Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Company Code:	KTE-C19
USAN Name:	axicabtagene ciloleucel
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CONFIDENTIALITY NOTICE

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ASCT	Autologous stem cell transplant
ATC	Anatomical therapeutic chemical
BCL	B-cell lymphoma
BSA	Body surface area
CAR	Chimeric antigen receptor
CR	Complete response
CRF	Case report form
CRR	Complete response rate
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
GBC	Germinal Center B Cell-like
KTE-C19	Company code for axicabtagene ciloleucel
HLGT	High-level group term
IPD	Important protocol deviation
IPI	International Prognostic Index
IWG	International Working Group
LTFU	Long Term Follow-up
MedDRA	Medical Dictionary for Drug Regulatory Activities
mITT	Modified intent-to-treat
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate

Abbreviation	Definition
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
RCR	Replication-competent retrovirus
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable disease
SIA	Systemic immune activation
SOC	System organ class
SPD	Sum of the product of the diameter
SOA	Schedule of Assessments
SRT	Safety review team
TEAE	Treatment-emergent adverse event
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) sets forth prospectively the details of statistical analyses that are outlined in protocol KTE-C19-106 entitled "A Phase 1–2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Combination with Atezolizumab in Subjects with Refractory Diffuse Large B-Cell Lymphoma (DLBCL)," dated 21 Sep 2017. The scope of this SAP includes all the statistical analyses that are outlined in the protocol.

2. OBJECTIVES

This study is organized into 2 phases: Phase 1 and Phase 2.

The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel and atezolizumab combination regimens.

The primary objective of Phase 2 is to evaluate the efficacy of axicabtagene ciloleucel infusion followed by atezolizumab, as measured by the complete response (CR) rate in subjects with refractory DLBCL. Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel followed by atezolizumab treatment as well as secondary endpoints efficacy, biomarker, pharmacokinetics (PK), and anti-therapeutic antibody endpoints listed in Section 4.

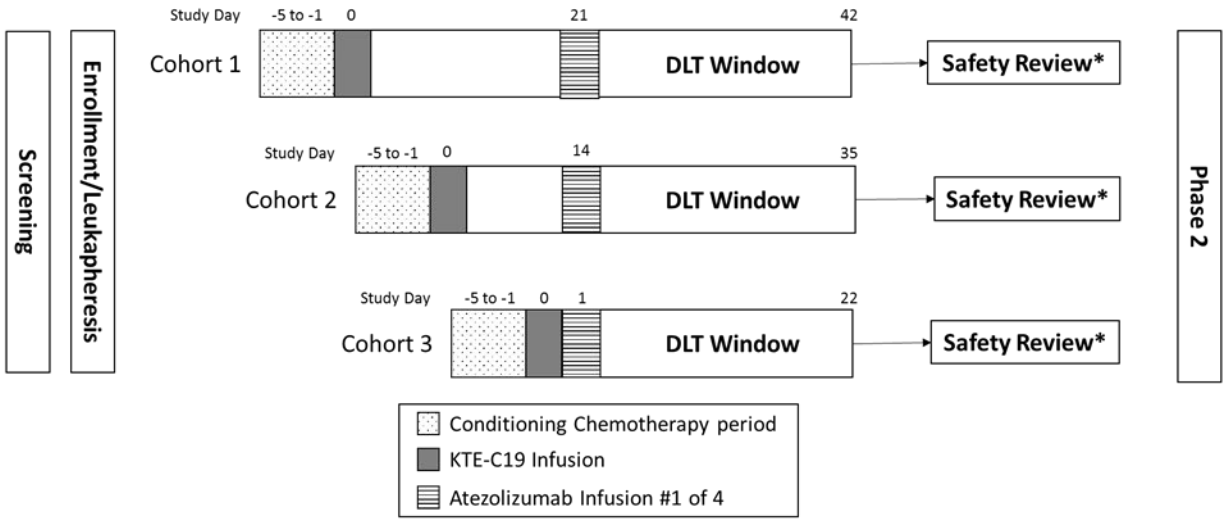
3. STUDY DESIGN

3.1. Study Overview

This is a Phase 1-2, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel followed by atezolizumab in subjects with refractory DLBCL. The trial will be separated into 2 distinct phases designated as Phase 1 and Phase 2.

Phase 1: Approximately 3–9 subjects with refractory DLBCL will be enrolled in up to 3 cohorts to evaluate the safety of axicabtagene ciloleucel followed by atezolizumab regimen. A safety review team (SRT), internal to the study sponsors and Phase 1 investigators, will review safety data after subjects in Phase 1 have completed the dose-limiting toxicities (DLT) part of the study. The SRT will make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 1.

Figure 1. Study Schema



Abbreviations: DLT, dose-limiting toxicity.
*During Phase 1, cohorts will be enrolled sequentially, beginning with Cohort 1. After each Phase 1 cohort has completed enrollment and subjects have cleared the DLT window, the SRT will meet and review the overall benefit/risk profile of the dosing schedule tested in that cohort. SRT recommendations for further study conduct may include addition of subjects to a cohort prior to opening a subsequent cohort, advancement to a subsequent cohort, exploration of alternative conditioning chemotherapy or KTE-C19 doses, advancement to Phase 2, or study termination.

Phase 2: Approximately 22 subjects will be enrolled to receive treatment with axicabtagene ciloleucel followed by atezolizumab based on the dose and schedule selected to move forward from the Phase 1 portion of the study as recommended by the SRT.

Independent of the cohort or phase of the study, each subject will proceed through the following study periods:

- Screening
- Enrollment/Leukapheresis
- Conditioning chemotherapy
- Investigational treatment (axicabtagene ciloleucel followed by atezolizumab)
- Post-treatment assessment
- Long-term follow-up

Details on the study requirements during each study period are presented in Section 7 of the study protocol.

3.2. Hypothesis

No formal hypothesis will be tested in this study. The Phase 2 portion of the study is designed to estimate the CR rate in subjects with refractory DLBCL treated with axicabtagene ciloleucel followed by atezolizumab.

3.3. Sample Size Considerations

Approximately 3–31 subjects will be recruited. The number of subjects to be recruited for each phase is as follows:

- Phase 1: approximately 3–9 subjects
- Phase 2: approximately 22 subjects

If the study proceeds to Phase 2, then approximately 22 subjects will be recruited. With a total sample size of at least 25 subjects at a given dosing schedule, of which at least 3 will have been treated in the Phase 1 portion, an observed CR rate of 72% (18/25) will yield 2-sided 95% confidence interval to estimate the true CR rate with a maximum half-width of 21%.

Table 1. Two-sided 95% and 80% Exact Confidence Intervals for Observed CR Rate based on 25 Subjects

Subjects with CR	Observed CR Rate	95% Confidence Interval	80% Confidence Interval
10	40%	[21%, 61%]	[27%, 55%]
12	48%	[28%, 69%]	[34%, 62%]
14	56%	[35%, 76%]	[41%, 70%]
16	64%	[43%, 82%]	[49%, 77%]
18	72%	[51%, 88%]	[57%, 84%]
20	80%	[59%, 93%]	[66%, 90%]

Abbreviations: CR, complete response.

3.4. Replacement of Subjects

Subjects will be replaced and continue to be enrolled until the specified number of subjects are attained in the DLT evaluable (Phase 1) and modified intent-to-treat (mITT) set (Phase 2). Subjects who receive between [redacted] PPD [redacted] anti-CD19 chimeric antigen receptor (CAR) T cells/kg and at least 1 dose of atezolizumab will be considered evaluable in the efficacy analysis. Subjects who have not received a target axicabtagene ciloleucel dose or have not received any dose of atezolizumab will be retained in the analyses of disposition and safety as appropriate.

3.5. Study Duration

3.5.1. Study Duration for Individual Subjects

A subject who completes all of the planned protocol activities from the date of informed consent through the completion of the long-term follow-up period will take approximately 5 years to complete. However, individual study duration will vary depending on a subject's screening requirements, response to treatment, and survival.

3.5.2. Completion of Study

Completion of the study is defined as the time at which the last subject completes the long-term follow-up period visit, is considered lost to follow-up, withdraws consent, or dies. The primary efficacy analysis will be conducted when the last treated subject in the mITT set has had the opportunity to complete the 6-month disease response assessment after axicabtagene ciloleucel infusion. The final analysis will occur when all subjects have completed the study.

3.5.3. Subject Eligibility

Subject screening, enrollment, and inclusion and exclusion criteria are presented in Section 4 and Section 5 of the protocol.

3.6. Protocol Planned Study Treatments

3.6.1. Conditioning Chemotherapy

All subjects will be administered conditioning chemotherapy, consisting of cyclophosphamide PPD and fludarabine PPD .

3.6.2. Study Treatment

3.6.2.1. Axicabtagene Ciloleucel

The study treatment axicabtagene ciloleucel will be administered as follows.

Subjects will receive a single infusion of axicabtagene ciloleucel consisting of anti-CD19 CAR-transduced autologous T cells administered intravenously at PPD

3.6.2.2. Atezolizumab Dosing and Administration

Atezolizumab is infused intravenously PPD

3.6.3. Dosage Modification

No reduction or modification of the atezolizumab dose is planned.

4. STUDY ENDPOINTS AND COVARIATES

4.1. Primary Endpoints

Phase 1: the incidence of DLT.

Phase 2: CR rate per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson et al, 2007) as determined by study investigators.

4.2. Secondary Endpoints

Phase 1 and Phase 2:

- Objective response rate (ORR; CR + partial response [PR]) per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) determined by study investigators
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Incidence of adverse events (AEs) and clinically significant changes in safety lab values
- Levels of axicabtagene ciloleucel in blood
- Incidence of anti-axicabtagene ciloleucel antibodies
- Atezolizumab PK
- Incidence of anti-atezolizumab antibodies in serum
- Levels of cytokines in serum

4.3. Exploratory Endpoints

PPD

4.4. 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, ≥ 65)
- Histologically proven DLBCL type
- Tumor Epstein-Barr virus (EBV) status (EBV^+, EBV^-, or unknown)
- Molecular subgroups (GBC, ABC, or unknown)
- Disease stage at study entry (I–II, III–IV)
- International Prognostic Index (IPI) total score at baseline (0–1, 2–3, 4–5)
- Prior transplant (autologous stem cell transplant [ASCT])(Y/N)
- Refractory subgroup (primary refractory, refractory to second line or greater, relapse post ASCT)
- Expression of CD19 in tumor tissue prior to treatment
- Expression of PD-L1 in tumor tissue prior to treatment
- Baseline bone marrow involvement
- 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)
- Total CAR T cells of the product infused (≤ median vs > median)
- Prior platinum

5. DEFINITIONS

5.1. General

Study enrollment: Subjects are considered enrolled in the study after the leukapheresis procedure is initiated.

Study Day 0: Defined as the day the subject received axicabtagene ciloleucel infusion. The day prior to study Day 0 will be study Day –1. Any days prior to study 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 otherwise specified.

Baseline of retreatment: If the subject is eligible for retreatment with axicabtagene ciloleucel, the last records on or prior to conditioning chemotherapy retreatment will be considered the baseline of retreatment, unless otherwise specified.

Refractory subgroup at baseline: Chemotherapy-refractory disease is defined as one or more of the following:

- 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 after at least 4 cycles of first-line therapy with duration of stable disease no longer than 6 months from the last dose of therapy.
- Refractory to second- or greater-line therapy: A subject is considered to be refractory to second- or greater-line therapy if the subject experienced progressive disease (PD) as best response to the most recent therapy regimen or experienced stable disease after at least 2 cycles of therapy with duration of stable disease no longer than 6 months.
- Relapse post-ASCT: A subject is considered to be relapsed post-ASCT if the subject experienced PD or relapse ≤ 12 months after 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 relapse post-ASCT > Refractory to second- or greater-line of therapy > primary refractory.

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 AE with onset on or after axicabtagene ciloleucel infusion.

Investigational treatment period: Beginning from the date axicabtagene ciloleucel infusion through 30 days after completing the final dose of atezolizumab or 3 months after the axicabtagene ciloleucel infusion, whichever is longer.

Investigational retreatment period: Beginning from the date of the axicabtagene ciloleucel retreatment infusion through 30 days after completing the final dose of atezolizumab retreatment or 3 months after the axicabtagene ciloleucel infusion in retreatment, whichever is longer.

Deaths: Any death occurring on or after the first dose of conditioning chemotherapy up through the end of study.

Adverse events of interest: The following AEs are of interest for the treatment of axicabtagene ciloleucel followed by atezolizumab.

Identified risks:

- Cytokine-release syndrome (CRS)
- Neurologic events
- Prolonged cytopenias
- Infections
- Hypogammaglobulinemia

Potential risks:

- Secondary malignancies
- Tumor lysis syndrome
- Immunogenicity (anti-axicabtagene ciloleucel or anti-atezolizumab antibodies)
- Replication-competent retrovirus (RCR)
- Systemic immune activation (SIA)

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 Drug Regulatory Activities (MedDRA) and linked to the corresponding CRS episode. Individual symptoms of CRS are graded per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, 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 because they will be reported separately with the neurologic events category and graded per CTCAE version 4.03.

Neurologic events: Neurologic AEs 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 (eg, CRS). Neurologic events will be reported separately from CRS.

Cytopenias: Cytopenias (neutropenia, anemia, and thrombocytopenia) are identified as the following:

- Neutropenia is identified using the following MedDRA preferred terms: febrile neutropenia, neutropenia, neutrophil count decreased.
- Anemia is identified using the standardized MedDRA query (SMQ) haematopoietic erythropenia (broad).
- Thrombocytopenia is identified using the SMQ haematopoietic thrombocytopenia (narrow).

Cytopenias present after 30 days from the axicabtagene ciloleucel infusion will be summarized as prolonged cytopenias.

Infections: Infections are identified as AEs within the MedDRA system organ class (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 is identified as AE coded as MedDRA preferred terms of hypogammaglobulinemia, blood immunoglobulin D decreased, and blood immunoglobulin G decreased.

Secondary malignancy: Secondary malignancies are identified via collection on a CRF in which the investigator classifies the event as a secondary malignancy. Additionally, AEs 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.

Tumor lysis syndrome: Tumor lysis syndrome is identified as events with MedDRA preferred terms in the Tumor Lysis Syndrome SMQ (MedDRA). The narrow version of this SMQ will be used.

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 stop day of the last AE in the event class—the start day of the first AE in the event class + 1.

5.3. Efficacy

Complete response rate (CRR): The proportion of subjects with a CR while on study. 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 1 dose of atezolizumab administration and prior to any subsequent therapies for non-Hodgkin lymphoma (NHL) (including SCT and retreatment with axicabtagene ciloleucel and atezolizumab). Responses will be assessed per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) as determined by study investigators.

Objective response rate (ORR): The proportion of subjects with a CR or PR while on study. 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 1 dose of atezolizumab administration and prior to any subsequent therapies for NHL (including stem cell transplant [SCT] and retreatment with axicabtagene ciloleucel and atezolizumab). Responses will be assessed per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) as determined by 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 revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) 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. DOR will be derived using disease assessments obtained on study prior to any subsequent therapies for NHL (including SCT and retreatment with axicabtagene ciloleucel and atezolizumab). The DOR for subjects who undergo SCT while in an axicabtagene ciloleucel-induced response will be censored at the last evaluable disease assessment prior to SCT. A sensitivity analysis will be conducted in which disease assessments obtained after SCT are included in the derivation of DOR. Additional details on the derivation of DOR are provided in Section 11.2, Appendix 2.

Progression-free survival (PFS): PFS is defined as the time from the axicabtagene ciloleucel infusion to the date of disease progression per the revised IWG Response Criteria for Malignant Lymphoma (Cheson et al, 2007) or death from any cause. Subjects not meeting the criteria for progression by the analysis data cutoff date will be censored at their last evaluable disease assessment date. PFS will be derived using disease assessments obtained on study prior to any subsequent therapies for NHL (including SCT and retreatment with axicabtagene ciloleucel and atezolizumab). The PFS for subjects who undergo SCT while in an axicabtagene ciloleucel-induced response will be censored at the last evaluable disease assessment prior to the SCT. A sensitivity analysis will be conducted in which disease assessments obtained after SCT will be included in the derivation of disease assessment. Additional details on the derivation of PFS are provided in Section 11.2, 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 Section 11.2, 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 (ie, subjects who underwent leukapheresis).

6.2. Modified Intent-to-treat Set

The mITT set will consist of all subjects enrolled and treated with the target dose of axicabtagene ciloleucel at [redacted] PPD [redacted]) and at least 1 dose of atezolizumab as determined upon completion of Phase 1 and Phase 2 portions of the study. This analysis set will be used for all efficacy analyses.

6.3. Safety Analysis Set

The safety analysis set (SAS) is defined as all subjects treated with any dose of axicabtagene ciloleucel.

6.4. DLT Evaluable Set (Phase 1 only)

The DLT evaluable set will include all subjects in each Phase 1 cohort treated with axicabtagene ciloleucel and at least 1 dose of atezolizumab who either:

- Received the target axicabtagene ciloleucel dose and were followed for at least 21 days after the first atezolizumab infusion; or
- Received a dose of axicabtagene ciloleucel lower than the target for that cohort and a subsequent atezolizumab infusion and experienced a DLT during the 21-day period following atezolizumab infusion.

For the Phase 1 portion of the study and the evaluation of DLT, the target axicabtagene ciloleucel dose is [redacted] PPD [redacted]

6.5. Safety Retreatment Analysis Set

The safety retreatment analysis set will include all subjects who undergo retreatment with any dose of axicabtagene ciloleucel. This set will be used for all retreatment safety analyses.

6.6. mITT Retreatment Analysis Set

The mITT retreatment analysis set will consist of all subjects who undergo retreatment with axicabtagene ciloleucel and at least 1 dose of retreatment of atezolizumab. This set will be used for all retreatment efficacy analyses.

7. SAFETY INTERIM ANALYSIS

The SRT will review safety data during Phase 1 of the study and will make recommendations on further study conduct in Phase 1 and progression to Phase 2 based on the incidence of axicabtagene ciloleucel-related DLTs and review of serious adverse events (SAEs).

The SRT will also meet once during the Phase 2 portion of the study when 6 subjects have completed their 1-month disease assessment. The SRT will review safety and efficacy data and is empowered to make trial conduct recommendations based on an analysis of risk vs benefit. The SRT may meet more often as needed.

8. HANDLING OF MISSING AND INCOMPLETE DATA

8.1. Efficacy Data

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 algorithms discussed in Section 11.2, Appendix 2 will be used.

8.2. Safety Data

Partial AE start dates will be imputed. If dates are missing or incomplete for AE start dates, the algorithm defined in Section 11.1, Appendix 1 will be used. Completely missing death dates or death dates with only a year reported will not be imputed.

8.3. Detection of Bias

A listing of subject incidence of important protocol deviations (IPD) will be generated. The deviations included in this list will include 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.

8.4. Outliers

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

9. STATISTICAL METHODS OF ANALYSIS

9.1. Overview of Analysis

Analyses of the Phase 1 and Phase 2 portions of the study will be presented separately, unless otherwise specified. Within the Phase 1 summaries, each dose cohort will be presented separately.

The primary efficacy analysis will be performed when the last treated subject in the mITT set has 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.

9.2. Subject Accountability

The number of subjects screened, leukapheresed, treated with conditioning chemotherapy, treated with axicabtagene ciloleucel and atezolizumab, or retreated with axicabtagene ciloleucel and atezolizumab will be summarized. The reasons for discontinuing treatment and discontinuing study will be summarized. Summaries of actual follow-up time 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 (if any) will be provided.

9.3. Important Protocol Deviations

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

9.4. Demographic and Baseline Characteristics

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

- Age at baseline and by category (< 65, ≥ 65)
- Sex
- Ethnicity
- Race
- Height
- Weight
- ECOG performance status at baseline
- Histologically proven DLBCL type
- Tumor EBV Status (EBV^+, EBV^-, or unknown)
- Molecular subgroups (GCB, ABC, or unknown)
- For subjects with cytogenetics testing performed:
    - BCL-2 alternations/over-expressions (Y/N)
    - BCL-6 alternations/over-expressions (Y/N)
    - C-MYC alternations/over-expressions (Y/N)

- Disease stage (I, II, III, IV) and extent (presence of B symptoms, splenic involvement, extra-nodal disease, bulky disease, bone marrow involvement)
- IPI risk category
- Refractory subgroup (primary refractory, second line or greater, relapse post-ASCT)
- Prior ASCT
- Lines of prior therapy for primary study disease
- Tumor burden at baseline, as measured by the SPD of target lesions at baseline
- CD19 expression in tumor intensity at baseline
- PD-L1 expression in tumor intensity and immune infiltrate tumor intensity at baseline
- Baseline bone marrow involvement
- Best response to prior anti-cancer therapy
- Prior radiotherapy information (Y/N)
- Best response to prior transplant
- Prior anti-CD20
- Prior anthracycline
- Prior platinum

9.5. Medical and Surgical History

Medical and surgical history will be coded using the latest version of MedDRA. The numbers and percentages of subjects with medical history will be reported by SOC and preferred term (PT).

9.6. Prior Therapy for Primary Study Disease and Prior Radiotherapy

Prior therapy for DLBCL will be coded by anatomical therapeutic chemical (ATC) code and PT using the latest version of World Health Organization Drug Dictionary (WHODrug) and will be summarized in frequency tabulations (subject counts and percentages) by PT.

Intent of prior radiotherapy and body site to receive the radiotherapy will be summarized in frequency tabulations (subject counts and percentages).

9.7. Efficacy Analyses

Efficacy analyses will be conducted on the mITT analysis set and will use investigator assessment of disease status per (Cheson et al, 2007).

For subjects retreated with axicabtagene ciloleucel and atezolizumab, disease assessments obtained prior to retreatment will be included in the primary summaries of objective and best response, DOR, PFS, and summaries of change in tumor burden. For such subjects, disease assessments obtained after retreatment

will be included in the summaries of objective and best response to retreatment with axicabtagene ciloleucel and atezolizumab and DOR after retreatment with axicabtagene ciloleucel and atezolizumab. The subject's OS time will be derived from the last date known alive regardless of retreatment time.

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 (Cheson et al, 2007). 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 4.4. 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.

A sensitivity analysis of DOR will be conducted in which disease assessments obtained after SCT (for subjects who undergo SCT while in an axicabtagene ciloleucel-induced response) are used in the derivation of 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. The reverse Kaplan-Meier approach (Schemper and Smith 1996) will be used to estimate the follow up time for PFS.

A sensitivity analysis of PFS will be conducted in which the disease assessments obtained after ASCT will be included in the derivation of disease assessment. Subgroup analyses of the PFS rate at 6 months may be generated in subgroups defined by the covariates in Section 4.4.

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

9.7.4. Overall Survival

The analysis of OS 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 percentages. 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 or SCT will not be included for the analyses.

9.8. Safety Analyses

Safety analyses will be conducted on the SAS. The primary analysis of safety data will summarize all TEAEs and laboratory values. For subjects who undergo retreatment with axicabtagene ciloleucel and atezolizumab, AEs occurring in this period may be summarized in an additional separate summary or listing that presents only the AEs occurring during the retreatment period.

AEs will be coded with the latest version of MedDRA. The severity of AEs will be graded using the NCI CTCAE version 4.03. The incidence and severity of 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 CTCAE version 4.03.

Subjects enrolled, but not dosed with the study combination treatment, 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 study data tabulation model (SDTM) and analysis data model (ADaM) datasets, but will not be tabulated in AE summaries.

9.8.1. Adverse Events

The subject incidence of the following TEAEs will be tabulated by SOC and PT:

- Summary of AEs (any, worst severity, serious, related)
- All AEs
- All SAEs
- All axicabtagene ciloleucel and/or atezolizumab related AEs
- All axicabtagene ciloleucel and/or atezolizumab related SAEs
- All Grade 3 or higher AEs
- All Grade 3 or higher axicabtagene ciloleucel and/or atezolizumab related AEs

- The most common AEs
- The most common Grade 3 or higher AEs
- AEs of interest, including identified risks (CRS, neurological event, infections, cytopenias, hypogammaglobulinemia), and potential risks (secondary malignancies, tumor lysis syndrome, SIA, and immunogenicity)
- 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 4.4 if applicable.

9.8.2. Laboratory Test Results

Laboratory results will be graded according CTCAE (version 4.03). Laboratory data collected at baseline and through the treatment and follow-up periods will be summarized. Shifts from baseline to minimum post-baseline and/or maximum post-baseline will be presented for selected analytes. The incidence of worst grade CTCAE shift for selected analytes will be provided.

9.8.3. 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.

9.8.4. Anti-therapeutic Antibodies to Atezolizumab

Atezolizumab PK and incidence of anti-therapeutic antibodies (ATA) in serum will be tabulated. For subjects testing positive for antibodies, the persistence of the antibody over time will be summarized.

9.8.5. 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.

9.8.6. Exposure to Study Treatment 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
- Summary of atezolizumab infusion

Separate summaries will be presented for retreated subjects if applicable.

9.8.7. 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 WHODrug coded term. The subject incidence of procedures will be tabulated.

9.8.8. Subsequent Anti-cancer Therapy

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

9.8.9. Duration of Study Treatment

Summary statistics will be provided for the following durations:

- Days from screening to commencement of leukapheresis
- Days from screening to administration of axicabtagene ciloleucel
- Days from leukapheresis to commencement of conditioning chemotherapy
- Days from leukapheresis to receipt of axicabtagene ciloleucel at the study site
- Days from leukapheresis to the administration of axicabtagene ciloleucel
- Days from conditioning chemotherapy to administration of axicabtagene ciloleucel
- Duration of hospitalization for the axicabtagene ciloleucel infusion

9.9. Pharmacokinetics

Refer to PK/pharmacodynamics SAP.

10. REFERENCES

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11. APPENDICES

11.1. 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:

- Adverse event (AE) start dates
- Deaths (refer to exceptions in Section 11.1.1)
- 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

Abbreviations: n/a, not available.
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.

11.1.1. Imputation Rules for Partial or Missing Death Dates

- 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.

- 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 subsequent anti-cancer therapy start dates:

- If year and month are available, but day is missing:
  - If the year and month are the same as last no-serious AE start date, then set the day as no-serious AE start date + 1
  - If the year or month is after the last no-serious AE start date, then set the day as the first day of the month.
- If year is available, and month and day are missing:
  - If the year is same as last no-serious AE start year, then set the date as AE start date + 1
  - If the year is after the last no-serious AE start year, then set January 1 as the date.
- If the date is completely missing, then set the date as last no-serious AE start date + 1.

11.2. 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 in Table 3, Table 4, Table 5, Table 6, and Table 7. Duration of response to retreatment will follow the same imputation rules as DOR.

11.2.1. 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

Circumstance	Event/Censored	Date of Event/Censoring
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 is earlier

Abbreviations: SCT, stem cell transplant.

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

Abbreviations: SCT, stem cell transplant.

*For all the other circumstances, follow the imputation rules described in Table 3.

11.2.2. Progression-free Survival

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

Circumstance	Event/Censored	Date of Event/Censoring
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

Abbreviations: SCT, stem cell transplant.

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

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

11.2.3. Overall Survival

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 afterward	Censored	Last date known to be alive, date up through the date of discontinuation of study, or data cutoff date, whichever is earlier

11.3. 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 of AE (including targeted AE)
- Leukapheresis date
- Conditioning chemotherapy administration date
- Axicabtagene ciloleucel infusion date
- Atezolizumab infusion date
- Computed tomography (CT) scan date
- Positron emission tomography (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