STATISTICAL ANALYSIS PLAN (SAP)

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	Axicabtagene Ciloleucel
Protocol	A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7)
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LIST OF ABBREVIATIONS AND DEFINTIONS OF TERMS

ADaM	Analysis data model
AE	Adverse event
ALC	Absolute lymphocyte count
ASCT	Autologous stem cell transplant
BSA	Bovine serum albumin
CAR	Chimeric antigen receptor
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30
EQ-5D-5L	European quality of life five dimensions five levels
FAS	Full analysis set
FISH	Fluorescence in situ hybridization
HDT	High-dose therapy
HLGT	High-level group term
IPI	International Prognostic Index
IXRS	Interactive Voice/Web (X) Response System
KM	Kaplan-Meier
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NALT	Next anti-lymphoma therapy
NCI	National Cancer Institute
NE	Neurologic event
ORR	Objective response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival

PR	Partial response
PRO	Patient reported outcome
QoL	Quality of life
RCR	Replication-competent retrovirus
r/r	Relapsed/refractory
SAE	Serious adverse event
scFv	Single-chain variable fragment
SCT	Stem cell transplant
SDTM	Study data tabulation model
SOC	Standard of care
SMQ	Standardized MedDRA query
SUSAR	Suspected unexpected serious adverse reaction
TBI	Total body irradiation
TEAE	Treatment-emergent adverse event
TFL	Transformed follicular lymphoma
VAS	Visual analog scale
WPAI	Work productivity and activity impairment

1. INTRODUCTION

This statistical analysis plan provides the pre-specification and details for the statistical analyses outlined within Protocol KTE-C19-107 entitled "A Phase 3, Randomized, Open-label Study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (ZUMA-7)." The scope of this plan includes the interim and primary analyses that are planned.

2. OBJECTIVES

The primary objective of this study is to determine whether axicabtagene ciloleucel is superior to standard of care (SOC) as measured by event-free survival (EFS).

The secondary objectives of this study are:

- To evaluate the effect of axicabtagene ciloleucel compared to SOC on objective response rate (ORR), defined as the incidence of partial response (PR) and complete response (CR)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on overall survival (OS)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on progression-free survival (PFS)
- To evaluate the effect of axicabtagene ciloleucel compared to SOC on duration of response (DOR) among responding subjects (CR and PR) and subjects attaining a CR
- To evaluate the safety of axicabtagene ciloleucel compared to SOC
- To evaluate the effect of axicabtagene ciloleucel on patient reported outcomes (PROs) and quality of life (QoL) compared to SOC

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3. STUDY OVERVIEW

3.1. Study Design

ZUMA-7 is a Phase 3 randomized, open-label, multicenter study evaluating the efficacy of axicabtagene ciloleucel versus SOC in adult subjects with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBLC). Adult subjects with r/r DLBCL after first-line rituximab and anthracycline-based chemotherapy will be randomized in a 1:1 ratio to receive axicabtagene ciloleucel or SOC. Randomization will be stratified by response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted International Prognostic Index (IPI) (0 to 1 versus 2 to 3) as assessed at the time of screening.

For subjects randomized to the control arm of the study, SOC will consist of a protocol-defined, platinum-based salvage combination chemotherapy regimen. Subjects who respond to second-line chemotherapy should proceed to high-dose therapy (HDT) and autologous stem cell transplant (ASCT).

An independent Data Safety Monitoring Board (DSMB) will meet every 6 months after the first subject is randomized to review safety data and will review safety and efficacy data at the time of the planned interim futility analysis of EFS. The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk versus benefit. The DSMB may meet more often as needed.

Subjects will be evaluated by the investigator for disease response and progression and blinded central review per the Lugano Classification {Cheson 2014}. Subjects in both treatment arms are to be assessed for response and progression at the same times relative to randomization: Day 50, Day 100, Day 150, Month 9, and then every 3 months thereafter until Month 24. Subjects will be assessed every 6 months from Month 30 to Month 60. New non-protocol-specified therapy for disease will be recorded for all subjects randomized until a subject completes the long-term follow-up period, is considered lost to follow-up, withdraws consent, or has died. Survival status will be ascertained at each clinic visit up through Month 9 after which subjects will be contacted every 3 months up through Month 24 and then every 6 months thereafter until Month 60.

The primary analysis of EFS will be conducted when all subjects have had the opportunity to be followed for the Month 9 disease assessment and approximately 250 EFS events have been observed. The acceptable lower limit for the observed total EFS events is 225, which is to maintain the power for the primary analysis of EFS to within 5% of the targeted 90%. One interim analysis of EFS is planned after 135 EFS events have been observed. This interim analysis is for safety and futility. The DSMB will review the futility analysis and make a recommendation on trial conduct based on an evaluation of risk versus benefit. The interim and primary analyses of EFS will be based on blinded central review of progression and censoring times. The primary analysis of ORR will occur at the time of the primary analysis of EFS. The primary analysis of OS will occur after 210 OS events have been observed or no later than

5 years after the first subject is randomized. Details on the testing methods and interim analyses are provided in Sections 3.3 and 3.4.

3.2. Hypothesis

The hypothesis for this study is that axicabtagene ciloleucel will prolong EFS compared to SOC therapy in adult subjects with relapsed/refractory DLBCL. The hypothesized treatment effect corresponds to a 50% improvement in EFS.

3.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 350 subjects.

An EFS hazard ratio (test/control arm) of 0.67 is hypothesized in the full analysis set (FAS). Assuming an exponential distribution for EFS and a median EFS of 4 months in the SOC arm, this implies a 50% relative improvement in EFS and corresponds to median EFS of 4 versus 6 months (control versus test arm). The primary analysis is planned when approximately 250 EFS events have been observed; the study has been sized to achieve approximately 90% power at the 1-sided 2.5% significance level to detect a 50% improvement in EFS. The minimum effect size that can be determined to be statistically significant is an EFS hazard ratio of 0.79 or a 27% relative improvement in EFS. Further, assuming a concave accrual distribution with 50% of accrual in the last 33% of the accrual period of 24 months and a 10% rate (5% by Month 1 and cumulative 10% by Month 8) of loss to follow-up in the axicabtagene ciloleucel arm and 15% rate (10% by Month 1 and cumulative 15% by Month 8) of loss to follow-up in the SOC arm, it is anticipated that the event goal will be achieved if 350 subjects are randomized (175/arm) and will occur approximately 31 months after the first subject is randomized. One interim futility analysis of EFS will be conducted after 135 EFS events have been observed.

The study will have an overall alpha of 2.5% with 1-sided testing. To preserve the overall significance level, statistical testing of the primary and key secondary efficacy endpoints will follow a hierarchical scheme. EFS will be tested first at the primary EFS analysis. Conditional on a statistically significant improvement in EFS, ORR will be tested at the 2.5% level at the time of the primary EFS analysis. Conditional on demonstrating a statistically significant improvement in EFS and ORR at the time of the primary EFS analysis, OS will be tested up to 3 times at an overall alpha level of 2.5%. If a statistically significant improvement in EFS is not demonstrated at the time of the primary EFS analysis, hierarchical testing of ORR and OS will not occur. If a statistically significant improvement in EFS is demonstrated, but a statistically significant improvement in ORR is not demonstrated at the time of the primary EFS analysis, hierarchical testing of OS will not occur.

For the analysis of ORR, response rates of 36% and 78% in the control and test arms are assumed. ORR will be tested with a stratified (randomization factors) Cochran-Mantel-Haenszel (CMH) test at the 2.5% level among subjects in the FAS.

An OS hazard ratio of 0.73 is hypothesized in the FAS. Assuming an exponential distribution for OS and a median OS of 15.8 months in the control arm, this implies a 37% relative improvement in OS and corresponds to median OS of 15.8 versus 21.6 months. The primary OS analysis is planned when approximately 210 deaths have been observed or no later than 5 years after the first subject is randomized, with a first interim analysis of OS occurring at the time of primary EFS analysis and a second interim analysis when approximately 160 deaths have occurred or no later than 4 years after the first subject is randomized.

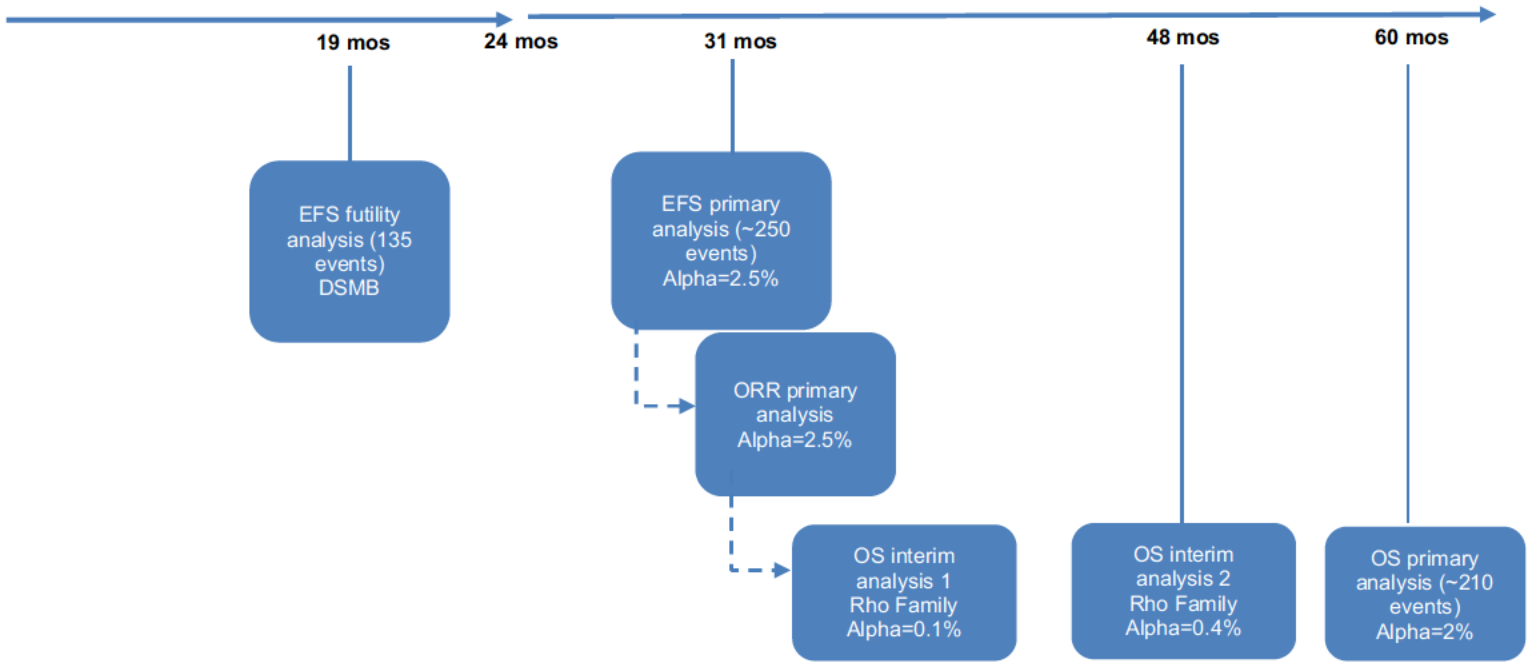
Stratified (randomization factors) log-rank tests will be used to test the null hypothesis of no difference in EFS and OS using an overall 1-sided alpha level of 2.5%. A stratified (randomization factors) CMH test will be used to test ORR at an overall 1-sided alpha level of 2.5%.

The EFS analysis is event-driven and will occur when the required number of events have been observed.

The study testing scheme is provided in Figure 1.

Figure 1. Study Testing Scheme

DSMB safety reviews Q6 months until the primary EFS analysis
Enrollment over 24 months



All testing will be performed at the 1 sided 2.5% level

Hierarchical testing of EFS, followed by ORR, followed by OS.

Three analyses of OS are planned; a first interim analysis at the time of the primary EFS analysis, a second interim analysis when approximately 160 deaths have occurred or no later than 4 years after the first subject is randomized, and a primary OS analysis when 210 deaths have been observed or no later than 5 years after the first subject is randomized.

EFS analysis is event driven and will occur when the required number of events have been observed regardless of anticipating timing.

The timing of the EFS, ORR, and OS analyses are described in Figure 1. The clinical study report (CSR) will be written at the time of the primary EFS analysis and will include results of the first interim analysis of OS. The study will continue to be conducted per the protocol, and the results of the second interim and primary analyses of OS will be written shortly after each analysis is completed.

3.4. Interim Analysis and Early Stopping Guidelines

3.4.1. Safety Interim Analysis

The DSMB will review safety data every 6 months from the time the first subject is randomized until the primary EFS analysis. Additionally, the DSMB will review safety and efficacy data at the time of the planned interim EFS analysis. The DSMB will also review serious adverse event (SAE) information and suspected unexpected serious adverse reactions (SUSARs) on a regular basis throughout the study. The sponsor may request additional reviews by the DSMB if safety concerns are identified. The DSMB may meet more often as needed. Timing of DSMB meetings will be further specified in the DSMB charter; meetings may be combined as practical depending on accrual and analysis milestone times.

3.4.2. Efficacy Interim Analysis

One interim analysis of EFS and 2 interim analyses of OS are planned.

The interim EFS analysis is for futility and will occur when 135 EFS events have been observed. An O'Brien-Fleming spending function of the Lan-DeMets family will be used to allocate the type II error between the interim and primary analyses. Under the null hypothesis, the probability of stopping for futility at this interim analysis is approximately 60%. One hundred thirty-five (135) EFS events are anticipated to occur approximately 19 months after the first subject is randomized.

Conditional upon statistically significant tests of EFS and ORR at the primary EFS analysis, testing of OS will be performed. A first interim analysis of OS will occur at the time of the primary EFS analysis and a second interim analysis when approximately 160 deaths have occurred or no later than 4 years after the first subject is randomized. A spending function of the Rho family with parameter (rho 6) will be used to allocate the alpha between the 2 interim analyses of OS and the primary analysis of OS. Approximately 110 OS events and 160 OS events are anticipated at the time of the first and second interim OS analyses, respectively. The 1-sided alpha of 0.1% and 0.4% will be allocated at the first and second interim analysis of OS, respectively.

This procedure preserves the designated 1-sided alpha level of 0.025 and has approximately 90% power. EAST 6.4 was used to evaluate the operating characteristics of this design.

3.5. Statistical Assumptions

This trial will enroll patients with r/r DLBCL after first-line chemotherapy. Outcomes for this patient population treated with SOC have been described in {Crump 2014, Gisselbrecht 2010, Gisselbrecht 2012, Van Den Neste 2016, van Imhoff 2017}. EFS and OS in the control arm were simulated based on results from these studies and assuming exponential time to event distributions. Based on these simulations, the median EFS in the control arm is assumed to follow an exponential distribution with median 4.0 months, and the median OS in the control arm is assumed to follow an exponential distribution with median 15.8 months.

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

Primary endpoint: EFS with progression events and censoring per blinded central review.

Key secondary endpoints:

- ORR per blinded central review
- OS

Secondary endpoints:

- EFS with progression and censoring events based on investigator disease assessments
- PFS with progression and censoring events based on investigator disease assessments
- DOR
- mEFS
- Incidence of adverse events (AEs) and clinically significant changes in safety laboratory test values, including antibodies to axicabtagene ciloleucel
- Changes from screening to post-baseline in the global health status QoL scale and the physical functioning domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30)
- Changes from screening to post baseline in the Euro-QOL, five dimensions, five levels (EQ-5D-5L) index and visual analog scale (VAS) scores

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4.2. Covariates

The following baseline covariates may be used to examine efficacy in subgroups or covariate analyses:

- Geographic region (North America, Europe)
- Eastern Cooperative Oncology Group (ECOG) performance status at screening (0, 1)
- Age at randomization (≥ 65, < 65)
- Sex
- Race/ethnicity
- Response to first-line therapy (primary refractory, relapse ≤ 6 months of initiation of first-line therapy versus relapse > 6 and ≤ 12 months of initiating first-line therapy)
- Second-line age-adjusted IPI (0 to 1 versus 2 to 3) at time of screening
- Disease type (DLBCL, transformed follicular lymphoma [TFL])
- Molecular subgroup (germinal center B-cell like [GCB] vs. activated B-cell like [ABC], or GCB vs. non-GCB)
- Double hit (C-MYC genomic alterations and either BCL-2 or BCL-6 genomic alterations) status by fluorescence in situ hybridization (FISH)
- Triple hit (BCL-2, BCL-6, and C-MYC alterations) status by FISH

For the primary analysis of efficacy, the Interactive Voice/Web (X) Response System (IXRS) values of response to first-line therapy and second-line age-adjusted IPI will be used. Sensitivity analyses may be conducted with values collected in the clinical trial database (EDC). Covariate levels that are sparse (ie, less than 30 events for time to event analyses or subjects for ORR analyses) may be collapsed for purposes of statistical modeling. If this occurs, the strata for relapse ≤ 6 months of first-line therapy and relapse from 6 to 12 months of first-line therapy will be collapsed first.

The following baseline covariates may be used to examine safety in subgroups or covariate analyses:

- Geographic region (North America, Europe)
- ECOG performance status at screening (0, 1)
- Age at randomization (≥ 65, < 65)

- Sex
- Race/ethnicity
- Response to first-line therapy (primary refractory, relapse ≤ 6 months of first-line therapy versus relapse > 6 and ≤ 12 months of first-line therapy, or PD vs. SD vs. PR as best overall response)
- Second-line age-adjusted IPI (0 to 1 versus 2 to 3) at time of screening
- Disease type (DLBCL, TFL, etc.)

Axicabtagene ciloleucel arm only:

- Ferritin measured prior to conditioning chemotherapy (≤ median value, > median value)
- Ferritin at Treatment Day 0 (≤ median value, > median value)
- C-reactive protein (CRP) measured prior to conditioning chemotherapy (≤ median value, > median value)
- CRP at Treatment Day 0 (≤ median value, > median value)
- Absolute lymphocyte count (ALC) measured prior to conditioning chemotherapy (≤ median value, > median value)
- ALC at Treatment Day 0 (≤ median value, > median value)

The following non-baseline covariates may be explored for efficacy subgroup or covariate analyses:

- Best response on study
- Occurrence of stem cell transplant (SCT) at any time after randomization
- Commencement of any non-protocol-specified cancer therapy

When these covariates are used in time-to-event analyses, the time to the event will be counted from the measurement time of the covariate, not study randomization.

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

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment is defined as randomization (e.g., the assignment of a randomization number to a subject) into the study.

Study Day 0: Randomization Study Day 0 is defined as the day of randomization.

Treatment Day 0: In the axicabtagene ciloleucel arm, Treatment Day 0 is defined as the day the subject received the first axicabtagene ciloleucel infusion. The day prior to Treatment Day 0 will be Treatment Day 1. The day of randomization and any days after randomization and before Treatment Day 1 will be sequential and negative integer-valued.

In the SOC arm, Treatment Day 0 is defined as the day the subject underwent SOC. The day prior to Treatment Day 0 will be Treatment Day 1. The day of randomization and any days after randomization and before Treatment Day 1 will be sequential and negative integer-valued.

Leukapharesis period: The leukapharesis period is defined for the axicabtagene ciloleucel arm and is defined as the day (negative integer-valued) the subject undergoes leukapheresis calculated relative to Treatment Day 0.

Conditioning chemotherapy period: The conditioning chemotherapy period is defined for the axicabtagene ciloleucel arm and begins on the day of the first chemotherapy administration until the day immediately prior to the axicabtagene ciloleucel infusion. These days are numbered as sequential negative integer values relative to Treatment Day 0.

SOC and HDT therapy period: The SOC and HDT period are defined for the SOC arm and begin the day of the first chemotherapy administration until the day immediately prior to SCT. These days are numbered as sequential negative integer values relative to Treatment Day 0.

Re-treatment conditioning chemotherapy period: The re-treatment conditioning chemotherapy period is defined for the axicabtagene ciloleucel arm and begins on the day of the first chemotherapy administration of re-treatment until the day immediately prior to the axicabtagene ciloleucel re-treatment infusion. In the event that the axicabtagene ciloleucel re-treatment infusion is delayed, the numbering of the re-treatment conditioning chemotherapy period will remain relative to the axicabtagene ciloleucel re-treatment infusion.

Baseline: The baseline value is defined as the last value taken prior to randomization.

Study therapy:

- Axicabtagene ciloleucel arm: Study therapy is defined as conditioning chemotherapy or axicabtagene ciloleucel.

- SOC arm: Study therapy is defined as induction chemotherapy, total body irradiation (TBI) (given as part of conditioning for ASCT), conditioning chemotherapy for ASCT (HDT), and ASCT.

On-study: Time from randomization to the last date of contact.

End of study: This will occur after both of the following criteria are met:

- Axicabtagene ciloleucel arm: all subjects have been followed for 15 years post-randomization, have withdrawn consent, been lost to follow-up, or have died.

- SOC arm: all subjects have been followed for 5 years post-randomization, have withdrawn consent, been lost to follow-up, or have died.

Actual follow-up time: Actual follow-up time is calculated as the time from the date of randomization (Study Day 0) to the date of death, last date known alive, lost to follow-up, or withdrawal of consent, whichever is later.

Potential follow-up time: Potential follow-up time is defined as the time from the date of randomization (Study Day 0) to the data cutoff date for the analysis.

Follow-up time for response: Follow-up time for response is derived as the time from the date of randomization (Study Day 0) to the last disease assessment or censoring date. Follow-up time for response is derived using the reverse Kaplan-Meier approach in which the censoring times and event times are reversed to derive the median follow-up time.

5.2. Safety

Treatment-emergent adverse event (TEAE):

Axicabtagene ciloleucel arm: Any AE with onset on or after the axicabtagene ciloleucel infusion. For subjects receiving retreatment with axicabtagene ciloleucel, TEAEs after retreatment may be summarized separately.

SOC arm: Any AE with onset on or after the first dose of induction chemotherapy.

Deaths: All deaths that occur from randomization up through the end of study.

Adverse events of interest: AEs of interest for axicabtagene ciloleucel treatment include AEs in the categories of:

Important identified risks:

- cytokine release syndrome (CRS)
- neurologic toxicity
- infections
- cytopenias, including
    - neutropenia
    - thrombocytopenia
    - anemia
- hypogammaglobulinemia

Important potential risks:

- Secondary malignancies
- Tumor lysis syndrome
- Bone marrow failure
- Graft-versus-host-disease (GVHD)
- Replication competent retrovirus (RCR)
- Immunogenicity (anti-axicabtagene ciloleucel antibodies)

Neurological toxicity (Neurotoxicity): Neurological AEs are identified with a search strategy based on known neurologic toxicities associated with anti-CD19 immunotherapy {Topp 2015}. The search strategy focuses on central nervous system toxicity, without regard to temporal relationship and concomitant conditions (eg, CRS). Additionally, the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes 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. Neurologic toxicity will be reported separately from CRS.

Cytokine release syndrome (CRS): CRS as a syndrome (ie, a collection of individual symptoms) is identified via collection of the syndrome on a case report form specifically designed to collect CRS. Individual symptoms of CRS are separately collected on the AE log and are linked to the CRS syndrome. CRS syndrome severity is graded according to a modification of the grading system proposed by Lee {Lee 2014}. In the modified grading scale, neurologic AEs are not reported as part of the CRS syndrome; rather, they are reported on the AE log form separately based on specific symptoms per Common Terminology Criteria for Adverse Events (CTCAE).

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

- Thrombocytopenia will be identified using the standardized MedDRA query (SMQ) for haematopoietic thrombocytopenia (narrow search)
- Neutropenia will be identified using Kite Pharma, Inc. (hereafter referred to as Kite)-specified MedDRA search term (MST)
- Anemia (including aplastic anemia) will be identified using the SMQ haematopoietic erythropenia (broad search)

Subjects with cytopenias (neutropenia or thrombocytopenia or anemia) present on or after Day 30 post study treatment will be summarized separately by cell lineage.

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

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

B-cell aplasia: Laboratory data will be used to assess the incidence of B-cell aplasia. B-cell aplasia will be assessed using a qualified flow cytometry assay on cryopreserved subject peripheral blood mononuclear cells (PBMCs) and is defined as B cells < lower limit of quantitation (LLOQ). The LLOQ is defined as CD19+, CD20+, or double positive CD19+ and CD20+ events < 0.017 B cells as a percentage of viable leukocytes, with 10000 or more viable leukocyte events required in the assay.

Infections: Infections are identified as AEs within the system organ class of Infections and Infestations that occur on or after Treatment Day 0 and in MedDRA high-level group terms (HLGT) that capture events of:

- Bacterial infection, encompassing preferred terms within the MedDRA HLGT of

  Bacterial infectious disorders

  Chlamydial infectious disorders
- Viral infection, encompassing preferred terms within the MedDRA HLGT of viral infectious disorders
- Opportunistic infections, encompassing preferred terms within the MedDRA HLGT of

  Fungal infectious disorders

  Mycobacterial infectious disorders
- Other infections, encompassing preferred terms within the MedDRA HLGT of Infections pathogen unspecified

B-cell aplasia will be examined as part of the analysis of infections.

Secondary malignancy: Secondary malignancies are identified with the AEs that are coded into the system organ class of Neoplasms benign, malignant, and unspecified (including cysts and polyps) 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.

Graft-versus-host disease (GVHD): GVHD will be identified using a MST search strategy defined by Kite by using subsets of PT from HLGT of procedural related injuries and complications NEC and HLT of immune and associated conditions NEC.

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

Cardiac failure: Cardiac failure will be identified using the SMQ of cardiac failure. The narrow version of this SMQ will be used.

Cardiac arrhythmias: Cardiac arrhythmias will be identified using the SMQ of cardiac arrhythmias. The narrow version of this SMQ with selected broad SMQ preferred terms will be used.

Time to Onset of Event/Syndrome: Time to onset of an event/syndrome is defined as the time from Treatment Day 0 to the day of the first occurrence of the event/syndrome. Time to Onset of Grade 3 or Higher Events/Syndromes are defined in the same way, but restricted to Grade 3 or higher events/syndromes.

Duration of Event/Syndrome: The duration across all events is the last day of the last event - first day of the first event +1, regardless of whenever the events are consecutive, overlapping, or neither.

Durations of events will not be calculated for events that are ongoing at the time of the data cutoff date or subject death. For events defined by laboratory criteria, time to onset and duration will not be calculated. For events defined by both laboratory criteria and AEs, only the AE component will be used to define time to onset and duration.

5.3. Efficacy

Event-free survival (EFS): EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification {Cheson 2014}, commencement of new lymphoma therapy, or death from any cause. The following criteria will be used to further define events and event times:

- Subjects with established PR or CR and subsequently commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of documented disease progression will have EFS time defined as the time from randomization to the last evaluable disease assessment prior to the new lymphoma therapy

- Subjects with best response of SD and subsequently commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of documented disease progression will have EFS time defined as the time from randomization to the first time SD was established prior to the new lymphoma therapy

- Subjects who commence new lymphoma therapy (including radiotherapy, except for TBI as noted below) in the absence of any evaluable disease assessment will have the EFS event date imputed as the randomization date

- Subjects with best response of SD up to and including Day 150 assessment post randomization will be considered to have an EFS event. For such subjects, the EFS time will be defined as the time from randomization to the first time SD was established up to and including the Day 150 disease assessment

The following criteria will be used to further define censoring times:

- Subjects alive, in response, and with no new therapy will be censored at the last evaluable disease assessment

- Subjects with no evaluable disease assessment by Day 150 assessment post randomization will not be considered to have an EFS event, and the EFS time will be censored at the randomization date

- The EFS time for subjects in the axicabtagene ciloleucel arm who undergo ASCT in the absence of any documented progression or new therapy will be censored on the day of ASCT

- For subjects in the SOC arm, TBI, HDT, and ASCT that occur while the subject is in response from protocol-specified induction therapy will not be considered an EFS event. The EFS time for SOC arm subjects alive, progression-free, and with no new lymphoma therapy will be censored at the last evaluable disease assessment date

- At the time of the interim analysis of EFS, subjects who have not had the opportunity to be followed to the Day 150 disease assessment and who do not have an EFS event will be censored at the last evaluable disease assessment prior to Day 150

For the primary analysis of EFS, disease progression events and censoring times will be determined by blinded central review. Events of new therapy and death will be based on the clinical trial database.

A sensitivity analysis for EFS in which subjects in the axicabtagene ciloleucel arm who undergo ASCT while in an axicabtagene ciloleucel-induced response are imputed to have an EFS event at the time of ASCT will be performed.

Objective response rate (ORR): ORR is defined as the incidence of either a CR or a PR by the Lugano Classification {Cheson 2014}. All subjects who do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders.

- For the SOC arm, the derivation of the primary analysis of ORR will include all disease assessments until an EFS event, including any assessments obtained after SCT.

- For the axicabtagene ciloleucel arm, the derivation of the primary analysis of ORR will include disease assessments up to any new therapy (including ASCT)

For the primary analysis of ORR, disease responses will be determined by blinded central review.

Overall survival (OS): Overall survival is defined as the time from randomization to death from any cause. Subjects who have not died by the analysis data cutoff date will have survival time censored at their last date known to be alive. For subjects alive or dead after the data cutoff date, survival time will be censored at the data cutoff date.

Modified event-free survival (mEFS): mEFS is defined the same way as EFS, with the exception that having SD as the best response by Day 150 assessment post randomization will not be considered as an event. mEFS will be analyzed per blinded central review and per investigator disease assessments.

Progression-free survival (PFS): PFS is defined as the time from randomization to disease progression per Lugano Classification {Cheson 2014} as determined by investigator review or death from any cause. Subjects alive and not meeting the criteria for progression at the analysis data cutoff date will have PFS time censored at the last evaluable disease assessment. Subjects who receive subsequent new lymphoma therapy (with the exception of HDT, TBI for HDT, and SCT while in a protocol therapy-induced response) in the absence of documented disease progression will be censored at their last evaluable disease assessment date prior to the commencement of the subsequent new lymphoma therapy. SCT that occurs while a subject is in response from a protocol therapy will not be considered a PFS event, and such subjects will be censored for PFS at the last evaluable disease assessment prior to the SCT for subjects in the axicabtagene ciloleucel arm and will be censored at the last evaluable disease assessment date (including assessments after SCT) for subjects in the SOC arm for the primary analysis of PFS. Disease outcomes will be based on investigator assessment. A sensitivity analysis for PFS in which subjects in the axicabtagene ciloleucel arm who undergo SCT while in an axicabtagene ciloleucel-induced response are imputed to have a PFS event at the time of ASCT.

Duration of response (DOR): DOR is derived only among subjects who experience an objective response per Lugano Classification {Cheson 2014} as determined by blinded central review and is defined as the time from first response to disease progression per the Lugano Classification or death from any cause. Subjects not meeting the criteria for progression or death by the analysis data cutoff date will have DOR censored at their last evaluable disease assessment date. Subjects who receive subsequent new lymphoma therapy (with the exception of HDT, TBI for HDT, and SCT while in a protocol therapy induced response) in the absence of documented progression will have DOR censored at the last evaluable disease assessment prior to the commencement of the new lymphoma therapy. For the primary analysis of DOR, DOR will be censored at the last evaluable disease assessment date prior to the SCT for subjects undergoing SCT while in protocol therapy induced response in the axicabtagene ciloleucel arm, and will be censored at the last evaluable disease assessment date (including assessments after SCT) for subjects in the SOC arm. A sensitivity analysis for DOR in which subjects in the axicabtagene ciloleucel arm who undergo ASCT while in an axicabtagene ciloleucel-induced response are imputed to have an event at the time of ASCT.

Time to next therapy: Time to next therapy is defined as the time from the randomization date to the start of the subsequent new lymphoma therapy or death from any cause. Subjects who have not received subsequent new therapy and are still alive will be censored at the last contact date.

6. ANALYSIS SUBSETS

The following analysis sets are defined.

6.1. Full Analysis Set (FAS)

The FAS consists of all randomized subjects. The primary analysis of EFS, ORR, PFS, and OS will be conducted on the FAS. The FAS will exclude some disease assessments as described in the definition of the endpoints for ORR. Subjects will be analyzed based on randomized treatment arm.

6.2. Safety Analysis Set

The safety analysis set is defined as the subset of all randomized subjects who receive at least 1 dose of axicabtagene ciloleucel as protocol therapy or SOC chemotherapy as protocol therapy. Subjects will be analyzed by the protocol therapy received.

6.3. Safety Analysis Set - ASCT

The safety analysis set ASCT is defined as the subset of subjects randomized to the SOC arm who undergo transplant as part of protocol therapy.

6.4. QoL Analysis Set

The QoL analysis set is defined as the subset of subjects in the FAS who have a baseline and Day 150 post-randomization QoL assessment.

6.5. Retreatment Analysis Sets

For any subjects in the axicabtagene ciloleucel arm who undergo retreatment, safety and efficacy will be examined in the set of subjects who receive any dose of axicabtagene ciloleucel as retreatment.

6.6. Subgroup Analysis Sets

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

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

7.1. Safety Interim Analyses

The DSMB will review safety data every 6 months from the time the first subject is randomized until the primary EFS analysis. Additionally, the DSMB will review safety and efficacy data at the time of the planned interim EFS analysis. The DSMB will also review SAE information and SUSARs on a regular basis throughout the study. The sponsor may request additional reviews by the DSMB if safety concerns are identified. The DSMB may meet more often as needed.

7.2. Efficacy Interim Analyses

One interim analysis of EFS and 2 interim analyses of OS are planned. The DSMB will review the interim analysis of EFS.

The interim EFS analysis is for futility and will occur when 135 EFS events have been observed. An O'Brien-Fleming spending function of the Lan-DeMets family will be used to allocate the type II error between the interim and primary analyses. Under the null hypothesis, the probability of stopping for futility at this interim analysis is approximately 60%. One hundred thirty-five (135) EFS events are anticipated to occur approximately 19 months after the first subject is randomized.

Conditional upon statistically significant tests of EFS and ORR at the primary EFS analysis, testing of OS will be performed. A first interim analysis of OS will occur at the time of the primary EFS analysis and a second interim analysis when approximately 160 deaths have occurred or no later than 5 years after the first subject is randomized. A spending function of the Rho family with parameter (rho 6) will be used to allocate the alpha between the interim analysis of OS and the primary analysis of OS with 0.1% and 0.4% at the first and second interim OS analyses respectively and 2% at the primary analysis of OS. Approximately 110 and 160 OS events are anticipated at the time of the first and second interim OS analyses, respectively.

7.3. Access to Aggregate and Subject-level Data and Individual Subject Treatment Assignments

This study is open label. Subjects, the study sponsor, and investigators will be aware of subject treatment assignments. Data handling procedures designed to maintain the trial credibility and validity in this study will be described in the Trial Integrity Document.

An independent statistician will perform the interim safety and efficacy analyses and provide these reports to the DSMB. Members of the DSMB and independent statistician will not have any direct contact with study center personnel or subjects. The DSMB will communicate recommendations to Kite in accordance with the DSMB charter.

8. DATA SCREENING AND ACCEPTANCE

8.1. General Principles

The database will be subject to the edit checks outlined in the Data Management Plan and additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analyses and the final database lock. For interim analyses, snapshots may include data that have not passed all data cleaning procedures at the time the data are extracted for snapshot.

8.2. Electronic Transfer and Archival of Data

The database for this study will be a Medidata RAVE system, managed and maintained by Kite or designee. Raw data, study data tabulation model (SDTM) data, and analysis data model (ADaM) datasets will be generated by Kite or designee and will be archived for all planned analyses. Any additional unplanned analyses that occur after the primary analyses 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.

Data from the central pathology laboratory, the product characteristics central laboratory assessment of subject serum samples (CAR T-cell levels in the peripheral blood, antibody assays, replication-competent retrovirus [RCR] testing), and central radiology review will be generated from contract laboratories and Kite. These data will be transferred to Kite and held in a peripheral directory and not built into the clinical trial database. At the time these data are required for analyses, they may be merged with the SDTM and ADaM datasets.

8.3. Handling of Missing and Incomplete Data

8.3.1. Efficacy

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

8.3.2. Safety

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

8.4. Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will include violations of eligibility criteria and use of exclusionary medication during the study. Lack of protocol compliance will be evaluated by summarizing the subject incidence of important protocol deviations. High rates of important protocol deviations may indicate bias.

Endpoints derived from investigator assessment of radiologic scans and disease assessments may be subject to assessment time bias due to unscheduled or off-schedule disease assessments per the protocol specified assessment times. The frequency and timing of scheduled and unscheduled tumor assessments will be tabulated by treatment arm. Sensitivity analyses will be conducted in which the time of detection of progressive disease is moved forward and backward to the closest scheduled assessment days.

The concordance between investigator and central review of radiologic scans and disease assessments will be summarized.

8.5. Outliers

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

8.6. Distributional Characteristics

A Cox regression model stratified by the randomization stratification factors will be used as the primary method to obtain estimates of the EFS and OS treatment effect. This is a semi-parametric model that assumes that the EFS hazards within each stratum for the 2 treatment groups are proportional over time. Section 9.5.1.1 provides details on the means by which this assumption will be assessed and the alternative analyses that may be performed if those assumptions are violated.

A stratified CMH test will be used to compare the observed response rates between the treatment arms. The CMH test produces valid results only if there is no substantial change in the magnitude and/or direction of the relationship between response and treatment arm across strata. To evaluate this assumption, the stratum-specific odds ratios describing the relationship between response and treatment arm study will be calculated along with exact 95% confidence intervals. The Breslow-Day test of the null hypothesis of homogeneity of the odds ratios across strata will be used.

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. The software and version used to generate analyses will be indicated in the archived documentation.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

The goal of the primary statistical analysis of the study is to test the difference in EFS between subjects treated with axicabtagene ciloleucel and subjects treated with SOC with a stratified log rank test. The primary analysis of EFS will be conducted when all subjects have had the opportunity to be followed for the Month 9 disease assessment, and approximately 250 EFS events have been observed. The acceptable lower limit for the observed total EFS events is 225, which is to maintain the power for the primary analysis of EFS to within 5% of the targeted 90%. If more than 250 EFS events are observed at the time of the data cutoff for the primary analysis, all observed events will be used in the analysis. At this time, the CSR will be written and will include results of the first interim analysis of OS. The study will continue to be conducted per the protocol, and the results of the second interim and primary analyses of OS will be written shortly after each analysis is completed.

Significance levels will be 2-sided unless stated otherwise. A 2-sided 95% confidence interval for the EFS treatment hazard ratio (axicabtagene ciloleucel relative to SOC) will be obtained from a Cox proportional hazards model stratified by the randomization stratification factors.

Descriptive statistics including confidence intervals, if appropriate, will be calculated for the study endpoints. Kaplan-Meier (KM) estimates will be provided for time-to-event endpoints.

9.2. Subject Accountability

The number of subjects screened, enrolled, leukapheresed, and treated with study therapy will be summarized. The reasons for discontinuing treatment and the disease assessment and survival follow-up periods will be summarized.

Summaries of actual and potential follow-up time will be provided.

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

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

9.3. Important Protocol Deviations

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

9.4. Demographic and Baseline Characteristics

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

- Geographic region (North America, Europe, Israel)
- ECOG performance status at screening (0, 1)
- Age at randomization (≥ 65, < 65)
- Sex
- Race/ethnicity
- Response to first-line therapy (primary refractory, relapse ≤ 6 months of initiation of first-line therapy versus relapse > 6 and ≤ 12 months of initiating first-line therapy, or PD vs. SD vs. PR as best overall response)
- Second-line age-adjusted IPI (0 to 1 versus 2 to 3) at time of screening
- Disease type (DLBCL, TFL, etc.)
- Molecular subgroup (germinal center B-cell like [GCB] vs. activated B-cell like [ABC], or GCB vs. non-GCB)
- Double hit (C-MYC alterations and either BCL-2 or BCL-6 alterations) status by FISH
- Triple hit (BCL-2, BCL-6, and C-MYC alterations) status by FISH

9.5. Efficacy Analyses

Efficacy analyses will be conducted on the FAS analysis sets as described in Section 6. For the primary analysis of EFS, ORR, and DOR, the blinded central assessment of disease status per Lugano Classification {Cheson 2014} will be used. Sensitivity analyses will be conducted with disease assessments based on the investigator review per Lugano Classification {Cheson 2014}.

For the primary analysis of efficacy, the IXRS values of response to first-line therapy and second-line age-adjusted IPI will be used. Sensitivity analyses may be conducted with values collected in EDC. Covariate levels that are sparse (ie, fewer than 30 events for time-to-event analyses or subjects for ORR analyses) may be collapsed for purposes of statistical modeling. If this occurs, the strata for relapse ≤ 6 months of first-line therapy and relapse from 6 to 12 months of first-line therapy will be collapsed first.

For subjects retreated with axicabtagene ciloleucel, disease assessments obtained prior to retreatment, but not disease assessment obtained after retreatment, will be included in the primary summaries of objective response, best response, DOR, and PFS. The subject's overall survival time will be derived from the last date known alive regardless of retreatment or subsequent therapy.

9.5.1. EFS

9.5.1.1. Primary Analysis of EFS

The analysis of EFS will be conducted on the FAS.

A stratified (randomization stratification factors) log-rank test will be used for the primary comparison of EFS.

Additionally, stratified (randomization factor) Cox regression models will be used to provide the estimated EFS hazard ratio and 2-sided 95% confidence intervals for axicabtagene ciloleucel relative to SOC. The median EFS time and event-free rates at 3-month intervals will be provided. The Breslow method and the Efron method will be used to handle the ties for the Cox regression models.

Non-proportionality among the treatment groups will be assessed by comparing the standardized martingale residuals over time to a normal distribution (SAS PHREG ASSESS option) {Lin 1993}. This comparison will be performed at the 5% level. A plot of the standardized residuals over time will be provided. If the comparison of the standardized martingale residuals over time is significant, a piece-wise Cox model will be used for the analysis. For the stratified piece-wise Cox model, 2 or more equal length intervals of length 12 weeks will be considered {Collett 2003}. This will include 1 scheduled tumor assessment in each interval. These models will allow estimation of the overall as well as within interval treatment hazard ratio. Additional sensitivity analyses may also be considered with alternative interval selection. The hazard ratio for relevant time point differences and intervals over which the proportional hazards assumption holds will be presented. The overall log hazard ratio will be calculated from the weighted average of the interval log hazard ratios. The weight for each interval log hazard ratio estimate will be inversely proportional to the variance of the interval log hazard ratio estimate. If there are intervals where one or more stratum is too sparse, the stratified piece-wise Cox model will be collapsed as specified for the primary analysis.

KM curves will be presented, and KM estimates and 2-sided 95% confidence intervals will be calculated for event time quartiles, event-free rate at 3-month intervals, and for the difference in event-free rates between treatment arms at these times. The primary analysis of EFS will utilize the stratification factors as collected via IXRS; a sensitivity analysis will be performed that utilizes the stratification factors as collected on the CRF. In addition, the un-stratified analyses will be conducted for EFS as a sensitivity analysis.

9.5.1.2. Subgroup Analyses of EFS

The consistency of the treatment effect on the EFS hazard ratio for axicabtagene ciloleucel versus SOC will be examined by estimating Cox model hazard ratios within meaningful subsets defined by the baseline covariates in Section 4.2. Non-proportionality may be assessed as described in Section 9.5.1.1. A forest plot of the hazard ratios across subsets will be provided.

9.5.1.3. Assessment Time Bias

Sensitivity analyses of EFS will be performed to assess ascertainment time bias in disease progression as follows:

- Progression events that occur between scheduled assessments will be moved forward to the next scheduled assessment after the observed progression.
- Progression events that occur between scheduled assessments will be moved backward to the last scheduled assessment prior to the progression.
- EFS events that occur after more than one missed visit will be censored at the last evaluable disease assessment or visit prior to the observed progression.

9.5.1.4. Additional Sensitivity Analyses of EFS

A sensitivity analysis for EFS in which subjects in the axicabtagene ciloleucel arm who undergo ASCT while in an axicabtagene ciloleucel-induced response are imputed to have an EFS event at the time of ASCT will be performed.

9.5.1.5. Investigator Assessment

EFS based on investigator disease assessments will be analyzed with the same methods as EFS per blinded central review. The concordance of progression events and EFS time per the investigator and per blinded central review will be summarized.

The tables that define EFS and censoring rules for the primary efficacy analysis and planned sensitivity analyses are provided in Appendix 2.

9.5.2. Analyses of Objective Response

9.5.2.1. Primary Analysis of ORR

The analysis of ORR will be conducted on the FAS and will be based on central blinded disease assessments. The subject incidence of objective response and best response will be summarized. An exact binomial 2-sided 95% confidence interval will be generated for the ORR and best response rates for each treatment arm. Wilson's score method with continuity correction will be used to calculate 95% confidence intervals for the difference in ORRs {Newcombe 1998} between treatment arms.

Conditional upon demonstrating a statistically significant improvement in EFS, testing of ORR will be performed with a stratified (randomization factor) CMH test for the common odds ratio of response.

9.5.2.2. Subgroup Analyses of ORR

Odds ratios for ORR will be assessed in subgroups defined by covariates in Section 4.2. A forest plot of response and CR rates by subgroups will be generated.

9.5.2.3. Investigator Assessment of ORR

ORR based on investigator disease assessments will be analyzed with the same methods as ORR. The concordance of response per the investigator and per blinded central review will be summarized.

9.5.3. Analyses of Overall Survival

The analysis of OS will be conducted on the FAS. The analysis of OS will be as per the analysis of EFS, except that sensitivity analyses for assessment time bias will not apply.

A stratified (randomization stratification factors) log-rank test will be used for the primary comparison of OS. Additionally, stratified (randomization factor) Cox regression models will be used to provide the estimated OS hazard ratio and 2-sided 95% confidence intervals for axicabtagene ciloleucel relative to SOC. The median OS time and event-free rates at 6-month intervals will be provided.

Sensitivity analyses of OS to address the confounding effect from treatment switching will be conducted using the Rank Preserving Structural Failure Time Model by {Robins 1991} with g-estimation and with the iterative parameter estimation algorism, and Inverse Probability of Censoring Weights, and 2-stage cox regression model, and other exploratory treatment switching adjustment methods.

OS hazard ratios will be assessed in subgroups defined by covariates in Section 4.2.

9.5.4. Analyses of Progression-free Survival, Duration of Response, and Time to Next Therapy

The analysis of PFS, DOR, and time to next therapy will be performed using the same methods as the analysis of EFS, with p-values from the log-rank test descriptive.

The analysis of PFS will be performed on the FAS. The analysis of DOR will be conducted on the FAS, with the exceptions noted in the definition of DOR.

9.6. Safety Analyses

Among subjects in the safety analysis set, all AEs will be reported from randomization up through the Day 150 post-randomization visit or change in lymphoma therapy, whichever occurs first. After the Day 150 visit, only targeted SAEs will be reported up to 5 or 15 years for SOC or axicabtagene ciloleucel arms, respectively, or until disease progression, whichever occurs first.

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 MedDRA at the time of each analysis. The version of the MedDRA may vary over time because the current version in use is updated. The severity of AEs will be graded using the National Cancer Institute (NCI) CTCAE version 4.03 or above. CRS will be graded using a modified CRS grading scale developed by Lee et al {Lee 2014}. The incidence and severity of CRS will be reported as a syndrome with severity per Lee et al. Individual symptoms associated with CRS will be graded per CTCAE version 4.03 or above.

AEs and deaths due to disease progression will be denoted as such on CRFs.

Subjects enrolled, but not dosed with study therapy, 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 AE summaries.

9.6.1. Adverse Events

A summary of the subject incidence of key AEs (any, worst severity, serious, related, CRS, NE) will be provided.

The subject incidence of the following AEs, serious AEs, and Grade 3 or higher AEs will be tabulated for:

- All TEAEs
- All AEs related to conditioning chemotherapy (for axicabtagene ciloleucel arm only)
- All TEAEs related to axicabtagene ciloleucel (for axicabtagene ciloleucel arm only)
- All SOC chemotherapy-related TEAEs (for SOC arm only)
- All ASCT-related TEAEs (for SOC arm only)
- Fatal TEAEs
- TEAEs of interest, including identified and potential risks

Summary statistics for the onset time, duration, and resolution of TEAEs of interest will be provided.

The subject incidence of deaths will be provided.

A subject listing of deaths and SAEs (including narratives) will be provided.

Subgroup analyses of TEAEs may be generated for the covariates listed in Section 4.2.

Besides TEAEs, the subject incidence of the following AEs by PT and severity will also be tabulated:

- AEs related to leukapheresis (for axicabtagene ciloleucel arm only)

9.6.2. Laboratory Test Results

Laboratory results will be graded according to NCI CTCAE version 4.03 or above. Laboratory data collected at baseline and throughout the axicabtagene ciloleucel treatment period or SOC and HDT therapy period will be summarized. Change from baseline to each visit at post-baseline will be presented for select analytes. The incidence of worst CTCAE grade post Treatment Day 0 by grade for all analytes will be provided. Additional laboratory tables for subjects who had worsening grade change from the last assessment prior to Treatment Day 0 to post Treatment Day 0 may be generated by the worst post-Treatment Day 0 CTCAE grade.

9.6.3. Anti-Axicabtagene Ciloleucel Antibodies

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

9.6.4. Replication Competent Retrovirus (RCR)

The subject incidence of RCR detected in blood samples will be tabulated overall and by assessment time. The persistence of RCR over time will be summarized.

9.6.5. Exposure to Study Treatment and Product Characteristics

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

- Total bovine serum albumin (BSA)-adjusted dose of cyclophosphamide
- Total BSA-adjusted dose of fludarabine
- Total dose of SOC chemotherapy
- Total dose of HDT for ASCT
- Weight-adjusted dose of axicabtagene ciloleucel

- Number and percentage of subjects who received a dose of axicabtagene ciloleucel within +/- 10% of the planned dose
- Total CAR T cells of the axicabtagene ciloleucel infusion
- Total T cells of the axicabtagene ciloleucel infusion
- Transduction ratio
- Percentages of CD4 and CD8 T cells
- Percentages of T-cell memory phenotypes

The analysis by patient demographics (age, sex, etc.) as well as by tumor burden may be provided.

Separate summaries will be presented for the second administration of axicabtagene ciloleucel for subjects in the safety retreatment analysis set.

9.6.6. Exposure to Concomitant Medications and Procedures

The subject incidence of concomitant medications will be provided and summarized by medication category (general, steroids, tocilizumab, vasopressors, nonsteroidal immunosuppressive agents, and immunoglobins) and WHO Drug coded term.

9.7. Health-related Quality of Life

Changes in EORTC QLQ-C30 domains from screening to the Day 150 post-randomization visit will be summarized with descriptive statistics.

Changes in the EQ-5D-5L index and VAS scores from screening to the Day 150 post-randomization visit will be summarized with descriptive statistics.

Further model-based analyses of these endpoints will be described in a supplemental statistical analysis plan.

9.8. Subsequent Lymphoma Therapy

The incidence and type (by WHO Drug coded term and categories) of subsequent lymphoma therapy and non-protocol-specified SCT (autologous, allogeneic) will be summarized.

9.9. Schedule of Study Treatment

Summary statistics will be provided for the following durations (for axicabtagene ciloleucel arm only):

- Days from leukapheresis to administration of axicabtagene ciloleucel
- Days from leukapheresis to axicabtagene ciloleucel product release
- Days from leukapheresis to receipt of axicabtagene ciloleucel at the study site
- Duration of hospitalization for the axicabtagene ciloleucel infusion

9.10. CAR T Cells Measured in Peripheral Blood

Summary statistics for the level of CAR T cells in serum following axicabtagene ciloleucel infusion will be provided for CAR T cells measured at Treatment Day 1, 3, and 7, Study Days 50, 100, and 150. The maximum CAR T cell level attained, the time at which the maximum level was attained, and the time at which there were no detectable CAR T cells in the serum will be summarized. The area under the curve (AUC) of CAR T cell levels from day 0 to day 28 and the peak value of CAR T cell levels from day 0 to day 28 will be summarized and may be used in subgroup analyses.

CCI [redacted]

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10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

No changes to protocol-specified analyses have been made.

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12. APPENDICES

Appendix 1. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates

The following data will be imputed using the following algorithm (refer to Table 1):

- AE start dates
- Deaths (see exceptions below)
- Concomitant medications start dates
- Subsequent new lymphoma therapy start dates

Table 1. Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date: Complete *yyyymmdd* < Treatment Day 0	Complete *yyyymmdd* ≥ Treatment Day 0	Partial *yyyymm* < Treatment Day 0 *yyyymm*	Partial *yyyymm* ≥ Treatment Day 0 *yyyymm*	Partial *yyyy* < Treatment Day 0 *yyyy*	Partial *yyyy* ≥ Treatment Day 0 *yyyy*	Missing
Partial *yyyymm*	**Treatment Day 0** *yyyymm*	2	1	2	1	n/a	1	1
	≠ **Treatment Day 0** *yyyymm*		2		2	2	2	2
Partial *yyyy*	Treatment Day 0 *yyyy*	3	1	3	1	n/a	1	1
	≠ Treatment Day 0 *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 impute the date of Treatment 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:

- 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.

Appendix 2. Planned Event and Censoring Rules for the EFS analysis

Table 2. Primary Analysis of EFS

Circumstance	Treatment Arm	Event / Censored	Date of Event / Censoring
Disease progression at planned disease assessment, prior to initiation of NALT or ASCT	Both	Event	Progression date
Disease progression in between planned disease assessments, prior to NALT or ASCT	Both	Event	Progression date
Subject with PR or CR and subsequently received NALT in the absence of disease progression	Both	Event	Last evaluable disease assessment date prior to NALT
Subject with best response of SD and subsequently received NALT in the absence of disease progression	Both	Event	Date of the first time SD was established prior to NALT
NALT in the absence of any evaluable disease assessment	Both	Event	Randomization date
Subject with best response of SD by Day 150 assessment post randomization in the absence of documented progression or death or NALT	Both	Event	Date of the first time SD was established up to and including Day 150 assessment
ASCT while in an axicabtagene ciloleucel induced response	Axicabtagene ciloleucel	Censored	ASCT Date
Remain event free after ASCT	SOC	Censored	Last evaluable disease assessment date
Remain event free without ASCT	Both	Censored	Last evaluable disease assessment date
Disease progression or death after ASCT	SOC	Event	Death or PD Date
Death without documented prior event	Both	Event	Death Date
Withdrawal of consent or lost to follow up prior to documented event	Both	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

Note: NALT next anti lymphoma therapy, it is defined the same as subsequent new lymphoma therapy
Note: For subjects without any evaluable disease assessment and any EFS event at the time of analysis, their EFS will be censored at the date of the randomization. Day 150 disease assessment includes any disease assessment up through the protocol specified window (+/ 14 days; up through Day 164).

Table 3. (Sensitivity Analysis 1): progression events that occur in between scheduled assessments will be moved forward to the next scheduled assessment after the observed progression

Circumstance	Treatment Arm	Event / Censored	Date of Event / Censoring
Disease progression in between planned disease assessments, prior to NALT or ASCT	Both	Event	First scheduled assessment after the observed progression
For all other circumstances, follow the same derivation rule as the primary analysis of EFS.			

Table 4. (Sensitivity analysis 2): progression events that occur in between scheduled assessments will be moved backward to the last scheduled assessment prior to progression

Circumstance	Treatment Arm	Event / Censored	Date of Event / Censoring
Disease progression in between planned disease assessments, prior to NALT or ASCT	Both	Event	Last scheduled assessment prior to the observed progression
For all other circumstances, follow the same derivation rule as the primary analysis of EFS.			

Table 5. (Sensitivity analysis 3): EFS events that occur after more than one missed disease assessment visit will be censored at the last evaluable disease assessment prior to the observed progression

Circumstance	Treatment Arm	Event / Censored	Date of Event / Censoring
Disease progression at planned disease assessment, prior to initiation of NALT or ASCT	Both	Event*	Progression date**
Disease progression in between planned disease assessments, prior to NALT or ASCT	Both	Event*	Progression date**
Subject with PR or CR and subsequently received NALT in the absence of disease progression	Both	Event*	Last evaluable disease assessment date prior to NALT **
Subject with best response of SD and subsequently received NALT in the absence of disease progression	Both	Event	Date of the first time SD was established prior to NALT

Circumstance	Treatment Arm	Event / Censored	Date of Event / Censoring
NALT in the absence of any evaluable disease assessment	Both	Event	Randomization date
Subject with best response of SD by Day 150 assessment post randomization in the absence of documented progression or death or NALT	Both	Event	Date of the first time SD was established up to and including Day 150 assessment
ASCT while in an axicabtagene-ciloleucel induced response	Axicabtagene ciloleucel	Censored	ASCT Date
Remain event-free after ASCT	SOC	Censored	Last evaluable disease assessment date
Remain event-free without ASCT	Both	Censored	Last evaluable disease assessment date
Disease progression or death after ASCT	SOC	Event*	Death or PD Date**
Death without documented prior event	Both	Event*	Death Date***
Withdrawal of consent or lost to follow-up prior to documented event	Both	Censored	Date of last evaluable disease assessment prior to data cutoff for analysis

Note: NALT next anti lymphoma therapy, it is defined the same as subsequent new lymphoma therapy
Note: For subjects without evaluable disease assessment or any EFS event at the time of analysis, their EFS will be censored at the date of the randomization. Day 150 disease assessment includes any disease assessment up through the protocol specified window (+/ 14 days; up through Day 164).
* if the progression, NALT, or death occurs after more than one missed disease assessment, this will be censored.
** if the progression, NALT, or death occurs after more than one missed disease assessment, the censor time will be at the last evaluable disease assessment prior to the observed progression, NALT, or death.

Table 6. (Sensitivity Analysis 4): subjects in the axicabtagene ciloleucel arm who undergo ASCT while in axicabtagene induced response are imputed to have an EFS event at the time of ASCT

Circumstance	Treatment Arm	Event / Censored	Date of Event / Censoring
ASCT while in an axicabtagene-ciloleucel induced response	Axicabtagene ciloleucel	Event	ASCT Date
For all other circumstances, follow the same derivation rule as the primary analysis of EFS.			

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 subsequent new lymphoma therapy
- Subsequent SCT date
- Leukapheresis dates
- Conditioning chemotherapy administration dates
- SOC therapy administration dates
- HDT administration dates
- Axicabtagene ciloleucel infusion dates (including retreatment)
- SCT dates
- Computed tomography (CT) scan dates
- Positron emission tomography (PET) scan dates
- Clinical symptoms of lymphoma assessment dates
- Target lesion assessment
- Non-target lesion assessment
- New lesion assessment
- Disease response assessment
- Long-term follow-up subject status date where status ”alive”
- End of treatment disposition where status is not equal to death, lost to follow-up
- End of post-treatment assessment period where status is not equal to death, lost to follow-up
- End of study data where end of study reason is not equal to death, lost to follow-up