Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Company Code:	KTE-X19
USAN Name:	Brexucabtagene Autoleucel
Product Name:	KTE-X19
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADaM	Analysis data model
AE	Adverse event
ANC	Absolute neutrophil count
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ASCT	Autologous stem cell transplant
CAR	Chimeric antigen receptor
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRi	Complete response with incomplete hematopoietic recovery
CRS	Cytokine release syndrome
CTCAE	Common terminology criteria for adverse event
DLT	Dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EOP1	End of phase 1
FAS	Full analysis set
HLGT	High-level group term
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal residual disease
MRD-	Minimum residual disease negative
MST	MedDRA search term
MTD	Maximum tolerated dose
OS	Overall survival
ORR	Objective response rate
PD	Progressive disease
PR	Partial response
RCR	Replication-competent retrovirus
R/R	Relapsed/Refractory
r/r CLL	Relapsed/Refractory chronic lymphocytic Leukemia
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable disease
SDTM	Study data tabulation model
SLL	Small lymphocytic lymphoma
SMQ	Standardized MedDRA query

SOC	System organ class
SRT	Safety review team
TEAE	Treatment-emergent adverse event
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 protocol KTE-C19-108 entitled "A Phase 1 Multicenter Study Evaluating the Safety and Tolerability of KTE-X19 in Adult Subjects with Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma" Amendment 2 dated 27 May 2020. The scope of this plan includes the end of phase 1 (EOP1) and final analyses.

2. OBJECTIVES

The primary objective of this study is to evaluate the safety and tolerability of KTE-X19 in subjects with relapsed or refractory (r/r) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

Secondary objectives are to characterize the safety profile and anti-KTE-X19 antibodies, and to evaluate the efficacy of KTE-X19 as measured by the objective response rate (ORR) per investigator review in subjects with r/r CLL treated with KTE-X19. Efficacy analysis for ORR will be performed only for the selected safe dose cohort.

CCI [redacted]

3. STUDY DESIGN

3.1. Overview

Study KTE-C19-108 is a Phase 1, multicenter, open-label study evaluating the safety and tolerability of KTE-X19 in adult subjects with r/r CLL and SLL. The trial will be separated into 2 different stages (Cohort 1 and 2 in the first stage and Cohort 3 and 4 in the second stage).

The anticipated total number of enrolled and treated subjects in this study is up to approximately 27 subjects (estimated based on actual enrollment in Cohort 1 is 6 and Cohort 2 is 3 during Protocol Amendment 2).

During the first stage of the study, subjects with r/r CLL will be enrolled using a 6+3 study design into cohorts described below:

- Cohort 1: Up to 9 subjects will be enrolled at $1x10^6$ anti-CD19 chimeric antigen receptor (CAR) T cells/kg. Decision to enroll in Cohort 2 will be based on incidence of dose limiting toxicity (DLT) in Cohort 1.

- Cohort 2: Up to 9 subjects will be enrolled at $2x10^6$ anti-CD19 CAR T cells/kg.

In the second stage (Protocol Amendment 2), subjects with r/r CLL and SLL will be enrolled into Cohort 3 and 4 as described below:

- Cohort 3: Three (3) subjects with r/r CLL and SLL with ≤ 1% malignant cells in peripheral blood or absolute lymphocyte count (ALC) < 5,000 cells/μL will be enrolled and dosed with KTE-X19 at a dose of $1x10^6$ anti-CD19 CAR T cells/kg. Subjects must have received at least 2 prior lines of treatment, one of which must include a BTK inhibitor. This is an exploratory cohort. No additional dose levels will be evaluated.

- Cohort 4: Up to approximately 15 subjects with r/r CLL who have been previously treated with at least two prior lines of therapy and are receiving ibrutinib as a single agent, or ibrutinib in combination with anti-CD20 antibodies, BCL-2 inhibitors, and PI3k inhibitors as the last line of therapy. Subjects must have received ibrutinib for at least 6 months prior to screening. Ibrutinib administration will continue up to 30 hours prior to leukapheresis. In case of treatment interruption with ibrutinib, the principal investigator (PI) should reach out to the medical monitor to discuss. A 3+3 study design will be used to evaluate two doses of KTE-X19.

  — Cohort 4A: Up to 6 subjects will be enrolled and dosed at $1x10^6$ anti-CD19 CAR T cells/kg. Decision to enroll in Cohort 4B will be based on SRT review of Cohort 4A.

  — Cohort 4B: Up to 6 subjects will be enrolled and dosed at $2x10^6$ anti-CD19 CAR T cells/kg.

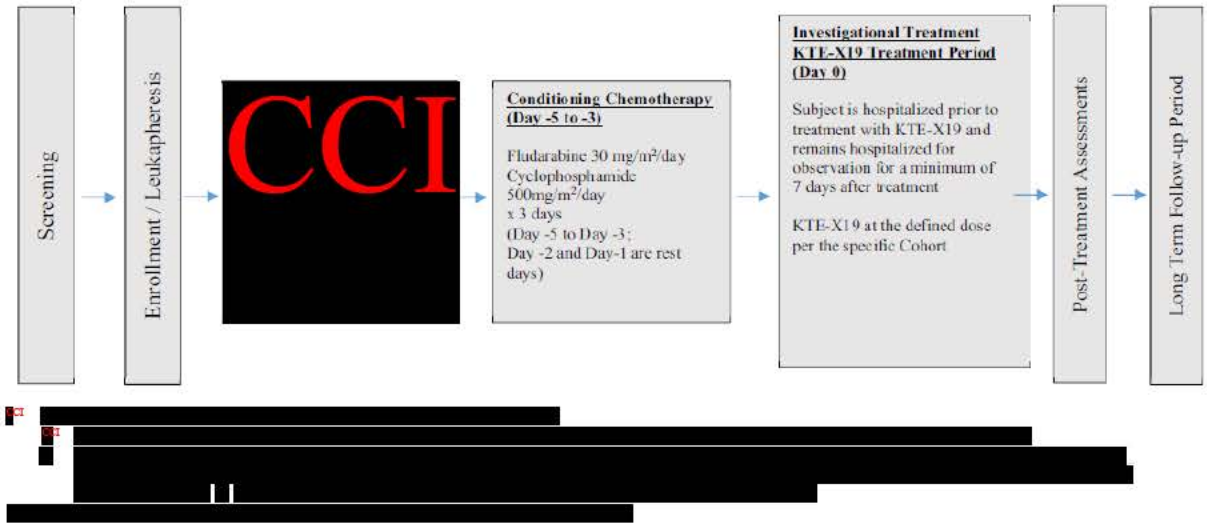
Once a safe dose is established in Cohort 4, additional subjects will be enrolled and dosed for a total of up to 12 subjects at the safe dose level. Up to 15 subjects in Cohort 4 who are evaluable for dose-limiting toxicities (DLTs) will be assessed to evaluate the safety of KTE-X19. A safety review team (SRT) that is internal to the study sponsor, and in collaboration with at least 1 study investigator, will review safety data and make recommendations regarding further enrollment based on the incidence of DLTs and overall safety profile of KTE-X19.

Each subject will proceed through the following study periods, as shown in the study schema (Figure 1):

- Screening
- Enrollment/Leukapheresis
- [redacted]
- Lymphodepleting/Conditioning chemotherapy
- Investigational product (IP) treatment
- Post-treatment assessment
- Long-term follow-up

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

Figure 1. Study Schema for Study KTE-C19-108



3.2. Hypothesis

No formal hypothesis testing is planned.

3.3. Sample Size Consideration

For Cohort 1 and Cohort 2, the study will enroll and dose up to 9 subjects who are DLT evaluable in each cohort. The anticipated total enrollment for Cohort 3 and Cohort 4 is up to approximately 18 subjects.

Cohort 3 will enroll and dose 3 subjects in an exploratory cohort. No additional subjects will be enrolled or dose levels evaluated.

For Cohort 4, the SRT will review safety and PK data after 3 to 6 subjects in the DLT-evaluable set at each dose level have had the opportunity to be followed for 28 days after the KTE-X19 infusion. If the lymphodepleting regimen and one or more KTE-X19 doses evaluated in the study are determined to be safe based on the incidence of DLT and to enable sufficient cell expansion, up to approximately total of 12 subjects may be enrolled in the dose cohort to further evaluate safety. The maximum number of subjects, including those enrolled and dosed in Cohort 4 will be approximately 15 subjects.

3.4. Statistical Assumptions

The independence of subject responses will be assumed.

4. THE INDEPENDENCE OF SUBJECT RESPONSES WILL BE ASSUMED. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

4.1.1. Primary

- Incidence of Dose Limiting Toxicities (DLTs) in subjects treated with KTE-X19.

4.1.2. Secondary

- Incidence of adverse events (AEs)
- Levels of anti-CD19 CAR T-cells in blood
- ORR (CR/CRi/PR) as defined by IWCLL 2018 criteria for selected safe dose cohort

CCI [redacted]

[redacted]

4.2. Covariates

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

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)
- Age (in years) at baseline (< 65, ≥ 65)
- Sex (male, female)
- Region: US, EU, Australia
- 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)
- Rai Disease stage (0, I-II, III-IV)
- Binet classification at time of diagnosis (A, B, C)
- Number of prior chemotherapy regimens (2, 3, >3)
- 17p deletion (Y, N)
- 11q deletion (Y, N)
- 13q deletion (Y, N)
- Trisomy 12 (Y, N)
- Complex Karyotype (Y, N)
- High risk feature (any of 17p deletion, 11q deletion, 13q deletion, trisomy 12, complex karyotype)
- Beta 2 microglobulin (≤ 3.5mg/L, >3.5mg/L)
- Baseline MRD (Positive, Negative)

5. DEFINITIONS

5.1. General

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

Study day 0: Study day 0 is defined as the day the subject received the first KTE-X19 infusion. The day prior to study day 0 will be study day -1. Any days after enrollment and prior to study day -1 will be sequential and negative integer-valued.

Baseline: The baseline value is defined as the last non-missing value taken prior to conditioning chemotherapy. For subjects without conditioning chemotherapy date, the baseline value is taken as the last non-missing value on the study.

CCI [redacted]

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

Actual follow-up time: Actual follow-up time among all subjects treated with KTE-X19 is calculated as the time from the first dose of KTE-X19 to the date of death, last date known 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 KTE-X19 infusion to the data cutoff date for the analysis.

5.2. Safety

Primary Safety Analysis Period: The primary analysis period includes the period on or after the first KTE-X19 infusion, CCI [redacted].

CCI [redacted]

Treatment-emergent adverse event (TEAE): Any adverse event with onset on or after the KTE-X19 infusion in the primary safety analysis period. CCI [redacted]

Deaths: All deaths that occur from the enrollment/leukapheresis up through the end of study will be summarized. Deaths that occur from the time of KTE-X19 infusion will also be summarized. CCI [redacted]

AEs of special interest: Adverse events of special interest for KTE-X19 treatment include important identified risks (Cytokine release syndrome [CRS], neurologic toxicities, cytopenias, infections, and hypogammaglobulinemia) and important potential risks (including but may not limit to immunogenicity, new malignancies, Replication-competent retrovirus [RCR], graft versus host disease [GVHD], and tumor lysis syndrome [TLS]).

CRS will be identified via a case report form (CRF) specifically designed to collect CRS as a syndrome. 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 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).

Neurologic toxicity (Neurotoxicity) AEs will be identified by 2 search strategies:

- Method 1: A Medical Dictionary for Regulatory Activities (MedDRA) search term list (MST) that was developed at Kite based on a modification of the search strategy described by Topp and colleagues {Topp 2015}.

- Method 2: MedDRA System Organ Classes (SOCs) of psychiatric disorders and nervous system disorders, excluding the following 2 High-Level Group Terms (HLGTs): sleep disorders and disturbances and sleep disturbances (incl subtypes). MedDRA preferred terms may be added or removed based on FDA feedback.

Prolonged Cytopenias (Neutropenia or Thrombocytopenia or Anemia) will be identified as cytopenias present on or after Day 30 post KTE-X19 infusion. Prolonged cytopenias will be summarized separately by the 3 blood cell lineages.

Immunogenicity will be identified by testing for reactivity against FMC63, the parent murine antibody used for the development of the single-chain variable region fragment (scFv) of the anti-CD19 CAR construct. Positive samples will then be tested to confirm the presence of antibody to the extracellular portions of anti-CD19 CAR.

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

Duration of an AE: The duration of an AE of 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 resolution day of the last AE in the event class – the start day of the first AE in the event class + 1.

Time to Onset of an AE: Time to onset of an AE of interest is defined as the interval from the date of the first infusion of KTE-X19 through the earliest onset date of the AEs in the event class, i.e., the start date of the first AE in the event class – the date of the first infusion of KTE-X19 + 1.

5.3. Efficacy

ORR: ORR is the proportion of subjects with either a CR, CRi or PR while on study as defined by IWCLL 2018 criteria. 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 CCI with KTE-X19). Responses are defined per investigator review.

Overall complete response rate (CR/CRi): The overall complete response includes both complete response (CR) and complete response with incomplete hematopoietic recovery (CRi) per investigator review prior to the subsequent anticancer therapy and allogeneic SCT.

Minimum Residual Disease (MRD) Negative Rate: The incidence of a minimal residual disease response (MRD-). MRD- is defined as MRD < 10^{-4} per the standard assessment conducted in a central lab, ie one CLL cell per 10,000 leukocytes. MRD negative rate will be estimated for all dosed subjects, and for subjects with CR/CRi.

DOR: DOR is defined only for subjects who experience an objective response (CR/CRi/PR) and is the time from the first objective response to disease progression (PD) per IWCLL 2018 or death. CCI Subjects not meeting the criteria for PD or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date before data cutoff. 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 new anti-cancer therapy including SCT CCI will be censored at the last evaluable disease assessment date prior to the subsequent therapy. Additional details on the derivation of DOR are provided in Appendix 3.

PFS: PFS is defined as the time from the KTE-X19 infusion date to the date of disease progression or death from any cause. CCI 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 before data cutoff. 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 new anti-cancer therapies including SCT while in response will be censored at the last evaluable disease assessment date prior to the subsequent therapy. Additional details on the derivation of PFS are provided in Appendix 3.

OS: OS is defined as the time from the KTE-X19 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. 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.

6. ANALYSIS SUBSETS

6.1. DLT Evaluable Set

All subjects treated with the target KTE-X19 dose and followed for at least 28 days, or received a dose of KTE-X19 lower than the target dose but experienced a DLT during the 28 day post infusion period, up to the time at which the maximum toxicity dose (MTD) is identified.

Additional subjects enrolled and treated subsequently for the purpose of assessment of the overall safety in the same dose level or a lower dose level will not be considered as part of the DLT evaluable set, and DLT will not be assessed for such subjects.

6.2. All Treated Subjects

All subjects treated with any dose of KTE-X19 are included in the analysis set.

6.3. Safety Analysis Set

The safety analysis set is defined as all subjects treated with any dose of KTE-X19.

6.4. Full Analysis Set

The full analysis set will consist of all enrolled subjects and may be used for the summary of subject disposition and subject listings of deaths.

CCI [redacted]

[redacted]

6.6. 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. Safety Interim Analysis

No formal interim analysis is planned for this phase 1 study. During the study, the SRT will review safety data after 3-9 DLT evaluable subjects at each dose level have had the opportunity to be followed for 28 days after the KTE-X19 infusion. The SRT will review the safety data and make recommendations on further study conduct and progression of the study. For details on the dose escalation/de-escalation plan based on the incidences of DLTs, please refer to the protocol. Please refer to SRT charter for details on safety data review.

7.2. Assessment of Criteria to Pause Enrollment

Study enrollment will be paused following any grade 5 adverse event that occurs within 30 days of KTE-X19 infusion regardless of attributions.

In the event that the enrollment is paused after the pausing criteria have been met, overall assessment of the benefit/risk ratio will be conducted. If the overall assessment of the benefit/risk ratio is favorable, the study can resume enrollment. Restart of the study may require prior approval if required by applicable regulatory requirements or mandated by in country Regulatory Agency.

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

- Incidence of the following Grade 4 KTE-X19-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)

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.

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 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.

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 partial missing 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.

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

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 Kite Standard Operating Procedures (SOPs). 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 timing of the EOP1 analyses will be based on subject accrual and safety or disease assessment milestones. The final analysis will occur when all subjects have completed the study.

All the analyses will be descriptive.

9.2. Subject Accountability

The number of subjects enrolled/leukapheresed, treated with bridging therapy, treated with conditioning chemotherapy, treated with KTE-X19, and retreated with KTE-X19 (if applicable) 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 KTE-X19 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 will be tabulated.

9.5. Efficacy Analyses

The primary efficacy analyses will be conducted on the all treated subjects for the selected safe dose cohort. The investigators will assess the disease response based on the IWCLL 2018 criteria. The investigators will provide the determination of disease status (CR, CRi, PR, SD, PD, not evaluable [NE]) at each time point. These assessments will be used to derive the best overall response (BOR), ORR, CR/CRi rate, MRD- rate, MRD- rate among CR/CRi subjects, DOR, and PFS. These efficacy analyses will also be performed only for the selected safe dose cohort.

In the event any subject undergoes an SCT or any additional anti-cancer therapy while on study, the subject's best response will be derived only based on disease responses assessed prior to SCT or initiation of new therapy, whichever is earlier. (See details in Appendix 3).

When the estimates are not generated due to small sample size, only descriptive statistics (mean, median, standard deviation, minimum and maximum, or percentages), as well as data listings by subject and visit, for each efficacy endpoint will be provided.

9.5.1. ORR

9.5.1.1. Analyses of ORR and Overall Complete Response Rate per Investigator Assessment

The subject incidence of objective response rate (CR/CRi/PR) will be calculated. 95% confidence intervals will be provided about the ORR, calculated with the Clopper-Pearson (an exact interval).

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

9.6. Safety Analyses

Safety analyses will be conducted on the safety analysis set. The primary analysis of safety data will summarize TEAEs, death, and laboratory values with onset on or after the KTE-X19 infusion date CCI [redacted] CCI [redacted]

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 5.0.

CRS will be graded using a revised CRS grading scale developed by Lee et al {Lee 2014}. Individual symptoms associated with CRS will be graded per CTCAE version 5.0.

Fatal AEs that are attributed to disease progression may be included in the death summary with a primary death reason of "chronic lymphocytic leukemia" regardless of the coded preferred term.

Subjects enrolled, but not dosed with KTE-X19, will be followed for AEs for 30 days after the last study-specific procedure, or until initiation of a new anti-cancer therapy, whichever occurs first. 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.

Safety summaries will be presented by cohorts.

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-related AEs
- All KTE-X19-related SAEs
- All Grade 3 or higher AEs
- All Grade 3 or higher KTE-X19-related AEs

- Fatal AEs
- AEs of special interest, including important identified risks and important potential risks

The subject incidence summary of deaths and a subject listing of deaths will be provided. The primary reasons of death will also be summarized.

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

The time to onset 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 the duration of neurologic events will be summarized.

Cytopenias will be summarized by categories of neutropenia, anemia, and thrombocytopenia; cytopenias present on or after 30 days from KTE-X19 infusion will also be summarized.

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

New malignancies are based on search criteria of SOC Neoplasms benign, malignant, and unspecified (including cysts and polyps), excluding benign neoplasms and those events related to the primary malignancy. New non-melanoma skin cancers are not included in the summary. New malignancies will be listed.

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 5.0. The incidence of post-infusion worst-grade lab toxicities for all analytes will be summarized. Additional summaries for the shift from before infusion to the worst toxicity grade after KTE-X19 infusion may also be generated.

9.6.4. Anti-KTE-X19 Antibodies

The subject incidence of any anti-KTE-X19 antibodies will be tabulated. For subjects testing positive for antibodies, the persistence of the antibody over time will be listed.

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 listed.

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
- Total CAR T cells of the KTE-X19 infusion
- Total T cells of the KTE-X19 infusion
- Transduction ratio

CCI [redacted]

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, according to the version in use at analysis. The subject incidence of procedures will be tabulated. The indication of concomitant medications of interest for systemic steroids, tocilizumab, vasopressors, nonsteroidal immunosuppressants other than tocilizumab, and IV immunoglobulins defined by Kite, may be summarized.

9.7. Product Characteristics

A subject listing of product characteristics will be provided. Please refer to the Translational SAP for details.

CCI [redacted]

9.10. Subsequent Anti-Cancer Therapy

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

9.11. Duration Metrics

Summary statistics will be provided for the following durations:

- Days from leukapheresis to commencement of conditioning chemotherapy
- Days from leukapheresis to KTE-X19 product release
- Days from leukapheresis to delivery of KTE-X19 at study site
- Days from leukapheresis to administration of KTE-X19
- Days from conditioning chemotherapy to administration of KTE-X19
- Duration of hospitalization for the KTE-X19 infusion

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

None.

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12. 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. IWCLL 2018 Response Criteria and Disease Response Assessment

The determination of CLL response and progression will be based on standardized International Workshop on CLL (IWCLL) 2018 criteria.

Table 2. IWCLL 2018 Response Criteria

Parameter	CR	PR	PD
Group A (indicating tumor load)			
Lymphadenopathy[1]	none ≥ 1.5 cm	decrease ≥ 50%	increase by ≥ 50% or new lymph nodes ≥ 1.5 cm
Hepatomegaly	none	decrease ≥ 50%	Increase by ≥ 50 %
Splenomegaly	none	decrease ≥ 50%	Increase by ≥ 50 %
Blood lymphocytes	< 4000/μL	decrease of ≥ 50% from baseline	Increase by ≥ 50% over baseline[2] to ≥ 5000/μL
Group B (indicating function of the hematopoietic system)			
Platelet count	≥ 100,000/μL	≥ 100,000/μL or increase by ≥ 50% from baseline	Decrease by ≥ 50% from baseline due to CLL
Hemoglobin	≥ 11 g/dL	≥ 11 g/dL or increase by ≥ 50% from baseline	Decrease by ≥ 2 g/dL
Bone Marrow	Normocellular for age, no increase in CLL lymphocytes, no clonal B-lymphoid nodules[3]	CLL cells or clonal B-lymphoid nodules present	Increase in CLL cells by ≥50% on successive biopsies

1 Assessed as sum of the products of up to 6 lymph nodes
2 Subjects with treatment-related lymphocytosis should not be rated PD and remain on study treatment if other criteria for progressive disease are absent.
3 In case of B-lymphoid nodules assessment is recommended to clarify if the population is clonal—if not, subjects can be assessed as CR/CRi if all other criteria are fulfilled.

Table 3. Disease Response Assessment

Overall Disease Response	IWCLL Criteria 2018	Additional Criteria
CR	All criteria for CR in Group A and B	No disease related symptoms should be present, neutrophil count ≥ 1500/μL
CRi	All criteria for CR are met except with platelet count <100,000/μl, hemoglobin < 11 g/dL or neutrophil count < 1500/μL	
PR	At least 1 criterion from Group A and 1 from Group B must be fulfilled.	If only one criterion is abnormal at baseline from Group A or B, only that criterion must improve.
SD	Failure to achieve a PR and absence of PD	
PD	Presence of at least 1 of the criteria from Group A or Group B	Constitutional symptoms alone do not define PD. A bone marrow biopsy should be performed to confirm progression if blood count changes are the only evidence of progression.

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) DOR

Table 4. Analysis of DOR for Treated Subjects with Objective Response

Earliest Scenario since First Objective Response among PD, Death, New Therapy, Study W/D and Lost to Follow Up	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death	Event	Death date
New anti-cancer therapy (including SCT CCI [redacted])	Censored	Last evaluable disease assessment date prior to the first new therapy (including SCT CCI [redacted])
Withdrawal of consent or lost to follow-up	Censored	Last evaluable disease assessment date prior to data cutoff date
Remain in response by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date

Abbreviations: DOR, duration of response; SCT, stem cell transplant.
Note: Time to event = Event / Censoring date - First response date + 1.

2) PFS

PFS is defined as the time from the KTE-X19 infusion date to the date of disease progression or death from any cause. CCI [redacted] 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 response 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.

Table 5. Analysis of PFS for Treated Subjects

Earliest Scenario since Infusion among PD, Death, New Therapy, Study W/D and Lost to Follow Up	Event/Censored	Date of Event/Censoring
Disease progression	Event	First progression date
Death	Event	Death date
New anti-cancer therapy (including SCT CCI [redacted])	Censored	Last evaluable disease assessment date prior to the first new therapy (including SCT CCI [redacted])
Withdrawal of consent or lost to follow-up	Censored	Last evaluable disease assessment date prior to data cutoff date

Earliest Scenario since Infusion among PD, Death, New Therapy, Study W/D and Lost to Follow Up	Event/Censored	Date of Event/Censoring
Progression-free and alive by data cutoff	Censored	Last evaluable disease assessment date prior to data cutoff date
Disease response yet to be assessed	Censored	KTE-X19 infusion date

Abbreviations: PFS, progression-free survival; SCT, stem cell transplant.
Note: Time to event = Event / Censoring date - First infusion date + 1

3) OS

OS is defined as the time from the KTE-X19 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.

Table 6. Analysis of OS for Treated Subjects

Circumstance	Event/Censored	Date of Event/Censoring
Death (non-missing death date ≤ cutoff date)	Event	Death date
Alive (either death date or last known alive date > cutoff date)	Censored	Data cutoff date
Alive (death date is missing and last known alive date ≤ cutoff date)*	Censored	Last known alive date

Abbreviation: OS, overall survival.
Note: Time to event = Event / Censoring date - First infusion date + 1
* If the subject withdrew full consent or was lost to follow up prior to data cutoff date, then such information will be indicated in the summaries of OS.

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 administration dates
- Conditioning chemo administration dates
- KTE-X19 infusion dates
- Computerized tomography (CT) scan dates
- Positron emission tomography (PET) scan dates

- Index lesion assessment
- Non-index lesion assessment
- New lesion assessment
- Other tumor assessment dates (Bone marrow, liver and spleen assessments)
- Disease response assessment
- Long-term follow-up subject status date where status = alive or death
- 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. Binet and Rai Staging Systems for the Classification of CLL

Binet

Stage	Lymph Node Areas	Hemoglobin < 10 g/dL	Platelet < 100 × 10^9/L
A	< 3	No	No
B	≥ 3	No	No
C	±	Either present	

Rai

Stage	Lymphocytosis	Lymph Node Enlargement	Spleen/Liver Enlargement	Hemoglobin < 11 g/dL	Platelet < 100 × 10^9/L
0	Yes	No	No	No	No
I	Yes	Yes	No	No	No
II	Yes	±	Yes	No	No
III	Yes	±	±	Yes	No
IV	Yes	±	±	±	Yes