up through data cutoff date and no further information available after data cutoff date	Censored	Last date known to be alive
Full withdrawal of consent or lost to follow-up prior to data cutoff date	Censored	Last date known to be alive

Abbreviation: OS, overall survival.

5) 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 administration dates
- Conditioning chemo administration dates
- anti-CD19 CAR T cells infusion dates
- Computerized tomography (CT) scan dates
- Positron emission tomography (PET) scan dates
- Clinical symptoms of lymphoma assessment dates
- Target lesion assessment
- Non-target lesion assessment
- New lesion assessment
- Other tumor assessment dates (Bone marrow and spleen assessments)
- Disease response assessment

- 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 Month 3 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

Appendix 4. Derivation of Simplified Mantle Cell Lymphoma International Prognostic Index

The simplified Mantle Cell Lymphoma International Prognostic Index (s-MIPI) will be derived as described in Hoster {Hoster 2008}.

Table 9. Simplified Mantle Cell Lymphoma International Prognostic Index

Points	Age, yr	ECOG	LDH, ULN	WBC, 10^9/L
0	< 50	0 to 1	< 0.67	< 6.700
1	50 to 59	NA	0.67 to 0.99	6.700 to 9.999
2	60 to 69	2 to 4	1.000 to 1.49	10.000 to 14.999
3	≥ 70	NA	≥ 1.5000	≥ 15.000

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NA, not applicable; ULN, upper limit of normal; WBC, white blood count; yr; year.

For each prognostic factor, 0 to 3 points will be given to each subject and points will be summed up to a maximum of 11 points. Subjects with 0 to 3 points in summary will be classified as low risk, subjects with 4 to 5 points as intermediate risk, and subjects with 6 to 11 points as high risk. Eastern Cooperative Oncology Group (ECOG) performance status will be weighted with 2 points if subjects are unable to work or bedridden (ECOG 2 to 4). Lactate dehydrogenase (LDH) will be weighted according to the ratio to the upper limit of normal. Thus, for an upper limit of normal of 240 U/L, the cutpoints will be 180 U/L, 240 U/L, and 360 U/L, for example.

That is, Simplified Mantle Cell Lymphoma International Prognostic Index (s-MIPI) score = sum of the points for age, ECOG performance status, LDH, and white blood count from the above table. The s-MIPI score can be classified into 3 risk categories as follows.

Table 10. Risk Category Based on s-MIPI

s-MIPI score	Risk Category
0 to 3	Low risk
4 to 5	Intermediate risk
6 to 11	High risk

Abbreviation: s-MIPI, simplified Mantle Cell Lymphoma International Prognostic Index.