STATISTICAL ANALYSIS PLAN

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Company Code:	KTE-C19
USAN Name:	Axicabtagene ciloleucel Rituximab
Protocol	A Phase 2 Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination with Rituximab in Subjects with Refractory Large B-Cell Lymphoma (ZUMA-14)
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CONFIDENTIALITY NOTICE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADaM	Analysis data model
AE	Adverse event
ASCT	Autologous stem cell transplant
BSA	Body surface area
CAR	Chimeric antigen receptor
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CTCAE	Common terminology criteria for adverse event
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
HLGT	High-level group term
IPD	Important protocol deviation
IPI	International Prognostic Index
IWG	International Working Group
MedDRA	Medical Dictionary for Regulatory Activities
MST	MedDRA search term
mITT	Modified intent-to-treat
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
RCR	Replication-competent retrovirus
OS	Overall survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable disease
SDTM	Study data tabulation model
SMQ	Standardized MedDRA query
SOC	System organ class
SPD	Sum of the product of the diameters
SRT	Safety review team
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) sets forth prospectively the details of statistical analyses that are outlined in protocol KT-US-471-0114 entitled "A Phase 2 Open-Label, Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination with Rituximab in Subjects with Refractory Large B-Cell Lymphoma (ZUMA-14)" dated 08 July 2020. This document was updated from Version 1.0 to 2.0 as the Lenalidomide cohort was discontinued per Protocol Amendment 4.

2. OBJECTIVES

The primary objective of the analyses is to estimate the efficacy of axicabtagene ciloleucel in combination with rituximab as measured by assessment of response rates in adult subjects with relapsed/refractory large B-cell lymphoma.

Secondary objectives of the analyses outlined herein are:

- To estimate the safety of axicabtagene ciloleucel in combination with rituximab as measured by assessment of adverse event (AE) rates in adult subjects with relapsed/refractory large B-cell lymphoma.
- To assess the efficacy of axicabtagene ciloleucel in combination with rituximab using additional efficacy endpoints.
- To determine levels of axicabtagene ciloleucel expansion and persistence in blood using chimeric antigen receptor (CAR) T-cell polymerase chain reaction (PCR) assay (pharmacokinetics [PK]), in combination with rituximab .

3. STUDY DESIGN

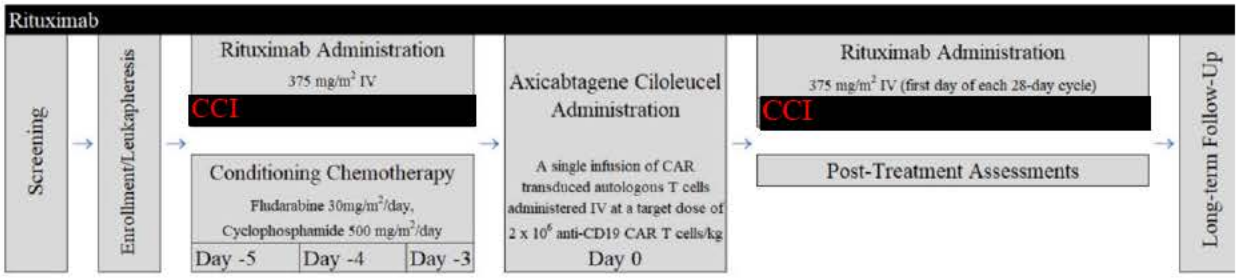
3.1. Overview

This is a phase 2, open-label, single arm, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with rituximab in subjects with relapsed/refractory large B-Cell lymphoma.

Approximately 30 subjects will receive a planned dose of rituximab CCI and conditioning chemotherapy with fludarabine and cyclophosphamide on Day -5, -4, and -3. After 2 days of rest on Day –2 and Day –1, subjects will receive axicabtagene ciloleucel, administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg on Day 0. Subjects will also receive rituximab CCI at 28-day intervals beginning CCI after axicabtagene ciloleucel infusion CCI. A second dosing strategy (Dose Level -1) will be to administer rituximab only after axicabtagene ciloleucel infusion. This dose level may be explored only if the planned dosing strategy (rituximab initiation concurrent with conditioning chemotherapy) has an unacceptable rate of toxicity.

Further details on study procedures can be found in the study protocol. A study schema is presented in Figure 1.

Figure 1. Study Schema



Abbreviations: CAR, chimeric antigen receptor; IV, intravenous

3.2. Hypothesis

No formal hypothesis will be tested in this study. The study is designed to estimate the complete response (CR) rate in subjects with relapsed/refractory large B-cell lymphoma treated with axicabtagene ciloleucel in combination with rituximab.

3.3. Sample Size Consideration

The anticipated enrollment in this study is approximately 30 subjects. With a total sample size of 30 subjects at a given dosing schedule, an observed CR rate of 70% will yield an 80% confidence intervals for the response rate with a maximum half width no greater than 13%, corresponding to a lower limit of at least 57%. This target CR rate, and the lower limit of the 80% confidence interval for the CR rate, is meaningful because it would represent a significant improvement in the response rate for the subjects with relapsed/refractory large B-cell lymphoma over existing therapies

Additional assumptions and corresponding two-sided 95% and 80% exact confidence intervals are provided in Table 1.

Table 1. 95% and 80% Exact Confidence Intervals for Observed CR Rate based on 30 Subjects

Subjects with CR	Observed CR Rate	95% Confidence Interval	80% Confidence Interval
15	50%	[31%, 69%]	[37%, 63%]
18	60%	[41%, 77%]	[47%, 72%]
21	70%	[51%, 85%]	[57%, 81%]
24	80%	[61%, 92%]	[68%, 89%]
27	90%	[73%, 98%]	[79%, 96%]

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

4.1.1. Primary Endpoint

Complete response rate (complete response [CR] per the International Working Group (IWG) Lugano Classification {Cheson 2014}, as determined by the study investigators.

4.1.2. Secondary Endpoints

- Incidence of AEs and clinically significant changes in safety lab values
- Objective Response Rate (ORR; CR + partial response [PR]) per the IWG Lugano Classification {Cheson 2014}, as determined by study investigators
- Duration of Response (DOR) per the IWG Lugano Classification {Cheson 2014}, as determined by study investigators
- Progression Free Survival (PFS) per the IWG Lugano Classification {Cheson 2014}, as determined by study investigators
- Overall Survival (OS)
- Pharmacokinetics (PK): Levels of axicabtagene ciloleucel in blood

4.2. Subgroups and Covariates

The following variables may be used to examine efficacy results in subgroups or covariate analyses, as well as safety analyses. Analyses might be subject to restrictions due to small sample size.

- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1)
- Age at baseline (<65 years, ≥65 years)
- Race
- Gender
- Histologically proven Diffuse large B-cell lymphoma (DLBCL) type
- Cell of origin
- Double/Triple hit status

- Disease stage at study entry
- International Prognostic Index (IPI) total score at baseline
- Refractory subgroup
- Number of prior chemotherapy regimens (1, 2-3, ≥ 4)
- Bulky disease (at least one lesion 10 cm in diameter))
- Tumor burden at baseline, as measured by the sum of the product of the diameters (SPD) of target lesions at baseline (≤ median vs. > median value)

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment occurs when a subject is confirmed to be eligible for the study, and commences leukapheresis.

Study Day 0: Defined as the day the subject receives the axicabtagene ciloleucel infusion. The day prior to Day 0 will be study Day -1. Any days prior Day 0 will be sequential and negative integer-valued.

Baseline: Defined as the last non-missing value measured on or prior to conditioning chemotherapy, unless specified otherwise.

Refractory Subgroup at Baseline:

Chemotherapy-refractory disease is defined as one or more of the following:

- Primary refractory disease
  - Progressive disease (PD) as best response to first-line therapy
  - Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g., 4 cycles of R-CHOP) with SD duration no longer than 6 months from last dose of therapy
- Refractory to second or greater lines of therapy
  - PD as best response to most recent therapy regimen
  - SD as best response after at least 2 cycles of last line of therapy with SD duration no longer than 6 months from last dose of therapy
- Refractory post-autologous stem cell transplantation (ASCT)
  - Disease progression or relapsed ≤ 12 months after ASCT (must have biopsy proven recurrence in relapsed subjects)
  - If salvage therapy is given post-ASCT, the subject must have had no response to or relapsed after the last line of therapy

In case a subject may meet the criteria for multiple refractory subgroups, this subject will be assigned to the subgroup based on the hierarchy of priority of Refractory post ASCT > Refractory to second or greater lines of therapy > Primary refractory disease.

5.2. Safety

Treatment-emergent adverse event (TEAE): Any worsening of a pre-existing medical condition that occurs on or after axicabtagene ciloleucel infusion or any adverse event with onset on or after axicabtagene ciloleucel infusion.

Deaths: Any death occurring after the leukapheresis up through the end of study.

Adverse events of interest: The following AEs are of interest for the treatments of axicabtagene ciloleucel in combination with rituximab:

Identified risks:

- Cytokine-release syndrome (CRS)
- Neurologic toxicity
- Cytopenias
- Infections
- Hypogammaglobulinemia

Potential risks:

- Secondary malignancy
- Replication competent retrovirus (RCR)
- Immunogenicity (anti-axicabtagene ciloleucel antibodies)
- Autoimmune disorders
- Bone marrow failure

CRS: CRS is identified via collection of the syndrome on a case report from (CRF) specifically designed to collect CRS. Specific individual symptoms of CRS (eg, fever) collected on the AE log are coded using Medical Dictionary for Regulatory Activities (MedDRA) and linked to the corresponding CRS episode. Individual symptoms of CRS are graded per the latest version of Common Terminology Criteria for Adverse Events (CTCAE), and CRS as a syndrome is graded per modified Lee criteria {Lee 2014}. In the modified grading scale, neurologic AEs are not reported as part of the CRS syndrome as they will be reported separately with the neurologic events category and graded per the latest version of CTCAE v5.0.

Neurologic toxicity: Neurologic adverse events are 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 toxicity, without regard to temporal relationship or concomitant conditions (e.g. 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.

Cytopenias: Cytopenias (neutropenia, anemia, or thrombocytopenia) are identified as:

- Neutropenia is identified using the latest version of the MedDRA search term (MST) documented prior to each analysis.
- Anemia (including aplastic anemia) is identified using the standardized MedDRA query (SMQ) haematopoietic erythropenia (broad search).
- Thrombocytopenia is identified using the SMQ haematopoietic thrombocytopenia (narrow search).

Subjects with cytopenias present on or after Day 30 post axicabtagene ciloleucel infusion will be summarized separately by cell lineage.

Infections: Infections are identified as AEs within the MedDRA SOC of Infections and Infestations that occur after treatment with axicabtagene ciloleucel. Subtypes of infections are identified using MedDRA high level group terms (HLGT) that capture events of:

- Bacterial infection, encompassing the MedDRA HLGTs of
  - Bacterial infectious disorders
  - Chlamydial infectious disorders
- Viral infection, encompassing the MedDRA HLGT of viral infectious disorders
- Opportunistic infections, encompassing the MedDRA HLGTs of
  - Fungal infectious disorders
  - Mycobacterial infectious disorders
- Other infections, encompassing the MedDRA HLGT of Infections – pathogen unspecified

Hypogammaglobulinemia: Hypogammaglobulinemia will be identified using a MST search strategy defined by Kite.

Secondary malignancy: Secondary malignancies are identified via collection on a case report form in which the investigator classifies the event as a secondary malignancy. Additionally, adverse events that are coded into the SOC of Neoplasms benign, malignant, and unspecified (including cysts and polyps) with the exception of preferred terms containing "B-cell" or "B cell" and "Lymphoma" will be reviewed to identify other potential events.

Immunogenicity (anti-axicabtagene ciloleucel antibodies): Immunogenicity will be identified for subjects who have treatment emergent anti-axicabtagene ciloleucel antibody and have developed any AE belonging to the SMQ of anaphylactic reaction and the SMQ of hypersensitivity. The narrow version of these 2 SMQs will be used.

Autoimmune disorders: Autoimmune disorders are identified via collection on a case report form in which the investigator classifies the event as an autoimmune disorder. Additionally, adverse events that are coded into the MedDRA high level group term of auto-immune disorders within the immune system disorders system organ class (SOC) will be reviewed to identify other potential events.

Bone marrow failure: Bone marrow failure will be identified using the narrow SMQ of haematopoietic cytopenias affecting more than one type of blood test.

Study day of onset of event/syndrome: Study day of onset of an event/syndrome is defined as the study day of the first occurrence of the event/syndrome. Study day of Onset of Grade 3 or Higher Events/Syndromes are defined in the same way, but restricted to Grade 3 or higher events/syndromes.

Study day of resolution of an event/syndrome: Study day of resolution of an event/syndrome is the last study day the event is present. If multiple events occur after axicabtagene ciloleucel infusion, the study day of resolution is the last day of the multiple events presented. Study day of resolution will not be calculated for events that are ongoing at the time of the data cutoff date or death.

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 time from the earliest onset date of the AEs in the event class of interest through the resolution date of the last AEs in the event class, regardless of the gaps of the days between multiple events, ie, the resolution date of the last AE in the event class – the start date of the first AE in the event class + 1.

The cumulative dose of rituximab is defined as the sum of all doses (in mg/m2) administered across the treatment period including Day -5 dosing.

5.3. Efficacy

Complete Response Rate (CR rate): The proportion of subjects with a CR after treatment with axicabtagene ciloleucel and rituximab and prior to any subsequent anti-lymphoma therapy. Subjects who do not meet the criteria for CR by the analysis cutoff date will be considered non-CR. The derivation of this endpoint will only include response assessments obtained after at least

one dose of rituximab administration after axicabtagene ciloleucel infusion, and prior to any subsequent therapies for non-Hodgkin lymphoma (NHL) (including stem cell transplant [SCT]). Responses will be assessed per the Lugano Classification {Cheson 2014}, as determined by the study investigators.

Objective Response Rate (ORR): The proportion of subjects with a CR or PR after treatment with axicabtagene ciloleucel and rituximab and prior to any subsequent anti-lymphoma therapy. Subjects who do not meet the criteria for objective response by the analysis cutoff date will be considered non-responders. The derivation of this endpoint will only include response assessments obtained after at least one dose of rituximab administration after axicabtagene ciloleucel infusion, and prior to any subsequent therapies for NHL (including SCT). Responses will be assessed per the Lugano Classification {Cheson 2014}, as determined by the study investigators.

Duration of response (DOR): DOR is defined only for subjects who experience an objective response (CR or PR) and is the time from the first objective response to disease progression per the Lugano Classification {Cheson 2014} as determined by study investigators or death due to any reason. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date and their response will be noted as ongoing. Subjects who receive additional anti-cancer therapy in the absence of documented progression will be censored at the last evaluable disease assessment prior to the additional therapy. Subjects who receive an SCT in the absence of documented progression will be censored at the last evaluable disease assessment prior to the date of the SCT. A sensitivity analysis will be conducted in which disease assessments obtained after SCT while in axicabtagene ciloleucel induced remission are included in the derivation of DOR. Additional details on the derivation of DOR are provided in Appendix 2.

Progression-free Survival (PFS): PFS is defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression per the Lugano Classification {Cheson 2014} as determined by study investigators or death from any cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will be censored at their last evaluable disease assessment date. The PFS for subjects who undergo SCT while in remission will be censored at the last evaluable disease assessment prior to the date of SCT; the PFS for subjects who undergo other new anti-cancer therapies in the absence of documented relapse will be censored at the last evaluable disease assessment prior to the new anti-cancer therapies. A sensitivity analysis will be conducted in which disease assessments obtained after SCT while in axicabtagene ciloleucel induced remission are included in the derivation of PFS. Additional details on the derivation of PFS are provided in Appendix 2.

Overall Survival (OS): OS is defined as the time from the axicabtagene ciloleucel infusion to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive or 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.

6. ANALYSIS SETS

The following analyses sets are defined for this study.

6.1. Modified Intent-to-treat Analysis Set

Modified intent-to-treat (mITT) analysis set consists of all subjects enrolled and treated with the target dose of axicabtagene ciloleucel at 2 x 10^6 (1.0 x 10^6 to 2.4 x 10^6) anti CD19 CAR T cells/kg, and at least one dose of rituximab after axicabtagene ciloleucel infusion. Subjects are considered to have received the target dose if they receive at least 1 x 10^6 anti-CD19 CAR T cells/kg. This analysis set will be used for all efficacy analyses.

6.2. Safety Analysis Set

Safety analysis set consists of all subjects treated with any dose of axicabtagene ciloleucel.

6.3. Full Analysis Set

Full analysis set consists of all enrolled subjects (i.e. commences leukapheresis) and will be used for summaries of subject disposition.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

Formal interim analysis of efficacy is not planned for the early trial stopping purpose.

7.1. Safety Interim Analysis

An internal safety review team (SRT), comprising the study sponsor medical monitor, drug safety physician, study statistician, and at least 1 active investigator, will meet after 6 subjects have completed their 28-day disease assessment and again after 15 subjects have completed their 28-day disease assessment. The SRT will review ongoing safety data and will be chartered to make study conduct recommendations based on an analysis of benefit vs. risk.

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.

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 will be included in the relevant SDTM and ADaM modules when the external data are available.

8.3. Handling of Missing and Incomplete Data

8.3.1. Efficacy

The method for handling missing data is described in the definition for each efficacy endpoint. Every effort will be made to obtain complete dates for deaths. In the event of a partial or missing death date and the corresponding censoring date for survival, the algorithm in Appendix 1 (Section 12) 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 (Section 12) 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 (IPDs) 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 IPDs. High rates of IPDs may indicate 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

The Clopper-Pearson (an exact interval) method is used to generate 95% CI for the CR rate. This method assumes that individual subject responses are independent with binomial distribution. While the Clopper-Pearson interval provides adequate coverage probability, it is commonly wider than necessary {Brown 2002}, leading to overly conservative estimates of the lower bound of response rate.

8.7. Validation and Configuration Management

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

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

The primary efficacy analysis will be performed when the last treated subject in the mITT set has had the opportunity to be evaluated for the 6-month disease assessment. The final analysis will occur when all subjects have completed the study. Additional analyses for additional internal review or publication may occur after the primary analysis.

9.2. Subject Accountability

The number of subjects screened, enrolled, treated with conditioning chemotherapy, treated with investigational treatments will be summarized. The reasons for discontinuing treatment and discontinuing study will be summarized.

Summaries of actual and potential follow-up time from axicabtagene ciloleucel infusion will be provided. Actual follow-up time is defined as time from the first dose of axicabtagene ciloleucel to the date of death or the last date known alive, and calculated as date of death or the last date known alive - axicabtagene ciloleucel infusion date + 1. Potential follow-up time is defined as the time from the axicabtagene ciloleucel infusion to the data cutoff date for the analysis, and calculated as data cutoff date - axicabtagene ciloleucel infusion date + 1.

The number of subjects enrolled by site will be summarized.

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

9.3. Important Protocol Deviations

The clinical study team will define IPD categories and review all potential IPDs 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 IPDs will be summarized overall and by deviation category.

9.4. Demographic and Baseline Characteristics

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

- Age (in years) at baseline and by category (< 65, ≥ 65)
- Sex
- Ethnicity and race
- Weight at leukapheresis

- ECOG performance status at baseline
- Number of prior chemotherapy regimens and best overall response to the last prior regimen
- Prior ASCT and best overall response corresponding to the ASCT
- Refractory subgroup
- Tumor burden, as measured by the SPD of selected nodes or lesions at baseline
- Disease stage at study entry (I, II, III, IV)
- Cell of origin
- Histologically proven DLBCL type
- Disease extent (presence of B symptoms, S [splenic involvement], E [extranodal disease], X [bulky disease], bone marrow involvement) as determined by the investigator at screening
- Double/Triple Hit Status
- IPI total score at baseline

9.5. Efficacy Analyses

Efficacy analyses will be conducted on the mITT analysis set, and the investigator assessment of disease status per the IWG Lugano Classification {Cheson 2014} will be used for disease response related analyses.

9.5.1. Complete Response and Objective Response

9.5.1.1. Analyses of Response Rate

The subject incidence of CR and objective response (CR+PR) will be calculated. Two-sided 95% Confidence Intervals will be generated using the Clopper-Pearson (an exact interval) method.

The number and percentage of subjects who initially do not attain CR and who subsequently attain a CR will be summarized.

9.5.1.2. Subgroup Analyses

The response rates and exact 2-sided 95% confidence intervals will be generated for subgroups of the mITT analysis set based on but not limited to the covariates defined in Section 4.2. A forest plot of the proportion of responders for each of these groups will be generated.

9.5.2. Duration of Response

The Kaplan-Meier approach will be used to estimate DOR. The number of subjects censored and the reasons for censoring will be summarized. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR.

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

9.5.3. Progression Free Survival

Kaplan-Meier plots, estimates and 2-sided 95% confidence intervals will be generated for PFS. Estimates of the proportion of subjects alive and progression-free at 3 month intervals will be provided. The number of subjects censored or having events, and the reasons for censoring or type of events (PD or death) will be summarized.

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

9.5.4. Overall Survival

The analysis of overall survival will use the same methods as the analysis of PFS. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow up time for overall survival.

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

9.5.5. Tumor Burden

The change in tumor burden, as measured by the SPD of the selected lesions, from baseline to post-baseline nadir will be summarized in absolute numbers (mm^2) and percentage. A graphical summary of this change will be presented in a vertical bar chart with each subject's change from baseline to nadir displayed as a vertical bar, with color coding that indicates best response attained ("waterfall" plot). Summary statistics will be provided for this change. Data collected after new anti-cancer therapy (including SCT) will not be included for the analyses.

9.6. Safety Analyses

Safety analyses will be conducted on the safety analysis set. The primary analysis of safety data will summarize all TEAEs and laboratory values.

AEs will be coded with the latest version of MedDRA. The severity of adverse events will be graded using the latest version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The incidence and severity of Cytokine release syndrome (CRS) will be graded using a revised CRS grading scale developed by Lee and colleagues {Lee 2014}. Individual symptoms associated with CRS will be graded per the latest version of CTCAE.

Subjects enrolled, but not received investigational treatments, will be followed for AEs for 30 days after the last study 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 adverse event summaries.

9.6.1. Adverse Events

The subject incidence of the following AEs will be tabulated:

- Summary of adverse events (any, worst severity, serious, related)
- All TEAEs by SOC and preferred term (PT)
- All serious adverse events (SAEs) by SOC and PT
- All leukapheresis/conditioning chemotherapy/ axicabtagene ciloleucel and/or rituximab related AEs/SAEs
- All Grade 3 or higher TEAEs
- All Grade 3 or higher axicabtagene ciloleucel and/or rituximab related TEAEs
- TEAEs of interest, including identified risks and potential risks
- Other clinically important adverse reactions
- Death (through the long term follow-up and treatment related SAEs)

Summary statistics for the study day of onset, the study day of resolution, and the duration of AEs of interest will be provided. A subject listing of deaths and SAEs (including narratives) will be provided by overall and by treatment period.

Subgroup analyses of AEs may be generated using the covariates listed in Section 4.2 if applicable.

9.6.2. Laboratory Test Results

Laboratory results will be graded according to the latest version of CTCAE. The incidence of worst grade CTCAE at post-baseline for selected analytes will be summarized.

9.6.3. Anti-axicabtagene Ciloleucel Antibodies

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

9.6.4. Replication Competent Retrovirus

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

9.7. Exposure to Study Treatments and Product Characteristics

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

- Total body surface area (BSA)-adjusted dose of cyclophosphamide
- Total BSA-adjusted dose of fludarabine
- Weight-adjusted dose of axicabtagene ciloleucel
- Total CAR T cells of the axicabtagene ciloleucel infusion
- Total T cells of the axicabtagene ciloleucel infusion
- Transduction percentage
- Ratio of CD4 and CD8 T cells
- Percentages of T cell memory phenotypes
- Interferon gamma (IFN-γ) production in co-cultures of axicabtagene ciloleucel product
- Number of infusion and cumulative dose of rituximab

9.8. Exposure to Concomitant Medications and Procedures

The subject incidence of concomitant medications will be provided and summarized by medication category (general, immunosuppressive, anti-infective, vasopressor, corticosteroid, and tocilizumab) and World Health Organization (WHO) Drug coded term. The subject incidence of procedures will be tabulated.

9.9. Subsequent Anti-Cancer Therapy

The incidence and type (by WHO Drug coded term and categories) of subsequent anti-cancer therapy and stem cell transplant (autologous, allogeneic) will be summarized.

9.10. Duration Metrics

Summary statistics will be provided for the following durations:

- Days from leukapheresis to commencement of conditioning chemotherapy
- Days from leukapheresis to administration of axicabtagene ciloleucel
- Days from conditioning chemotherapy to administration of axicabtagene ciloleucel
- Duration of hospitalization for the axicabtagene ciloleucel infusion

9.11. Axicabtagene Ciloleucel Delivery Time

Summary statistics will be provided for the following delivery time:

- Days from leukapheresis to axicabtagene ciloleucel release
- Days from leukapheresis to delivery of axicabtagene ciloleucel at study site among dosed subjects

9.12. Pharmacokinetics

Refer to separate PK/PD SAP.

CCI [redacted]

[redacted]

10. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Not applicable.

11. REFERENCES

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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 algorithm shown in Table 2 below:

- Adverse event start dates
- Deaths (please see exceptions below)
- Concomitant start dates

Table 2. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date						
		Complete: *yyyymmdd*		Partial: *yyyymm*		Partial: *yyyy*		Missing
		< day 0	≥ day 0	< day 0 *yyyymm*	≥ day 0 *yyyymm*	< day 0 *yyyy*	≥ day 0 *yyyy*	
Partial *yyyymm*	= day 0 *yyyymm*	2	1	2	1	n/a	1	1
	≠ day 0 *yyyymm*		2		2	2	2	2
Partial *yyyy*	= 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 contact date = mmyyyy for death date, set death date to the day after the last date known to be alive.
- If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.

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

Imputation rules for original date of diagnosis:

1. If year and month are available but day is missing, then impute the first day of the month.

2. If year is available but month and day are missing, then impute January 1 of the year.

Appendix 2. Derivation of Time to Event Endpoints

The derivations of Duration of Response (DOR), Progression-free Survival (PFS), and Overall Survival (OS) are provided below.

Duration of Response

Table 3. Primary Analysis of DOR

Circumstance	Event / Censored	Date of Event / Censoring
Disease progression prior to initiation of new anti-cancer therapy (including SCT) , and prior to data cutoff for analysis	Event	Progression date
Death without disease progression and without new anti-cancer therapy (including SCT) prior to data cutoff for analysis	Event	Death date
New anti-cancer therapy (including SCT) started before disease progression or death, and prior to data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to initiation of new therapy or SCT, whichever is earlier.
Disease progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
Remain in response without new anti-cancer therapy (including SCT) through the discontinuation of study, and prior to data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to the discontinuation of study, or prior to data cutoff for analysis, whichever earlier

Table 4. Sensitivity Analysis of DOR

Circumstance*	Event / Censored	Date of Event / Censoring
Disease progression after initiation of SCT, but prior to other new anti-cancer therapy	Event	Progression date
Death after SCT without disease progression or other new anti-cancer therapy	Event	Death date
Remain in response after SCT without other new anti-cancer therapy	Censored	Last evaluable disease assessment date
Remain in response after SCT prior to other initiated new anti-cancer therapy	Censored	Last evaluable disease assessment prior to other initiated new anti-cancer therapy
Death without disease progression and without new anti-cancer therapy (including SCT) prior to data cutoff for analysis	Censored	Last evaluable disease assessment date before death date

*For data from SCT after axicabtagene ciloleucel infusion. For all the other circumstances, follow the imputation rules described in Table 3.

Progression-free Survival (PFS):

Table 5. Primary Analysis of PFS

Circumstance	Event / Censored	Date of Event / Censoring
Disease progression prior to initiation of new anti-cancer therapy (including SCT) , or prior to the data cutoff for analysis	Event	Progression date
Death without disease progression and without new anti-cancer therapy (including SCT) prior to the data cutoff for analysis	Event	Death date
New anti-cancer therapy (including SCT) started before disease progression or death, or prior to the data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to initiation of new therapy or SCT, whichever is earlier
Disease progression or death documented after data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis
No disease progression through the discontinuation of study, or prior to data cutoff for analysis	Censored	Date of last evaluable disease assessment prior to the discontinuation of study, or prior to data cutoff for analysis, whichever is earlier
No disease assessment done after axicabtagene ciloleucel infusion by the cutoff date	Censored	Axicabtagene ciloleucel infusion date

Table 6. Sensitivity Analysis of PFS

Circumstance*	Event / Censored	Date of Event / Censoring
Disease progression after initiation of SCT, but prior to other new anti-cancer therapy	Event	Progression date
Death after SCT without disease progression or other new anti-cancer therapy	Event	Death date
Remain no disease progression after SCT without other new anti-cancer therapy	Censored	Last evaluable disease assessment date
Remain no disease progression after SCT prior to other initiated new anti-cancer therapy	Censored	Last evaluable disease assessment prior to other initiated new anti-cancer therapy

*For data from SCT after axicabtagene ciloleucel infusion. For all the other circumstances, follow the imputation rules described in Table 5.

Overall Survival (OS):

Table 7. Imputation Rule of OS Event/Censoring Date

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 the discontinuation of study, or data cutoff date and no further information available afterwards	Censored	Last date known to be alive date up through the date of discontinuation of study, or data cutoff date, whichever is earlier

Appendix 3. Derivation of Last date known to be alive

The last date known to be alive will be derived by obtaining the maximum complete date among the following data modules, and more date points may be considered based on actual data collected:

- Leukapheresis date
- Conditioning chemo admin date
- Axicabtagene ciloleucel infusion date
- Rituximab infusion date
- CT scan date
- PET scan date
- Target lesion assessment date
- Non-target lesion assessment date
- New lesion assessment date
- Disease response assessment date
- 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