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Protocol:	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINTIONS OF TERMS

ADaM	Analysis data model
AE	Adverse event
ALL	Acute Lymphoblastic Leukemia
allo SCT	Allogeneic stem cell transplant
BFBM	Blast-free hypoplastic or aplastic bone marrow rate
CAR	Chimeric antigen receptor
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRh	CR with partial hematological recovery
CRi	CR with incomplete hematologic recovery
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
DMP	Data management plan
DOR	Duration of response
DORR	Duration of response to retreatment
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EQ-5D-5L	European quality of life five dimensions five levels
FAS	Full analysis set
GVHD	Graft versus host disease
HDT	High-dose therapy
HLGT	High-level group term
IVIG	Intravenous immunoglobulin
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MLL	Mixed lineage leukemia
MRD	Minimal residue disease
NE	Neurologic event
OCR	Overall complete remission
OS	Overall survival

PFS	Progression-free survival
PR	Partial remission
PRO	Patient reported outcome
RCR	Replication-competent retrovirus
RFS	Relapse free survival
r/r	Relapsed/refractory
SAE	Serious adverse event
SCT	Stem cell transplant
SDTM	Study data tabulation model
SOC	System organ class
SOP	Standard operating procedures
SMQ	Standardized MedDRA query
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TFL	Tables, figures, and listings
TID	Trial integrity document
TKI	Tyrosine kinase inhibitor
VAS	Visual analog scale
WHO	Would health organization

1. INTRODUCTION

This statistical analysis plan provides the prespecification and details for the statistical analyses outlined within protocol KTE-C19-103 entitled "A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-3)". The scope of this plan includes the interim, primary, and final analyses that are planned.

2. OBJECTIVES

The primary objective of Phase 1 is to evaluate the safety of KTE-X19 and determine the dosage for Phase 2.

The primary objective of Phase 2 is to evaluate the efficacy of KTE-X19, as measured by the overall complete remission (OCR) rate defined as the proportion of subjects achieved either complete response (CR) or CR with incomplete hematologic recovery (CRi) in this study. Secondary objectives will include assessing the safety and tolerability of KTE-X19 and additional efficacy endpoints.

3. STUDY OVERVIEW

3.1. Study Design

Study KTE-C19-103 is a Phase 1/2 multicenter, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with r/r ALL. The trial will be separated into 2 distinct phases designated as Phase 1 and Phase 2.

During Phase 1, approximately 3 to 12 subjects with high-burden [M3 marrow (> 25% leukemic blasts) or ≥ 1000 blasts/mm^3 in the peripheral circulation] r/r ALL disease who are evaluable for dose-limiting toxicity (DLT) 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 the safety data and make recommendations regarding further enrollment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19. Up to approximately 40 additional subjects with high- or low-burden disease may be enrolled to further assess safety in Phase 1. The DLT definition and assessment is described in the study protocol.

During Phase 2, approximately 50 subjects with r/r ALL treated with KTE-X19 will be assessed to evaluate the efficacy and safety of KTE-X19. One interim and one primary analysis will be performed. A Data Safety Monitoring Board (DSMB) will review safety data after 20 subjects in Phase 2 have been treated and followed for 30 days.

The primary analysis will occur when the overall study enrollment is complete, and the last subject treated with KTE-X19 has had the opportunity to complete the 6-month disease assessment. The final analysis will occur when all subjects have completed the study.

3.2. Hypothesis

This study is designed to differentiate between a treatment that has a true OCR rate of 40% or less and a treatment with a true OCR rate of 65% or more. The hypothesis is that the OCR rate with KTE-X19 treatment is significantly greater than the historical control rate of 40%, ie,

$$H_0: p \leq 0.4 \; vs. \; H_1: p \; > 0.4$$

3.3. Sample Size Considerations

Three to 12 subjects will be enrolled to evaluate for DLT in Phase 1, and up to approximately 40 additional subjects will be enrolled into Phase 1 of this study.

If the study proceeds to Phase 2, approximately 50 subjects will be enrolled into Phase 2. Approximately 100 subjects may be enrolled and treated in the entire study (both Phase 1 and Phase 2).

KTE-X19 doses will range from 0.5 x 10^6 to 2 x 10^6 cells/kg. For the Phase 1 portion of the study and the evaluation of DLT, the doses are 2.0 x 10^6 anti-CD19 CAR T cells/kg (± 20%), 1.0 x 10^6 anti-CD19 CAR T cells/kg (± 20%), or 0.5 x 10^6 anti-CD19 CAR T cells/kg (± 20%). For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8, 1 x 10^8, or 0.5 x 10^8 anti-CD19 CAR T cells will be administered.

Efficacy analyses will be based on a modified intent-to-treat (mITT) population consisting of all subjects enrolled in the Phase 2 portion of the study who receive KTE-X19 at any dose.

Efficacy analyses may also be based on a full analysis set (FAS) population consisting of all subjects enrolled in the Phase 2 portion of the study.

Safety analyses will be based on all subjects dosed with KTE-X19.

DLT analyses will be based on the DLT-evaluable analysis set, defined in Section 6.7.

This study uses a single-arm design to test for an improvement in OCR rate. A sample size of 50 KTE-X19 subjects in Phase 2 provides approximately 93% power to distinguish between an active therapy with a 65% true OCR rate from a therapy with a response rate of 40% or less, with the one-sided alpha level of 0.025. A step-down test of the secondary endpoint minimal residual disease negative (MRD) rate will be performed against an MRD rate of 30% if the testing of the OCR rate is significant. EAST version 6 was used to evaluate the operating characteristics of this design.

The hypothesis of MRD- will only be performed if the primary efficacy endpoint OCR rate reaches statistical significance, so that the family-wise type I error will be controlled at one-sided 2.5% level under this hierarchical testing scheme.

During Phase 2, 1 interim and 1 primary analysis will be performed.

- The interim analysis will occur after 20 subjects in the mITT analysis set have had the opportunity to be followed for 30 days; this analysis will be for the assessment of safety only. The DSMB will review the 20-patient interim analysis.
- The primary analysis will occur when the overall study enrollment is complete and the last treated subject in the mITT analysis set has had the opportunity to complete the 6-month disease assessment after KTE-X19 infusion.

At the time of the primary analysis, if either less than or more than 50 subjects are eligible for the mITT analysis set, all mITT-eligible subjects will be included in the analysis.

3.4. Statistical Assumptions

This study assumes that the underlying overall complete remission rate (in the absence of treatment with investigational therapy) is 40% and that an improvement in the overall complete remission rate to 65% provides clinically meaningful benefit. The responses from subjects in the study population are assumed to be independent and follow binomial distribution; therefore, an exact binomial test will be used to test the statistical hypothesis.

For MRD rate, it is assumed that the underlying response rate (in the absence of treatment with investigational therapy) is 30%.

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

Primary endpoint (Phase 1): The incidence of adverse events (AEs) defined as DLTs in the DLT-evaluable set

Primary endpoint (Phase 2): OCR (CR + CRi) rate per independent review

Secondary endpoints (Phase 2, unless noted):

- MRD remission rate
- CR rate per independent review
- CRi rate per independent review
- Duration of Remission (DOR) per independent review
- OCR (CR + CRi) rate per investigator review
- Allogeneic stem cell transplant (allo-SCT) rate
- Rate of MRD CR
- Rate of MRD CRi
- Overall survival (OS)
- Relapse-free survival (RFS)
- Incidence of AEs and clinically significant changes in safety laboratory values
- Incidence of anti-CD19 CAR antibodies
- Changes over time in the EQ-5D scale score and EQ-5D visual analogue scale (VAS) score

Exploratory endpoint:

- The OCR (CR + CRi) rate, rate of MRD negative remission, and DOR among subjects retreated with KTE-X19
- Survival rate and non-relapse survival rate 100 days after allo-SCT
- CR with partial hematological recovery (CRh)
- Blast-free hypoplastic or aplastic bone marrow rate (BFBM)

- Rate of MRD CRh
- Rate of MRD BFBM
- Partial remission (PR) rate
- Level and activity of CAR T cells, as well as presence and status of CD19+ cells in blood and bone marrow
- Levels of cytokines in serum and cerebrospinal fluid (CSF)

Endpoints related to product characterization (level and activity of CAR T cells), presence and status of CD19+ cells in blood and bone marrow, as well as analyses related to these endpoints will be described in a supplemental statistical analysis plan.

4.2. 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 at baseline (< 65 years, ≥ 65 years)
- Sex (male, female)
- Race: white, black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other (categories may be collapsed or expanded based on accrual)
- Region (North America, Europe)
- Relapsed or refractory (r/r) Subgroup (primary refractory [refractory to first-line therapy], first relapse if duration of first remission was < 12 months, r/r to 2nd or greater line therapy, r/r after allo-SCT)
- Prior blinatumomab treatment (yes, no)
- Prior inotuzumab treatment (yes, no)
- Prior allo-SCT (yes, no)
- Extramedullary disease (yes, no)
- Lines of prior therapies (1, 2, > 2; categories may be modified based on accrual)
- % bone marrow blasts at screening (< 50%, ≥ 50%)

- Peripheral blasts (0, > 0 to 1000, > 1000 blasts/mm^3)
- Normal karyotype
- CD19 expression based on central read (positive, negative)
- Philadelphia chromosome t(9;22) (yes, no)
- Mixed lineage leukemia (MLL) translocation t(4;11) t(8;14) (yes, no)
- Complex karyotype (≥ 5 chromosomal abnormalities) (yes, no)
- Low hypodiploidy (30-39 chromosomes) (yes, no)
- Near triploidy (60-78 chromosomes) (yes, no)
- Bridging chemotherapy (yes, no)

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

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment occurs when the 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 value taken prior to conditioning chemotherapy.

Study therapy: Study therapy includes bridging chemotherapy, CSF prophylaxis, conditioning chemotherapy, and KTE-X19.

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

r/r subgroup: The r/r subgroups are defined as below:

- r/r disease after allo-SCT: A subject is considered to be r/r after allo-SCT if the subject experienced relapse or failed to achieve CR after allo-SCT
- Primary refractory: A subject is considered to be primary refractory if the subject failed to achieve CR to first-line therapy.
- r/r to 2nd- or greater-line therapy: A subject is considered to be r/r to 2nd- or greater-line therapy if the subject failed to achieve CR or relapsed after the 2nd- or greater-line therapy.
- First relapse with first remission ≤ 12 months: A subject is considered to be first relapse with first remission ≤ 12 months if the subject achieved CR but relapsed within 12 months.

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 or last date known to be alive, 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

Treatment-emergent AE (TEAE): Any AE with an onset on or after the KTE-X19 infusion. For subjects who are retreated with KTE-X19, TEAEs during the retreatment period may be summarized separately.

KTE-X19 Retreatment period (defined only for subjects who undergo retreatment with KTE-X19): The KTE-X19 retreatment period begins on the day of the first dose of conditioning chemotherapy for retreatment or retreatment enrollment date, whichever is earlier.

Deaths: All deaths that occur after leukapheresis will be summarized. For subjects who undergo retreatment with KTE-X19, deaths that occur during the retreatment period may also be summarized separately.

AEs of special interest: AEs of interest for KTE-X19 treatment include the following categories:

Identified risks:

- Cytokine release syndrome (CRS)
- Neurologic events, including cerebral edema
- Cytopenias (thrombocytopenia, neutropenia, and anemia)
- Infections
- Hypogammaglobulinemia

Potential risks:

- Secondary malignancy
- Immunogenicity
- Replication-competent retrovirus (RCR)
- Tumor lysis syndrome
- Graft-versus-host disease (GVHD)

Time to onset and duration of the important identified risks CRS and neurologic events will be summarized.

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 the 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) version 4.03, and CRS as a syndrome will be graded per modified Lee criteria {Lee 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 against CAR-expressing cells using flow cytometry. In addition, a manual review of the AE terms indicative of autoimmunity will be performed, including infusion-related events and anaphylactic reactions among subjects who test positive for anti-CD19 CAR antibodies.

For other AEs of special interest, specific AEs may be mapped to these categories using dictionary-coded event terms 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 interest: 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 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

OCR (CR + CRi) rate: The proportion of subjects with either CR or CR with incomplete hematologic recovery (CRi) per independent review or investigator review prior to the subsequent anticancer therapy and allo-SCT.

CR rate: The proportion of subjects who experience CR, which will be analyzed per independent review and investigator review separately.

DOR: DOR is defined only for subjects who experience CR or CRi per independent review or investigator review and is the time from the first CR or CRi to relapse or death from any cause in the absence of documented relapse. Subjects not meeting the criteria for relapse and who have not died by the analysis data cutoff date will be censored at their last evaluable disease assessment date or disease status follow-up assessment. DOR will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy and allo-SCT (excluding resumption of tyrosine kinase inhibitor (TKI)). Disease assessments obtained after new anticancer therapies including allo-SCT will not contribute to the derivation of DOR. The DOR for subjects who undergo allo-SCT while in remission will be censored at the last evaluable disease assessment prior to the allo-SCT; the DOR for subjects who undergo other new anticancer therapies in the absence of documented relapse is censored at the last evaluable disease assessment prior to the new anticancer therapies. A sensitivity analysis will be conducted in which the DOR in subjects who received subsequent allo-SCT will not censor at the last disease assessment prior to SCT, and instead, the response after SCT will contribute to the derivation of DOR.

In subjects who resume TKI therapy, disease assessments obtained after resumption of TKI therapy will contribute to the derivation of DOR. A sensitivity analysis will be conducted in which the DOR in such subjects is censored at the last evaluable disease assessment prior to the resumption of TKI therapy.

A sensitivity analysis may be conducted in which receiving allo-SCT or subsequent anti-cancer therapy are considered events.

Further details on the derivation of DOR are provided in Appendix 2.

DOR analysis will be conducted per independent review and investigator review separately. Both the mITT analysis set and the full analysis set (FAS) will be used.

MRD remission rate: The incidence of an MRD response. MRD is defined as MRD < 10^{-4} per the standard assessment as described in the protocol. MRD remission rate will be estimated for all dosed subjects, subjects with a CR, subjects with a CRi, and subjects with either a CR or a CRi combined. MRD remission rate will also be estimated for subjects with CRh and blast-free hypoplastic or aplastic bone marrow.

Allo-SCT rate: the incidence of allo-SCT among subjects who have been treated with KTE-X19.

OS: OS for the mITT analysis set is defined as the time from the KTE-X19 infusion to the date of death from any cause.

OS for all enrolled subjects in the FAS is defined as the time from enrollment to the date of death from any case.

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.

Further details on the derivation of OS and the specific data modules that will be used to derive the last date known to be alive are provided in Appendix 2.

Relapse-free Survival (RFS): RFS for the mITT analysis set is defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause. RFS for all enrolled subjects in the FAS is defined as the time from enrollment to the date of disease relapse or death from any cause. Subjects who have not achieved a CR or CRi at the analysis data cutoff will be evaluated as having an RFS event at Day 0 for RFS analysis on mITT set, or at the date of enrollment for RFS analysis on FAS set. Subjects not meeting the criteria for relapse by the analysis data cutoff date will be censored at their last evaluable disease assessment date or disease status follow up assessment. RFS will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy and allo-SCT (excluding resumption of a TKI). A sensitivity analysis will be conducted in which the RFS in subjects who received subsequent allo-SCT will not be censored at the last disease assessment prior to SCT, and instead, the response after SCT will contribute to the derivation of RFS.

In subjects who resume TKI therapy, disease assessments obtained after resumption of TKI therapy will contribute to the derivation of RFS. A sensitivity analysis will be conducted in which the RFS in such subjects is censored at the last evaluable disease assessment prior to the resumption of TKI therapy. Further details on the derivation of RFS are provided in Appendix 2.

OCR (CR + CRi) rate for retreatment: the incidence of OCR rate for subjects in the retreatment period.

DOR to retreatment (DORR): DORR is defined only for subjects who experience OCR to retreatment and is the time from the first OCR after retreatment to relapse after retreatment or death from any cause in the absence of documented relapse.

MRD remission rate for subjects with CRh: The incidence of an MRD response for subjects who had the best response of CRh. MRD is defined as MRD < 10^{4}.

MRD remission rate for subjects with blast-free hypoplastic or aplastic bone marrow: The incidence of an MRD response for subjects who had the best response of blast-free hypoplastic or aplastic response. MRD is defined as MRD < 10^{4}.

Mortality rate 100 days after allo-SCT: The rate of deaths within 100 days after allo-SCT for subjects who undergo allo-SCT.

PR rate: The incidence of PR.

Changes over time in the EQ-5D scale score and EQ-5D VAS score: The changes of the EQ-5D scale score and EQ-5D VAS score at each assessment time compared to baseline will be presented.

6. ANALYSIS SUBSETS

The following analysis sets are defined for each study phase separately.

6.1. mITT

The mITT analysis set will consist of all subjects enrolled and treated with KTE-X19 in Phase 2. This analysis set will be used for all efficacy analyses unless specified otherwise.

6.2. Safety Analysis Set

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

6.3. FAS

The FAS will consist of all enrolled (leukapheresed) subjects and will be used for the summary of subject disposition, subject listings of deaths, and efficacy analyses, which is specified in Section 9.5.

6.4. mITT Retreatment Analysis Set

The mITT retreatment analysis set will consist of all subjects who undergo retreatment with KTE-X19 at any dose administered in Phase 2. This set will be used for all retreatment efficacy analyses.

6.5. Safety Retreatment Analysis Set

The safety retreatment analysis set will consist of all subjects who undergo retreatment with KTE-X19. This set will be used for all retreatment safety analyses.

6.6. Subgroup Analysis Sets

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

6.7. DLT-evaluable Analysis Set

The DLT-evaluable analysis set includes the first 3-6 subjects in Phase 1 who are 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 postinfusion period, up to the time at which a dose level has been evaluated for DLT and deemed safe. Additional subjects who are subsequently enrolled and treated in Phase 1 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 analysis set, and DLT will not be assessed for such subjects.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

The SRT will review the safety data during Phase 1 of the study and make a recommendation to progress the study from Phase 1 to Phase 2 based on the incidence of DLT and review of SAEs.

The DSMB will meet once during the Phase 2 portion of the study. The DSMB will review safety data and will be chartered to make trial conduct recommendations based on the risk versus benefit of treatment with KTE-X19. No early stopping for efficacy or futility is planned in the interim analysis.

7.1. Phase 1 – Safety Interim Analyses

The SRT will evaluate the incidence of DLTs and SAEs after 3 subjects have been treated in a dose cohort and have met the criteria for the DLT-evaluable analysis set. The SRT may recommend progression to the Phase 2 portion of the trial.

Study enrollment may be paused in Phase 1 (DLT Evaluation Period) following any Grade 5 AE that occurs within 30 days of KTE-X19 dosing, regardless of attributions.

7.2. Phase 2 – Interim Safety Analyses

An independent DSMB will be chartered to make recommendations on study conduct. The DSMB will meet once during the study. Details may be found in the Data Safety Monitoring Board Charter.

The interim analysis will be conducted after 20 subjects in the mITT analysis set in Phase 2 have had the opportunity to be followed for 30 days after the KTE-X19 infusion. This interim analysis will be for safety only.

As part of its oversight of the study, the DSMB also will assess whether to pause enrollment in Phase 2 after 10, 20, and 35 subjects enrolled in Phase 2 have been treated with KTE-X19 and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following is met:

- Subject incidence of the following Grade 4 KTE-X19-related AEs lasting more than 7 days is > 33%:

  Neurotoxicity

  CRS (per Lee 2014 criteria)

  Other nonhematological SAE

  Treatment-related infection

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. Data handling procedures, designed to maintain the trial credibility and validity in this open-label single-arm study, are described in the Trial Integrity Document (TID).

8. DATA SCREENING AND ACCEPTANCE

8.1. General Principles

The database will be subject to the edit checks outlined in the Data Management Plan (DMP) 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. 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, the product manufacture (total T cells, CAR T cells (transduction ratio), duration of manufacturing time), central laboratory assessment of subject serum samples (CAR T cell levels in the peripheral blood, cytokine levels, antibody assays, RCR testing), MRD, and central radiology and clinical review will be generated from contract laboratories, Kite Pharma, and central imaging vendor. These data will be transferred to Kite study team 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 AE 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 violations of eligibility criteria and violations that may have an impact on the efficacy evaluation. 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 clinical disease assessments may be subject to bias; the concordance between investigator and central review of radiologic scans and clinical disease assessments will be summarized.

8.5. Outliers

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

8.6. Distributional Characteristics

The primary analysis of the primary endpoint is an exact binomial test used to compare the observed OCR rate (CR + CRi) in the mITT analysis set to an OCR rate of 40%. This test assumes the independence of the individual subject responses.

An exact 95% confidence interval (CI) will be generated about the response rate. 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 (TFL) will be developed and maintained according to Kite Standard Operating Procedures (SOP). 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 OCR (CR + CRi) rate in the mITT analysis set to a historical control rate of 40% using an exact binomial test. Hypothesis testing will be 1 sided, and all 95% CIs will be 2 sided. At the time of the test of the overall study population, 95% CIs for the OCR rate in Phase 2 will be presented.

The timing of the interim and primary analyses will be based on subject accrual and disease assessment milestones. The primary analysis clinical study report (CSR) will be written at the primary analysis.

Analyses of the Phase 1 and Phase 2 portions of the study will be presented separately.

9.2. Subject Accountability

The number of subjects screened, enrolled/leukapheresed, treated with bridging chemotherapy, treated with intrathecal chemotherapy for CSF prophylaxis, treated with conditioning chemotherapy, treated with KTE-X19, and retreated with KTE-X19 will be summarized. The reasons for discontinuing treatment and survival follow-up periods will be summarized. Summaries of actual and potential follow-up time will be provided.

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

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

9.3. Important Protocol Deviations

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

Efficacy analyses will be conducted on the mITT analysis set.

The key efficacy analyses will also be presented in the following populations:

- Phase 2 FAS
- Phase 1 by cohort in the safety analysis set

- Combined Phase 1 and Phase 2 at 1.0 x 10^6 anti-CD19 CAR T cells/kg dose levels, both on

  Subjects who have been treated with KTE-X19

  FAS.

For subjects retreated with KTE-X19, disease assessments obtained prior to retreatment but not disease assessment obtained after retreatment will be included in the primary summaries of OCR rate, rate of MRD remission, DOR, and RFS. Disease assessments obtained after retreatment may be included in the summaries of OCR rate, rate of MRD remission, DOR, and RFS after retreatment with KTE-X19. The subject's OS time will be derived from the last date known to be alive regardless of retreatment time.

9.5.1. OCR (CR + CRi) Rate

9.5.1.1. Primary Analysis of OCR (CR + CRi) Rate

The subject incidence of OCR (CR + CRi) will be calculated. An exact binomial test will be used to compare the observed OCR rate per independent review in the mITT analysis set to the hypothesized historical control rate of 40%. The subject incidence of best response of CR and CRi will be tabulated. CIs will be provided about the OCR (CR + CRi) rate, as well as the CR rate and CRi rate separately, calculated with the Clopper-Pearson method.

The primary analysis of OCR rate will include subjects from the mITT analysis set in Phase 2. A sensitivity analysis of the OCR rate will be conducted in the FAS.

The CR rate will be calculated for the mITT analysis set and FAS. A 95% CI will be provided about the CR rate using the Clopper-Pearson method.

9.5.1.2. Subgroup Analyses of OCR (CR + CRi) Rate

The OCR (CR + CRi) rate with 95% CIs will be generated for subgroups of the mITT analysis set defined by the selected covariates as listed in Section 4.2.

A forest plot of the proportion (and 95% CI) of subjects achieving CR or CRi for each of these subgroups will be generated.

9.5.1.3. Analyses of OCR Rate Phase 1

Analyses of OCR rate in Phase 1 based on investigator assessment may occur at any time during Phase 1. The purpose of these analyses may include publications, preliminary evaluation of benefit-risk, and to inform decisions on dose.

At a minimum, CR + CRi rates, CR rates and 95% CIs will be generated for each dose cohort (if applicable) in Phase 1.

9.5.2. DOR

The primary analysis of DOR will use the Kaplan-Meier method and consider all relapses and deaths as events for DOR. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR. Kaplan-Meier plots, and estimate of the median DOR, and 2-sided 95% CIs will be generated. Estimates of the proportion of subjects who remained in response at 3-month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. DOR will be analyzed in both mITT and FAS.

A sensitivity analysis will be conducted in which disease assessments obtained after allo-SCT are included in the derivation of DOR.

A sensitivity analysis of DOR will be conducted in which the DOR for subjects undergoing TKI is censored at the last disease assessment prior to the resumption of TKI therapy.

A sensitivity analysis of DOR will be conducted in which receiving allo-SCT or subsequent anti-cancer therapy are considered events.

A sensitivity analysis of DOR may be conducted with non-disease mortality considered a competing risk.

In the cases where subjects missed at least two consecutive visits and deemed relapse in the next following up visit, a sensitivity analysis of DOR may be conducted in which such cases will be censored at the last disease assessment before the consecutively missed disease assessment visits.

9.5.3. Rate of MRD Remission

The MRD remission rate and 95% CIs will be estimated for all treated subjects, subjects with a CR, subjects with a CRi, and subjects with either a CR or CRi combined.

9.5.4. Allo-SCT Rate

The subject incidence rate of on-study allo-SCT will be summarized overall, by subjects achieving a CR + CRi, by subjects achieving a CR, and by subjects achieving a CRi. Corresponding 95% CIs may be generated.

9.5.5. Relapse-free Survival

Kaplan-Meier (KM) plots, estimate of the median RFS, and 2-sided 95% CIs will be generated. Estimates of the RFS rates at 3-month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. Median RFS may be estimated for MRD responders and MRD+ responders.

A sensitivity analysis of RFS will be conducted in the FAS. RFS for enrolled subjects is defined as the time from enrollment until relapse or death from any cause.

A sensitivity analysis will be conducted in which disease assessments obtained after allo-SCT are included in the derivation of RFS.

A sensitivity analysis of RFS will be conducted in which the RFS for subjects undergoing TKI is censored at the last disease assessment prior to the resumption of TKI therapy.

In the cases where subjects missed at least two consecutive visits and deemed relapse in the next following up visit, a sensitivity analysis of RFS may be conducted in which such cases will be censored at the last disease assessment before the consecutively missed disease assessment visits.

9.5.6. Overall Survival

KM plots, estimate of the median OS, and 2-sided 95% CIs will be generated. Estimates of OS rates at 3-month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. Median OS may be estimated for MRD responders and MRD+ responders.

Graphical summaries of the time to CR or CRi, DOR, retreatment, relapse, and death times from the time of KTE-X19 infusion depicted on a horizontal time axis for each subject ("swim lane plot") may be provided.

The OS will also be analyzed in the FAS. OS for enrolled subjects is defined as the time from enrollment until death from any cause.

9.5.7. OCR (CR + CRi) Rate Among Subjects Retreated with KTE-X19

The subject incidence of subjects retreated with KTE-X19 will be tabulated. The subject incidence of CR, CRi, and CR and CRi combined after retreatment among subjects retreated with KTE-X19 will be tabulated. Corresponding CIs will be provided.

9.5.8. DOR Among Subjects Retreated with KTE-X19

The analysis of DOR to retreatment among subjects responding to retreatment with KTE-X19 will use the same methods as the analysis of DOR.

9.6. Safety Analyses

Safety analyses will be conducted on the safety analysis set. The primary analysis of safety data will summarize all AEs and laboratory values with an onset on or after the KTE-X19 infusion date and prior to the 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 KTE-X19, AEs occurring in the KTE-X19 retreatment period may be summarized separately.

AEs will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of AEs will be graded using the CTCAE version 4.03.

CRS will be graded using a revised CRS grading scale (see details in protocol) developed by Lee and colleagues {Lee 2014}. Individual symptoms associated with CRS will be graded per CTCAE version 4.03.

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 KTE-X19 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:

- 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 interest, including identified risks and potential risks

By-subject listings of deaths through 30 days after KTE-X19 infusion and SAEs 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.

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.

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).

Potential secondary malignancies will be identified within the system organ class of neoplasms benign, malignant, and unspecified (including cysts and polyps). Potential secondary 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 CTCAE version 4.03. The incidence of post-infusion worst-grade laboratory toxicities for all analytes will be provided. Additional summaries for the shift from baseline to the worst toxicity grade after KTE-X19 infusion may also be generated.

9.6.4. Anti-CD19 CAR Antibodies

The subject incidence of any anti-KTE-X19 antibodies will be tabulated. For subjects testing positive for antibodies, the persistence of the antibodies over time will be 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
- Total CAR T cells of the KTE-X19 infusion
- Total T cells of the KTE-X19 infusion

Separate summaries will be presented for retreatment with conditioning chemotherapy and KTE-X19 among subjects in the safety retreatment analysis set.

9.6.7. Exposure to Concomitant Medications and Procedures

The subject incidence of concomitant medications will be provided and 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 (eg, steroids and tocilizumab) may be summarized.

9.6.8. EQ-5D for Subjects in Phase 2

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

Further analyses of these quality-of-life data may be described in a supplemental statistical analysis plan.

9.7. Subsequent Anticancer Therapy

The incidence and type (by WHO drug coded term) of subsequent anticancer therapy will be summarized.

9.8. Schedule of Study Treatment

Summary statistics will be provided for the following durations:

- Days from leukapheresis to product release
- Days from leukapheresis to receipt of KTE-X19 at the study site
- Days from leukapheresis to administration of KTE-X19
- Duration of hospitalization following the KTE-X19 infusion

9.9. Lymphocyte Subsets

Summary statistics for the levels of lymphocytes and the subject incidence of lymphopenia, B-cell aplasia, recovery after lymphopenia, and recovery after B-cell aplasia will be provided for each subject based on lymphocyte subsets measured prior to conditioning chemotherapy, on the day of the KTE-X19 infusion, and at Week 4, Month 3, Month 6, Month 12, Month 15, and Month 24. Graphical summaries of the median value and interquartile range over time may be provided. Among subjects who experience lymphopenia or B-cell aplasia, summary statistics for the time to the onset of these conditions will be provided. The duration of lymphopenia and B-cell aplasia will be summarized; the duration of these events for subjects with persistent lymphopenia or B-cell aplasia at the last lymphocyte measurement will be censored at that time. The use of IVIG treatment in the presence of B-cell aplasia may be summarized.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

None.

11. REFERENCES

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

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17 (4):343-6.

Topp MS, Gokbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16 (1):57-66.

12. HISTORY OF REVISIONS

Version	Date	Protocol	Description of Changes
Original (1.0)	16 May 2018	Original to Amendment 5	N/A
2.0	30 May 2020	Amendment 6	• Remove reference and definitions of study administrative periods that are irrelevant to the analysis from the SAP in Section 3.1; • Patients with prior Blinatumomab will be more than 5 patients, so the primary endpoints and selected secondary endpoints will be evaluated in subgroup analysis by subjects with or without prior Blinatumomab; • Definition of 'on-study' is updated to include death event; • Definition of 'actual follow-up time' is updated to include last date known alive; • Added "Time to onset, and duration of important identified risks CRS and neurologic events will be summarized." • Methods of confidence interval calculation – only keep the main method: clopper-pearson and remove the sensitivity methods; • Added the definition of secondary malignancy. • Added the analysis of "Days from leukapheresis to receipt of KTE-X19 at the study site" • Minor format changes. • Re-treatment period definition updated in Section 5.2 • RFS and OS for all enrolled subjects are added. • A sensitivity analysis of DOR in which allo-SCT and subsequent anti-cancer therapy are considered as events is added.

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:

- AE start dates
- Deaths (please see exceptions below)
- Concomitant medication start dates
- Subsequent anticancer therapy start dates

Table 1. Imputation Rules for Partial or Missing Start Dates

		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		
Start Date		**< Day 0**	**≥ Day 0**	**< Day 0 *yyyymm***	**≥ Day 0 *yyyymm***	**< Day 0 *yyyy***	**≥ Day 0 *yyyy***	**Missing**
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

1 impute the date of Day 0
2 impute the first of the month
3 impute January 1 of the year
4 impute January 1 of the stop year
Note: if the start date imputation leads to a start date that is after the stop date, then do not impute the start date.

Imputation rules for partial or missing death dates:

1) If death year and month are available but day is missing:

- If mmyyyy for the last 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.

2) If both month and day are missing for death date or a death date is completely missing, do not impute and censor the subject survival time at the analysis data cutoff date or the last date known to be alive, whichever is later.

Appendix 2. Derivation of Time-to-event Endpoints and Last Date Known to Be Alive

Additional details on the derivations of duration of remission (DOR), relapse-free survival (RFS), and overall survival (OS) are provided below.

1) **DOR**: DOR is defined only for subjects who experience a CR or CRi and is the time from the first OCR (CR or CRi) to relapse or death due to any cause.

- **Primary analysis of DOR:**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT)	Event	Relapse date
Death without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Event	Death date
Remain in remission without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including allo-SCT
Remain in remission without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date prior to data cutoff

- **Sensitivity analysis of DOR (not censoring at SCT):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (excluding allo-SCT)	Event	Relapse date
Death without documented relapse and without new anti-cancer therapy (excluding allo-SCT and resumption of TKI)	Event	Death date
Remain in remission without new anti-cancer therapy (excluding allo-SCT and resumption of TKI)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (excluding allo-SCT and resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy excluding allo-SCT
Withdrawal of consent or lost to follow-up prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to data cutoff

- **Sensitivity analysis of DOR (censoring for TKI):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT and resumption of TKI)	Event	Relapse date
Death without documented relapse and without new anti-cancer therapy (including allo-SCT and resumption of TKI)	Event	Death date
Remain in remission without new anti-cancer therapy (including allo-SCT and resumption of TKI)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including allo-SCT and resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including allo-SCT and resumption of TKI
Withdrawal of consent or lost to follow-up prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to data cutoff

- **Sensitivity analysis of DOR (both allo-SCT and subsequent therapy as events):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT)	Event	Relapse date
Death without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Event	Death date
Remain in remission without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Censored	Last evaluable disease assessment date
Initiated new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) prior to documented relapse or death	Event	Start date of new therapy including allo-SCT
Remain in remission without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date prior to data cutoff

2) RFS: RFS for all dosed subjects on the mITT set is defined as the time from the KTE-X19 infusion date to the date of disease relapse or death from any cause.

- **Primary analysis of RFS:**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT)	Event	Relapse date
Subject has CR or CRi, then died without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Event	Death date
Subject has disease assessment done but does not have a CR or CRi, or subject died or received new anti-cancer therapy (including allogenic SCT but excluding resumption of TKI) before any disease assessment	Event	KTE-X19 infusion date
Remain in remission and alive without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Censored	Last evaluable disease assessment date
Subject has a CR or CRi and subsequently initiated new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including allo-SCT.
Remained in remission without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date.
Subject enrolled and treated with KTE-X19 but the disease assessment has not been done and the subject is still alive and has not received any new anti-cancer therapy	Censored	KTE-X19 infusion date

- **Sensitivity analysis of RFS (not censoring at SCT):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (excluding allo-SCT)	Event	Relapse date
Subject has CR or CRi, then died without documented relapse and without new anti-cancer therapy (excluding allo-SCT and resumption of TKI)	Event	Death date
Subject has disease assessment done but does not have a CR or CRi, or subject died or received new anti-cancer therapy (excluding allogenic SCT and resumption of TKI) before any disease assessment	Event	KTE-X19 infusion date

Circumstance	Event/Censored	Date of Event/Censoring
Remain in remission and alive without new anti-cancer therapy (excluding allo-SCT and resumption of TKI)	Censored	Last evaluable disease assessment date
Subject has a CR or CRi and subsequently initiated new anti-cancer therapy (excluding allo-SCT and resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy excluding allo-SCT.
Remained in remission without new anti-cancer therapy (excluding allo-SCT and resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date.
Subject enrolled and treated with KTE-X19 but the disease assessment has not been done and the subject is still alive and has not received any new anti-cancer therapy	Censored	KTE-X19 infusion date

- **Sensitivity analysis of RFS (censoring at TKI):**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT and resumption of TKI)	Event	Relapse date
Subject has CR or CRi, then died without documented relapse and without new anti-cancer therapy (including allo-SCT and resumption of TKI)	Event	Death date
Subject has disease assessment done but does not have a CR or CRi, or subject died or received new anti-cancer therapy (including allo-SCT and resumption of TKI) before any disease assessment	Event	KTE-X19 infusion date
Remain in remission and alive without new anti-cancer therapy (including allo-SCT and resumption of TKI)	Censored	Last evaluable disease assessment date
Subject has a CR or CRi and subsequently initiated new anti-cancer therapy (including allo-SCT and resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy **(**including allo-SCT and resumption of TKI)
Remained in remission without new anti-cancer therapy (including allo-SCT and resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date.
Subject enrolled and treated with KTE-X19 but the disease assessment has not been done and the subject is still alive and has not received any new anti-cancer therapy	Censored	KTE-X19 infusion date

3) RFS for all enrolled subjects is defined as the time from the enrollment date to the date of disease relapse or death from any cause.

- **Analysis of RFS for all enrolled subjects:**

Circumstance	Event/Censored	Date of Event/Censoring
Relapse prior to initiation of new anti-cancer therapy (including allo-SCT)	Event	Relapse date
Subject has CR or CRi, then died without documented relapse and without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Event	Death date
Subject has disease assessment done but does not have a CR or CRi, or subject died or received new anti-cancer therapy (including allogenic SCT but excluding resumption of TKI) before any disease assessment	Event	Enrollment date
Remain in remission and alive without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI)	Censored	Last evaluable disease assessment date
Subject has a CR or CRi and subsequently initiated new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) prior to documented relapse or death	Censored	Last evaluable disease assessment date prior to initiation of new therapy including allo-SCT.
Remained in remission without new anti-cancer therapy (including allo-SCT but excluding resumption of TKI) until withdrawal of consent or loss to follow-up	Censored	Last evaluable disease assessment date.
Subject enrolled but the disease assessment has not been done and the subject is still alive and has not received any new anti-cancer therapy	Censored	Enrollment date

4) **OS:** OS is defined as the time from the KTE-X19 infusion to the date of death from any cause.

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 prior to full consent withdrawal or lost to follow-up

5) OS for all enrolled subjects, which is defined as the time from the enrollment date to the date of death from any cause, will use the same censoring strategy as described above.

6) 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 (including targeted AE)
- Leukapheresis dates
- Conditioning chemotherapy administration dates
- KTE-X19 infusion dates
- Bone marrow assessment dates
- Cerebrospinal fluid analysis dates
- Hematology specimen collection dates
- Minimal residual disease analysis dates
- Extramedullary disease assessment dates (including positron emissions tomography assessment, target lesion assessment, non-target lesion assessment, new lesion assessment, and disease response assessment dates)
- Long-term follow-up subject status date where status ‘alive’
- End-of-treatment disposition where status is not equal to death or lost to follow-up
- End of post-treatment assessment period where status is not equal to death or lost to follow-up
- End-of-study data where end-of-study reason is not equal to death or lost to follow up