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	Lenzilumab
Protocol	A Phase 1/2 Open-label, Multicenter Study of Lenzilumab and Axicabtagene Ciloleucel in Subjects with Relapsed or Refractory Large B-cell Lymphoma (ZUMA-19)
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CONFIDENTIALITY NOTICE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADaM	Analysis data model
AE	Adverse event
ASCT	Autologous stem cell transplant
BSA	Body surface area
CAR	Chimeric antigen receptor
CNS	Central nerve system
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
GM-CSF	Granulocyte macrophage-colony stimulating factor
ICANS	Immune Effector Cell-Associated neurotoxicity syndrome
ICE	Immune effector cell –associated encephalopathy
IPD	Important protocol deviations
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
RCR	Replication-competent retrovirus
RP2D	Recommended Phase 2 Dose
OS	Overall survival

Abbreviation	Definition
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
SOP	Standard operating procedure
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-471-0119 entitled "A Phase 1/2 Open-label, Multicenter Study of Lenzilumab and Axicabtagene Ciloleucel in Subjects with Relapsed or Refractory Large B-cell Lymphoma (ZUMA-19)".

2. OBJECTIVES

The primary objective of Phase 1 of the study is to evaluate the safety of sequenced therapy with lenzilumab and axicabtagene ciloleucel in subjects with relapsed or refractory large B-cell lymphoma.

In Phase 2, the primary objective is to evaluate the incidence of Grade 2 or higher neurologic events with sequenced therapy given at the recommended Phase 2 dose (RP2D) of lenzilumab in subjects with relapsed or refractory large B-cell lymphoma.

Secondary objectives will include evaluating the safety and efficacy of sequenced therapy, the extent of granulocyte macrophage-colony stimulating factor (GM-CSF) axis suppression in the blood, and the levels of chimeric antigen receptor (CAR) T cells and cytokines in the blood.

3. STUDY DESIGN

3.1. Overview

This is a Phase 1/2, open-label, multicenter study evaluating lenzilumab use to prevent axicabtagene ciloleucel treatment-related toxicities in subjects with relapsed or refractory large B-cell lymphoma. The addition of lenzilumab to the approved axicabtagene ciloleucel treatment regimen will hereafter be referred to as sequenced therapy.

In Phase 1, a 3+3 design will be used to determine the RP2D of lenzilumab within sequenced therapy for large B-cell lymphoma. The RP2D of lenzilumab will be determined primarily by clinical assessment of the incidence of dose-limiting toxicity (DLT) related to sequenced therapy. In addition to evaluation of DLT incidence, the extent of GM-CSF axis suppression as assessed by translational analysis may be assessed in defining the RP2D.

Once the RP2D is determined, the study will convert to Phase 2 and assume a Simon 2-stage design. After 14 subjects have been treated with sequenced therapy at the RP2D of lenzilumab and followed for 28 days across Phase 1 and Phase 2, futility of sequenced therapy to demonstrate a significant decrease, compared to historical controls as seen in ZUMA 1 Cohorts 1 and 2, in the incidence of Grade 2 or higher neurologic events will be assessed. If the futility threshold is not met, an additional 16 subjects will be treated with sequenced therapy at the RP2D of lenzilumab to complete accrual.

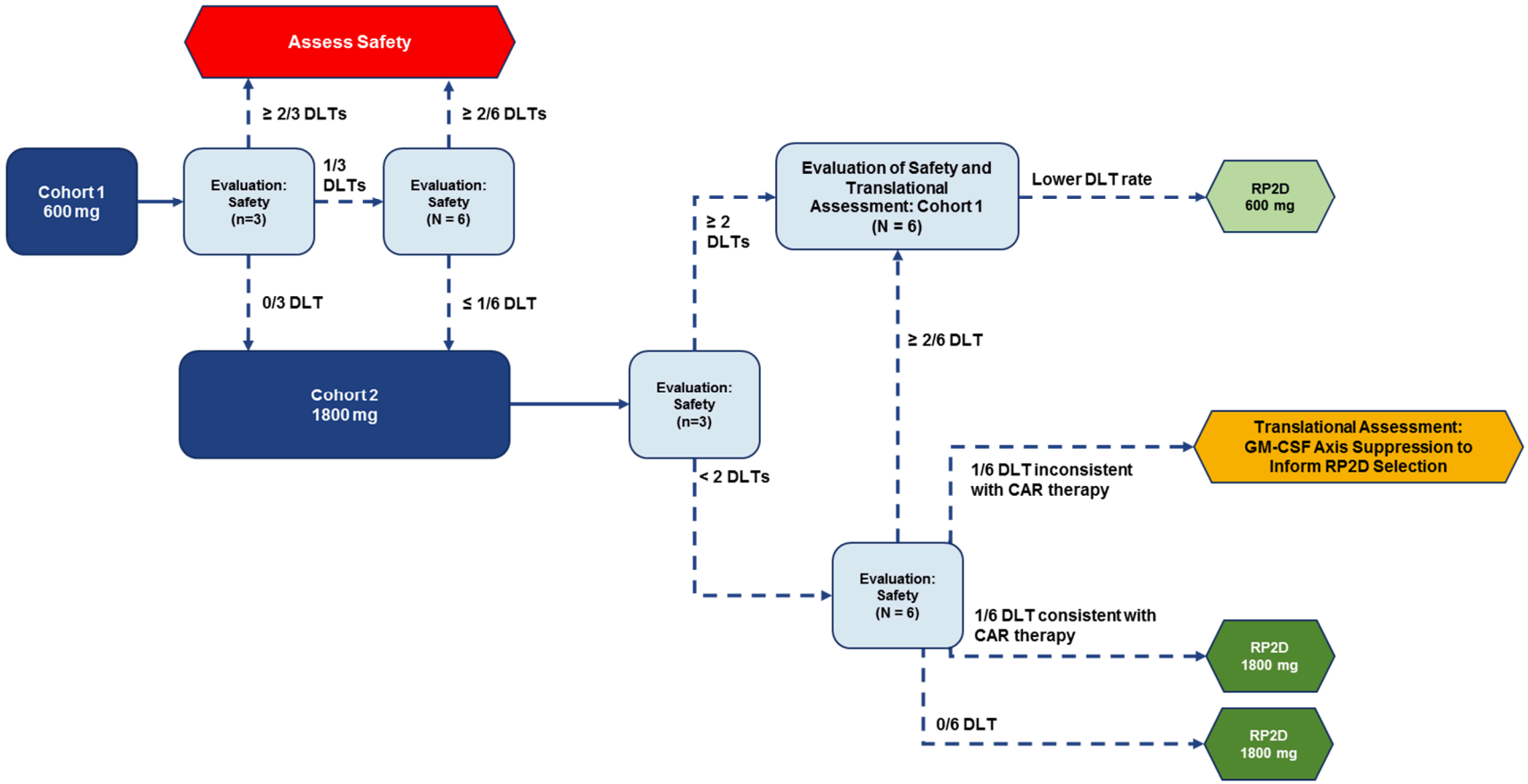
In total, approximately 36 subjects will be enrolled and treated during the study.

In Phase 1, a Safety Review Team (SRT) will pause enrollment to review safety data after 3 and 6 (as needed) subjects have been followed for 28 days after sequenced therapy in each dose escalation cohort. At the conclusion of dose escalation, the SRT will determine the RP2D of lenzilumab and conversion to Phase 2. The SRT can meet more often if needed.

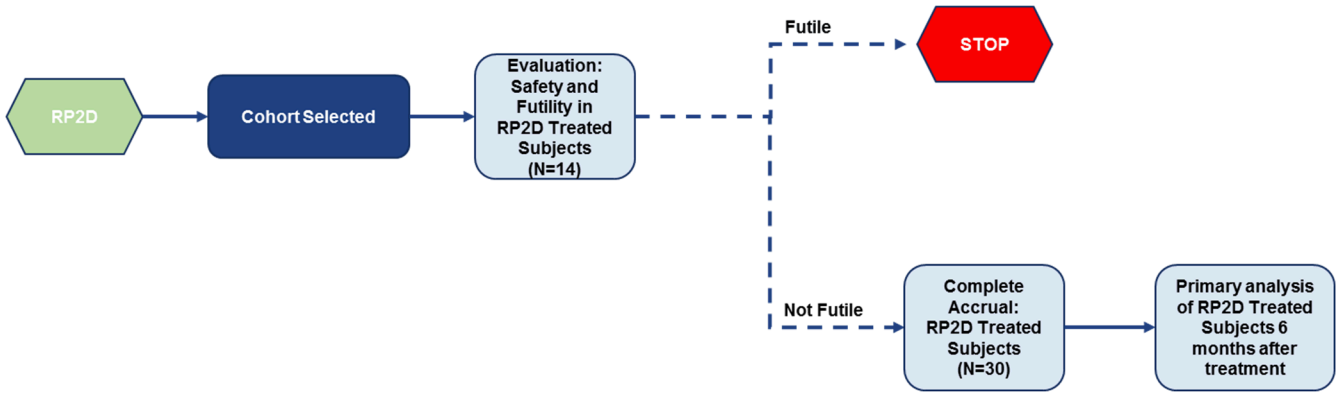
Once the study converts to Phase 2, the SRT will convene after a total of 14 subjects have been treated at the RP2D across Phase 1 and Phase 2, and have been followed for at least 28 days after axicabtagene ciloleucel administration. At this time, enrollment will be paused for safety data review and interim/futility analysis. If the SRT determines that the study does not meet criteria for futility, an additional 16 subjects will be enrolled to complete accrual.

Figure 1. Schematic of Study Design

A) Phase 1



B) Phase 2



Abbreviations: CAR, chimeric antigen receptor; DLT, dose limiting toxicity; RP2D, recommended Phase 2 dose.

3.2. Hypothesis

This Phase 2 portion of the study is designed to differentiate between a treatment that has a true event rate of 20% or less and a treatment with an event rate of 45% or more. The hypothesis is that the Grade 2 or higher neurologic event rate related to sequenced therapy is significantly less than 45%. No hypothesis will be tested during Phase 1 of the study.

3.3. Sample Size Consideration

The anticipated enrollment in this study is approximately **3** to **36** subjects.

Up to 6 subjects in each cohort will be enrolled and treated in Phase 1 of this study.

If the study proceeds to the Phase 2, up to an additional 24 subjects will be enrolled at the RP2D for assessment of the reduction in the incidence of Grade 2 or higher neurologic event seen by adding lenzilumab to the axicabtagene ciloleucel regimen.

Simon's 2-stage design {Simon 1989} is used to calculate the sample size for the RP2D cohort. The null hypothesis that the event rate is 45% will be tested against the alternative hypothesis that the event rate is 20% or less at 1-sided alpha of 2.5%. In Stage 1, 14 subjects will be accrued and treated at the RP2D (including subjects treated at the RP2D under both Phase 1 and Phase 2). If there are 5 or more subjects with Grade 2 or above neurologic events in these 14 Stage 1 subjects, the study will be stopped for futility at the discretion of the SRT. Otherwise, 16 additional subjects will be accrued and treated at the RP2D for a total of 30. The null hypothesis will be rejected if 8 or fewer subjects with Grade 2 or above neurologic events are observed in the 30 subjects. This design yields a 1-sided type I error rate of 0.025 for rejecting true null hypothesis and power of 80% when the true event rate is 20% or less. The probability of early stopping when the null hypothesis is true is 0.8328 CCI [redacted]

Table 1 Simon's Two-stage Design for RP2D[1] Cohort

Stages	Total Number of Subjects	Target Number of Subjects with Events
Stage 1	14	< 5
Stage 2	30	< 9

[1]RP2D: recommended phase 2 dose

All analyses for the incidence of Grade 2 or higher neurologic event in Phase 1 and Phase 2 portions of the study will be based on a primary objective analysis set consisting of all subjects who receive axicabtagene ciloleucel at a minimum dose of 1.6×10^6 anti-CD19 CAR T cells/kg (or a minimum dose of 1.6×10^8 anti-CD19 CAR T cells for subjects who weigh more than 100 kg) and target dose of lenzilumab.

Inferential testing will be performed only for the primary endpoint in Phase 2 of the study.

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

4.1.1. Primary Endpoint

Phase 1: Incidence of DLT related to sequenced therapy with lenzilumab and axicabtagene ciloleucel

Phase 2: Incidence of Grade 2 or higher neurologic events within 28 days of axicabtagene ciloleucel administration

4.1.2. Secondary Endpoints

Phase 1 and 2:

- The incidence AEs and SAEs, including CRS and neurologic events
- Objective Response Rate (complete response [CR] + partial response [PR]) per the Lugano Classification (Cheson et al, 2014), as determined by study investigators
- Complete Response rate per the Lugano Classification (Cheson et al, 2014), as determined by study investigators
- Axicabtagene ciloleucel pharmacodynamics: levels of cytokines (including free GM-CSF) in blood
- Axicabtagene ciloleucel pharmacokinetics (PK): levels of anti-CD19 CAR T cells in blood

Phase 2:

- Duration of Response (DOR), as determined by study investigators
- Progression Free Survival (PFS), as determined by study investigators
- Overall Survival (OS)

4.2. Subgroups and Covariates

The following variables may be used to examine efficacy results in subgroups 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 screening
- Age-adjusted International Prognostic Index (IPI) total score at screening
- Relapse/refractory subgroup
- Lines of prior therapies for the study disease
- Bulky disease (at least one lesion with largest diameter ≥10 cm))
- Tumor burden at baseline, as measured by the sum of the product of the diameters (SPD) of target lesions at baseline

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment occurs when subject commences leukapheresis.

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

Relapse/refractory Subgroup at Baseline:

- Primary refractory: A subject is considered to be primary refractory if the subject experienced disease progression as best response to first line therapy or had stable disease (SD) after at least 4 cycles of first line therapy with duration of SD no longer than 6 months from the last dose of therapy.

- Refractory to 2nd or greater line therapy: A subject is considered to be refractory to 2nd or greater line therapy if the patient experienced progressive disease (PD) as best response to the most recent therapy regimen or experienced SD after at least 2 cycles of therapy with duration of SD no longer than 6 months.

- Relapsed to 2nd or greater line therapy: A subject is considered to be relapsed to 2nd or greater line therapy if the patient experienced PR/CR as best response to the most recent therapy regimen and then subsequently had PD.

- Relapse post ASCT: A subject is considered to be relapsed post-ASCT if the subject experienced relapse ≤ 12 months of ASCT.

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/relapse to second or greater line of therapy > Primary refractory disease.

- Actual follow-up time: Actual follow-up time among all subjects treated with axicabtagene ciloleucel is calculated as the time from the axicabtagene ciloleucel infusion to the date of death, last date known to be alive, lost to follow-up, or full withdrawal of consent, whichever is later.

- Potential follow-up time: Potential follow-up time is defined as the time from the axicabtagene ciloleucel infusion to the data cutoff date for the analysis.

5.2. Safety

Treatment-emergent adverse event (TEAE): any adverse event with onset on or after lenzilumab administration.

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 lenzilumab:

Identified risks:

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

Potential risks:

- Secondary malignancy
- Replication competent retrovirus (RCR)
- Autoimmune disorders

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 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 et al, 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 v4.03.

Neurologic events: Neurologic adverse events are identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy (Topp et al, 2015). The search strategy focuses on central nervous system toxicity, without regard to temporal relationship or concomitant conditions (e.g. CRS). This method will be used to identify neurologic AEs for primary endpoint. 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, and thrombocytopenia) are identified as:

- Neutropenia is identified using the latest version of MedDRA search terms (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).

Longest consecutive period with cytopenias is calculated as the greatest number of consecutive days (without gaps between events) that subjects experiencing the AE of interest without gaps between events. For subjects who have AEs without reported ending dates, the longest consecutive period will be calculated with the ending dates of such AEs imputed using the earliest date of the data extraction date (or the data cutoff date, if applicable), study discontinuation date and the death date (if applicable). Prolonged cytopenias (neutropenia or thrombocytopenia or anemia) will be summarized separately by the three blood cell lineages.

Infections: Infections are identified as AEs within the MedDRA SOC of Infections and Infestations that occur after treatment with anti-CD19 CAR T cells. 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.

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 HGLT of auto-immune disorders within the immune system disorders SOC will be reviewed to identify other potential events.

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.

DLT: DLT is defined as the following sequenced therapy-related events with onset within the first 28 days following axicabtagene ciloleucel infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer
- Grade 4 thrombocytopenia lasting longer than 28 days from the day of cell transfer
- Any sequenced therapy-related AE requiring intubation, including Grade 4 encephalopathy requiring intubation for airway protection, is considered to be a DLT
- Any sequenced therapy-related Grade 5 event
- All other clinically significant Grade 3 toxicities lasting more than 3 days and all Grade 4 toxicities, with the exception of the following conditions which are not considered DLT's:

  Encephalopathy that resolves to at worst Grade 1 within 2 weeks and to baseline within 4 weeks

  Grade 3 fever

  Myelosuppression (includes bleeding in the setting of platelet count < 50 $x10^9$/L and documented bacterial infections in the setting of neutropenia), defined as lymphopenia, decreased hemoglobin, neutropenia, and thrombocytopenia unless neutropenia and thrombocytopenia meet the DLT definition described above

Immediate hypersensitivity reactions occurring within 2 hours of cell or lenzilumab infusion that are reversible to Grade 2 or less within 24 hours of administration with standard therapy

Renal toxicity which requires dialysis for ≤ 7 days

Tumor lysis syndrome including associated manifestations attributable to tumor lysis syndrome (eg, electrolyte abnormalities, renal function, hyperuricemia)

Grade 3 transaminase, alkaline phosphatase, bilirubin or other liver function test elevation, provided there is resolution to ≤ Grade 2 within 14 days

Grade 4 transient serum hepatic enzyme abnormalities provided there is resolution to ≤ Grade 3 within < 72 hours

Grade 3 or 4 hypogammaglobulinemia

Grade 3 nausea or anorexia

CRS will be graded according to a revised grading system {Lee 2014}, as described in the current axicabtagene ciloleucel IB. Adverse events attributed to CRS will be mapped to the overall CRS grading assessment for the determination of DLT. If Grade 3 or 4 CRS per Lee 2014 is due to one of the exceptions above, the event will not be considered a DLT.

5.3. Efficacy

Complete Response Rate (CRR): The proportion of subjects with a CR while after treatment with axicabtagene ciloleucel 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 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 et al, 2014), as determined by the study investigators.

Objective Response Rate (ORR): The proportion of subjects with a CR or PR while after treatment with axicabtagene ciloleucel 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 axicabtagene ciloleucel infusion, and prior to any subsequent therapies for NHL (including SCT). Responses will be assessed per the Lugano Classification (Cheson et al, 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 et al, 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 subsequent anti-cancer therapy in the absence of documented progression will be censored at the last evaluable disease assessment prior to the subsequent 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 et al, 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. Full Analysis Set

The full analysis set (FAS) will consist of all enrolled subjects (i.e., commences leukapheresis) and will be used for the summary of subject disposition and list of death.

6.2. Primary Objective Analysis Set

The primary objective analysis set will consist of all subjects enrolled and treated with axicabtagene ciloleucel at a minimum dose of CCI anti-CD19 CAR T cells/k CCI [redacted] and target dose of lenzilumab at the recommended phase 2 dose (RP2D) (including Phase 1 and Phase 2) prior to axicabtagene ciloleucel infusion. This analysis set will be used for the primary endpoint analysis. Sensitivity analysis for neurologic events/assessments, CRS, and SAE may be performed using primary objective analysis set.

6.3. Modified Intent-to-treat Analysis Set

The modified intent-to-treat set will consist of all subjects enrolled and treated with axicabtagene ciloleucel at a minimum dose of CCI anti-CD19 CAR T cells/kg CCI [redacted] and target dose of lenzilumab at the RP2D (including Phase 1 and Phase 2) prior to axicabtagene ciloleucel infusion. This analysis set will be used for all efficacy analyses.

6.4. Safety Analysis Set

Safety analysis set is defined as all subjects treated with any dose of axicabtagene ciloleucel and/or any dose of lenzilumab. This analysis set will be used for all safety analyses except for the primary endpoint.

6.5. DLT Evaluable Set

DLT evaluable set defined for each dosing cohort in Phase 1, will include subjects treated in the Phase 1 dosing cohort who:

- Received the target dose of lenzilumab (within ±10% of the planned dose) and axicabtagene ciloleucel (within ±20% of the planned dose) and were followed for at least 28 days after the anti-CD19 CAR T cell infusion; or

- Received a dose of lenzilumab lower than the target for that cohort and experienced a DLT during the 28-day after the anti-CD19 CAR T cell infusion.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

During Phase 1, the Safety Review Team (SRT) will review safety data after 3 and 6 (as needed) subjects have been followed for 28 days after their axicabtagene ciloleucel administration in each dose escalation cohort and will make recommendations on further study conduct and progression of the study. At the conclusion of dose escalation, the SRT will determine the RP2D and conversion to Phase 2.

During Phase 2, the SRT will assess safety and futility through an interim analysis once 14 subjects are enrolled and treated with axicabtagene ciloleucel at a minimum dose of[redacted] anti-CD19 CAR T cells/k [redacted] and lenzilumab at the RP2D (including Phase 1 and Phase 2) prior to axicabtagene ciloleucel infusion, and have had the opportunity to be followed for 28 days after the axicabtagene ciloleucel dose. According to Simon's optimal 2-stage design, if there are 5 or more subjects with events in the 14 Stage 1 subjects, the study will be stopped at the discretion of the SRT. This timing will coincide with an interim analysis.

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 interim analysis, 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 (IPD) 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 IPD. High rates of IPD 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 primary analysis of the primary endpoint is an exact binomial test used to compare the Grade 2 or higher neurologic events rate in the primary objective analysis set to an event rate of 45%. This test assumes only the independence of the individual subject events.

An exact 95% confidence interval will be generated about the event rate. The Clopper-Pearson (an exact interval) method is used to generate this interval. While the Clopper-Pearson interval provides adequate coverage probability, it is commonly wider than necessary (Brown et al, 2002), leading to overly conservative estimates of the lower bound of event 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 analysis will be performed after 30 subjects in the primary objective analysis set have had the opportunity to be evaluated for response 6 months after the axicabtagene ciloleucel infusion. The final analysis will occur when all subjects have completed the study. Additional analyses of safety and efficacy may occur at any time 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.

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 IPD 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 screening (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
- Age-adjusted International Prognostic Index Total Score at screening

9.5. Grade 2 or Higher Neurologic Events Rate

The primary endpoint of incidence of Grade 2 or higher neurologic event within 28 days of axicabtagene ciloleucel infusion will be based on investigator review of neurologic assessments, signs, and symptoms in the primary objective analysis set. Neurologic 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 (CNS) toxicity, without regard to temporal relationship and concomitant conditions (eg, CRS).

The hypothesis testing for the event rate will be based on the exact binomial distribution. The incidence of Grade 2 or higher neurologic events and the exact 2-sided 95% confidence interval will be generated using Clopper-Pearson method.

Additional analyses for Grade 2 or higher neurologic events may be performed:

- Including all the Grade 2 or higher neurologic events with onset after axicabtagene ciloleucel infusion
- Using safety analysis set.
- Including all the Grade 2 or higher neurologic events with onset after axicabtagene ciloleucel infusion that are related to axicabtagene ciloleucel
- If there are subjects who receive axicabtagene ciloleucel that is out of specification (e.g., low viability), each case will be reviewed and a sensitivity analysis may be performed to exclude these subjects.

9.6. Safety Analyses

The incidence of DLT in the Phase 1 portion of the study will be summarized using DLT-evaluable set. All other 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 version 4.03 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 et al, 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 TEAEs will be tabulated:

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

Subjects with prolonged cytopenias (neutropenia or thrombocytopenia or anemia) will be identified with the following method:

- Subjects with cytopenias (neutropenia or thrombocytopenia or anemia) present on or after Day 30 post axicabtagene ciloleucel infusion

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. Neurological Assessment

The Immune Effector Cell-Associated Encephalopathy (ICE) score will be collected at screening, pre-infusion on Day 0, daily during the 7-day post-infusion period, and daily during any period of ongoing Grade 2 or higher neurologic event, as well as the Week 2, Week 4, and Month 3 visits. Descriptive summary for the values and change from baseline values will be provided for baseline, Day 0, best value during 7-day post-infusion period, worst value during 7-day post-infusion period, Week 2, Week 4, and Month 3. Overall worst value during the study and change from baseline will also be summarized using safety analysis set. The same analysis may be repeated using primary objective analysis set.

Immune Effector Cell-associated neurotoxicity syndromes (ICANS) and its associated AEs will be summarized by worst grade.

Subject listings will be provided for both ICE score and ICANS with grade.

9.6.3. Laboratory Test Results

Laboratory results will be graded according to the latest version of CTCAE. Laboratory data collected at baseline and through the treatment and follow-up periods will be summarized. The incidence of worst CTCAE grade post-infusion by grade for selected analytes will be provided. Additional lab tables for subjects who had worsening grade change from the last assessment prior to infusion to post-infusion may be generated by the worst post-infusion CTCAE grade.

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. Efficacy Analyses

Efficacy analyses will be conducted on the mITT analysis set, and the investigator assessment of disease status per the Lugano Classification (Cheson et al, 2014) will be used for disease response related analyses. The same analyses may be repeated using primary objective analysis set.

9.7.1. Complete Response and Objective Response

9.7.1.1. 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.

9.7.1.2. 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.

9.7.2. 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 and Smith 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.

9.7.3. 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.

9.7.4. Overall Survival

The analysis of overall survival will use the same methods as the analysis of PFS. The reverse Kaplan-Meier approach (Schemper and Smith 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.

9.7.5. 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.

9.8. 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
- Total dose of Lenzilumab administered

9.9. 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 WHO Drug coded term. The subject incidence of procedures will be tabulated.

The following summaries related to systemic steroid use and tocilizumab use may be performed:

- Number of subjects who received systemic steroid as treatment for neurological events or CRS
- Number of subjects who received tocilizumab as treatment for neurological events or CRS
- Time to first systemic steroid use
- Time to first tocilizumab use
- Duration of systemic steroid use
- Duration of tocilizumab use

- Cumulative systemic steroid use

9.10. Subsequent Anti-Cancer Therapy and Subsequent Stem Cell Transplant

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.

9.11. 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

9.12. 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

9.13. Hospitalization and Health Care Facility Use

Summary statistics may be provided for the following health care facility use:

- Incidence and duration of hospitalization for axicabtagene ciloleucel administration
- Incidence and duration of intensive care unit (ICU) use

9.14. Additional Analysis

Descriptive statistics for disease characteristics at baseline will be evaluated against the available descriptive statistics from existing DLBCL studies (e.g., ZUMA 1 cohort 1 and 2). If different distributions are identified for some characteristics, additional analysis may be explored. Key safety and efficacy endpoints may be evaluated based on some matching method.

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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:

- Start date and stop date of AE (including targeted AE)
- Start date and stop date of concomitant medication
- Start date and stop date of new anti-cancer therapy
- Subsequent SCT date
- Leukapheresis date
- Conditioning chemo admin date
- axicabtagene ciloleucel infusion date (including retreatment date)
- Lenzilumab infusion date for Cohort 1
- 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