STATISTICAL ANALYSIS PLAN

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	Axicabtagene ciloleucel
Protocol:	A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)
Version Number:	Version 3.0
Release Date:	08 July 2019
Replaces Previous Version(s):	Version 2.0; dated 28 August 2016

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis data model
AE	Adverse event
ASCT	Autologous stem cell transplant
CAR	Chimeric antigen receptor
CIF	Cumulative incidence
CR	Complete response
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Event
DLBCL	Diffuse large B cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
DORR	Duration of response to retreatment
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EQ-5D	European quality of life-5 dimensions
FAS	Full analysis set
HGBCL	High grade B-cell lymphoma
HLGT	High-level group term
IRRC	Independent Radiology Review Committee
mITT	Modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MST	MedDRA search terms
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PMBCL	Primary mediastinal B cell lymphoma
PR	Partial response
RCR	Replication-competent retrovirus
SAE	Serious adverse event
SCT	Stem cell transplant
SD	Stable disease
SDTM	Study data tabulation model
SMQ	Standardized MedDRA query
SMS	Safety management study

Abbreviation	Definition
SOC	System organ class
SPD	Sum of the product of the diameter
TEAE	Treatment-emergent adverse event
TFL	Transformed follicular lymphoma
TLS	Tumor lysis syndrome
VAS	Visual analogue scale

1. INTRODUCTION

This statistical analysis plan provides the pre-specification and details for the statistical analyses outlined within protocol KTE-C19-101 entitled "A Phase 1-2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (NHL)". The scope of this document is to provide details on the planned interim, primary, and final analyses.

2. OBJECTIVES

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

The primary objective of Phase 2 pivotal study is to evaluate the efficacy of axicabtagene ciloleucel, as measured by objective response rate (ORR) in subjects with diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL). Secondary objectives will include assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints.

The primary objective of the Phase 2 safety management study is to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, or prophylactic steroid use on the rate and severity of cytokine release syndrome (CRS) and neurologic toxicities. The key secondary objectives include assessment of efficacy, levels of anti-CD19 chimeric antigen receptor (CAR) T cells, cytokines in blood/serum, and the change in European Quality of Life-5 Dimensions (EQ-5D) scores from baseline to Month 6.

3. STUDY OVERVIEW

3.1. Study Design

Study KTE-C19-101 is a Phase 1-2 multicenter, open-label study evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with refractory NHL. Study KTE-C19-101 will be separated into 3 distinct parts designated as Phase 1 study, Phase 2 pivotal study (Cohort 1 and Cohort 2), and Phase 2 safety management study (SMS) (Cohort 3, Cohort 4, Cohort 5 and Cohort 6).

Each subject will proceed through the following study periods:

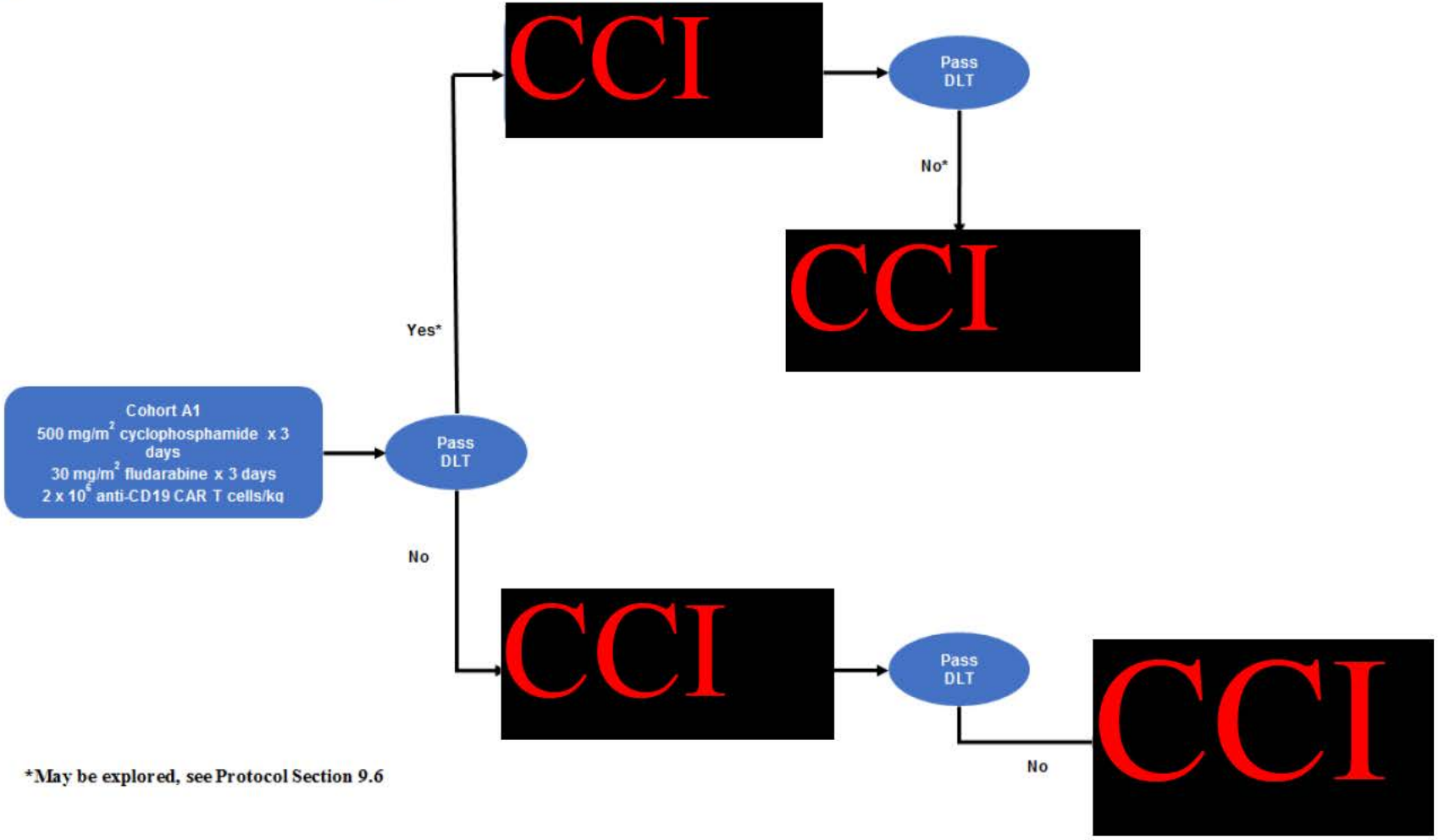
- Screening
- Enrollment/Leukapheresis
- Bridging therapy (if applicable, for Phase 2 SMS) or debulking therapy (if applicable, Phase 2 SMS, Cohort 5)
- Conditioning chemotherapy
- Investigational product treatment
- Post-treatment assessment
- Long-term follow-up

Further details on study procedures may be found in the study protocol.

Phase 1 Study

During Phase 1, approximately 6-24 subjects with DLBCL, PMBCL, or TFL will be enrolled to evaluate the safety of axicabtagene ciloleucel regimens. If the initial regimen is determined to be safe, a higher dose of conditioning chemotherapy may be investigated. If the regimen is determined to not be safe, reduced doses of conditioning chemotherapy and/or axicabtagene ciloleucel may be explored. A safety review team (SRT), internal to the study sponsor, will review the safety data and make recommendations on further study conduct of Phase 1 and progression to Phase 2 as depicted in Figure 1 and outlined in Figure 3.

Figure 1. **Phase 1 Dosing Cohorts and Regimens**



*May be explored, see Protocol Section 9.6

Phase 2 Pivotal Study

In Phase 2 pivotal study, subjects will enroll into 2 separate Cohorts designated as Cohort 1 and Cohort 2.

- Cohort 1 will enroll adult subjects with refractory DLBCL.
- Cohort 2 will enroll adult subjects with refractory PMBCL and TFL. TFL is defined as subjects who received prior chemotherapy for follicular lymphoma.

Phase 2 Safety Management Study

In the Phase 2 SMS, subjects will enroll sequentially into 3 separate Cohorts designated as Cohort 3, Cohort 4, Cohort 5 and Cohort 6.

- Cohort 3 will enroll adult subjects with relapsed or refractory transplant ineligible DLBCL, PMBCL, or TFL.
- Cohort 4 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after two systemic lines of therapy.
- Cohort 5 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after two systemic lines of therapy.
- Cohort 6 will enroll adult subjects with relapsed or refractory DLBCL, PMBCL, TFL, or HGBCL after 2 systemic lines of therapy.

The DSMB will review safety and efficacy data two times during the Phase 2 pivotal portion of this study, when 20 and 50 subjects in Cohort 1 have been treated with the target dose of axicabtagene ciloleucel and have had the opportunity to complete the 3 month disease assessment. The DSMB will review Cohorts 3, 4, 5 and 6 safety data when 20 subjects in each Cohort have had the opportunity to be followed for 30 days. The DSMB will also review enrollment pausing criteria after 10, 20, 30, and 50 subjects in the Phase 2 pivotal portion of the study have been dosed with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days.

The DSMB will be chartered to make trial conduct recommendations based on an analysis of risk vs benefit. The DSMB may meet more often as needed.

The primary analyses will be conducted when 72 subjects in the mITT- set of the Phase 2 pivotal Cohort 1 and 20 subjects in the mITT set of Cohort 2 have completed the 6 month disease response assessment, are lost to follow-up, withdraw from the study, or die, whichever occurs first (see details in Section 3.3)

The primary analysis of efficacy endpoints will be based on investigator review of disease assessments and evaluated per the revised International Working Group Criteria for Malignant Lymphoma {Cheson 2007}, henceforth referred to throughout this document as "Investigator read – {Cheson 2007}". Secondary efficacy analyses will be based on central radiologic review of disease assessments per {Cheson 2007}; these assessments will be referred to throughout this document as "Central read – {Cheson 2007}". CCI [redacted]

3.2. Hypothesis

Phase 2 pivotal study Cohort 1 and Cohort 2: This study is designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the ORR to axicabtagene ciloleucel in Cohort 1 and Cohort 2 is significantly greater than 20%.

Phase 2 SMS Cohort 3, Cohort 4, Cohort 5 and Cohort 6: No hypothesis will be tested in Cohort 3, Cohort 4, Cohort 5 and Cohort 6, which will be used to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, or prophylactic steroid use on the rate and severity of CRS and neurologic toxicities.

3.3. Sample Size Considerations

The anticipated enrollment in this study is approximately 268 to 286 subjects.

Six to 24 subjects will be enrolled into Phase 1 of this study.

If the study proceeds to Phase 2, approximately 72 subjects will be enrolled into Cohort 1 and approximately 20 subjects will be enrolled into Cohort 2.

In the Phase 2 SMS, approximately 40 subjects will be enrolled into Cohort 3, approximately 40 subjects will be enrolled and dosed into Cohort 4, approximately 50 subjects will be enrolled and dosed into Cohort 5, and approximately 40 subjects will be enrolled and dosed into Cohort 6.

As indicated in Section 3.1, axicabtagene ciloleucel may be dosed at doses ranging from 1×10^6 to 2×10^6 mg/kg. The target dose of axicabtagene ciloleucel for each Cohort is provided in Table 1.

Table 1. Planned and Target Doses of Axicabtagene Ciloleucel

Cohort	Regimen and Planned Dose of Axicabtagene Ciloleucel	Target Dose of Axicabtagene Ciloleucel
A1	500 mg/m^2 cyclophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 2 x 10^6 anti-CD19 CAR T cells/kg	• 2 x 10^6 (+/- 20%) (1.6 x 10^6 up to and including 2.4 x 10^6) anti-CD19 CAR T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells
CCI		
Phase 2 (all Cohorts)	500 mg/m^2 cyclophosphamide x 3 days 30 mg/m^2 fludarabine x 3 days 2 x 10^6 anti-CD19 CAR T cells/kg	• 1 x 10^6 to 2 x 10^6 anti-CD19 CAR T cells/kg • For subjects weighing > 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells

Efficacy analyses will be based on a modified intent to treat (mITT) population consisting of all subjects enrolled in the Phase 2 portion of the study who receive the target dose of axicabtagene ciloleucel.

Safety analyses will be based on all subjects dosed with axicabtagene ciloleucel.

DLT analyses will be based on the DLT evaluable set, defined in Section 6.6.

CCI [redacted]

Primary analyses of Phase 2 Cohort 1, Cohorts 1 and 2 combined, Cohort 3, Cohort 4, Cohort 5 and Cohort 6 are specified separately. If subject accrual and treatment is such that the primary analysis of Phase 2 Cohort 1 occurs at the same time as the primary analysis of Cohorts 1 and 2, then one clinical study report (CSR) will be written that includes both the primary analysis of Cohort 1 and the primary analysis of Cohorts 1 and 2 combined. Otherwise, the primary analysis CSR will be written when the first primary analysis occurs. The CSR will be amended or a CSR addendum will be written to summarize the results of the primary analysis of Cohorts 3, 4, 5 and 6, respectively.

3.3.1. Phase 2 Pivotal Study, Cohorts 1 and 2

This study uses a single arm design to test for an improvement in response rate CCI [redacted]. For the test of efficacy, this study has ≥ 90% power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a 1-sided alpha of 0.025.

The overall 1-sided alpha level of 0.025 CCI [redacted]

Within Cohort 1, CCI [redacted] 1 primary analyses will be performed.

- [redacted]

- [redacted]

- The primary analysis of Cohort 1 will occur after 72 subjects in the mITT set of Cohort 1 have had the opportunity to be assessed for response 6 months after the axicabtagene ciloleucel infusion.

An alpha spending function will be used CCI [redacted] the nominal 1-sided alpha used to test for efficacy at the primary analysis is 0.011.

Within Cohorts 1 and 2 combined, 1 primary analysis will be performed when 72 subjects in the mITT set of Cohort 1 and 20 subjects in the mITT set in Cohort 2 have had the opportunity to be assessed for response at 6 months after the axicabtagene ciloleucel infusion. This testing will be performed at a 1-sided alpha level of 0.0075. Confidence intervals about the ORRs within Cohorts 1 and 2 will be presented with the inferential analysis of the overall study population.

As indicated above, inferential testing of Cohort 1 will occur when 72 subjects in the mITT set in Cohort 1 have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion. The efficacy data from any additional subjects (beyond 72) enrolled into Cohort 1 will be analyzed descriptively and included in analyses of all secondary endpoints. Similarly, inferential testing of Cohorts 1 and 2 will occur when 72 subjects in the mITT set of Cohort 1 and 20 subjects in the mITT set of Cohort 2 have had the opportunity to be followed for 6 months following the axicabtagene ciloleucel infusion. The efficacy data from any additional subjects (beyond 92) enrolled into Cohorts 1 and 2 will be analyzed descriptively. In the event that 72 subjects in the mITT set in Cohort 1 and 20 subjects in the mITT set in Cohort 2 are accrued at the same time, the primary analysis of Cohort 1 and the primary analysis of Cohorts 1 and 2 combined will be performed at the same time.

The derivation of the alpha levels for the test of Cohort 1 and Cohorts 1 and 2 combined were originally obtained under the assumption of 40 subjects enrolled into Cohort 2. These original derivations are retained in this protocol amendment as they result in a more conservative alpha level for the test of Cohort 1.

This procedure preserves the designated 1-sided alpha level of 0.025 and has $\geq$ 90% power. CCI [redacted]

3.3.2. Phase 2 SMS, Cohorts 3, 4, 5 and 6

The primary objective of Phase 2 safety management study Cohort 3, Cohort 4, Cohort 5, and Cohort 6 is to assess the impact of prophylactic regimens, earlier interventions, debulking therapy, or prophylactic steroids on the rate and severity of CRS and neurologic toxicities. The assessment of ORR is a secondary objective, and the analysis will be descriptive.

The planned primary analyses of Cohorts 3, 4, 5 and 6 will occur after all subjects treated with axicabtagene ciloleucel in each of these Cohorts have had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion.

A schema of the Phase 2 study design is provided in Figure 2.


CCI

3.4. Statistical Assumptions

Phase 1 and Cohorts 1 and 2 of this trial will enroll patients with chemo-refractory lymphoma, as evidenced by failure to achieve even a transient or partial response to prior biologic and combination chemotherapy or by early recurrence after ASCT.

CCI

This study assumes that the underlying response rate (in the absence of treatment with investigational therapy) in Cohorts 1 and 2 is 20% and that an improvement in the response rate to 40% provides clinically meaningful benefit.

CCI


CCI

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

4.1.1. Primary

- Phase 1: the incidence of adverse events (AEs) defined as DLTs
- Phase 2 pivotal study (Cohorts 1 and 2): ORR (Investigator read – {Cheson 2007}
- Phase 2 SMS (Cohorts 3, 4, 5 and 6): the rate and severity of CRS and neurologic toxicities

4.1.2. Secondary (all Phases, unless noted)

- ORR (Investigator read – {Cheson 2007}) for subjects in Phase 1 and Phase 2 SMS (Cohorts 3, 4, 5 and 6)
- Duration of response (DOR) (Investigator read – {Cheson 2007})
- Progression-free survival (PFS) (Investigator read – {Cheson 2007})
- Overall survival (OS)
- ORR (CR + PR) (Central read – {Cheson 2007}) in Phase 2 pivotal study
- DOR (Central read – {Cheson 2007}) in Phase 2 pivotal study
- Best objective response (Central read – {Cheson 2007}) in Phase 2 pivotal study
- PFS (Central read – {Cheson 2007}) in Phase 2 pivotal study
- The incidence of AEs, including identified and potential risks for axicabtagene ciloleucel
- The incidence of significant laboratory abnormalities
- The incidence and persistence of anti- axicabtagene ciloleucel antibodies and anti-product impurity antibodies
- Levels and persistence of anti-CD19 CAR T cells in blood samples
- Levels and persistence of cytokines in blood samples
- The subject incidence of replication competent retrovirus (RCR) detected in blood samples
- Changes over time in the EQ-5D scale score and EQ-5D VAS score in Phase 2 SMS (Cohorts 3, 4, 5 and 6)

[redacted]

4.2. Covariates

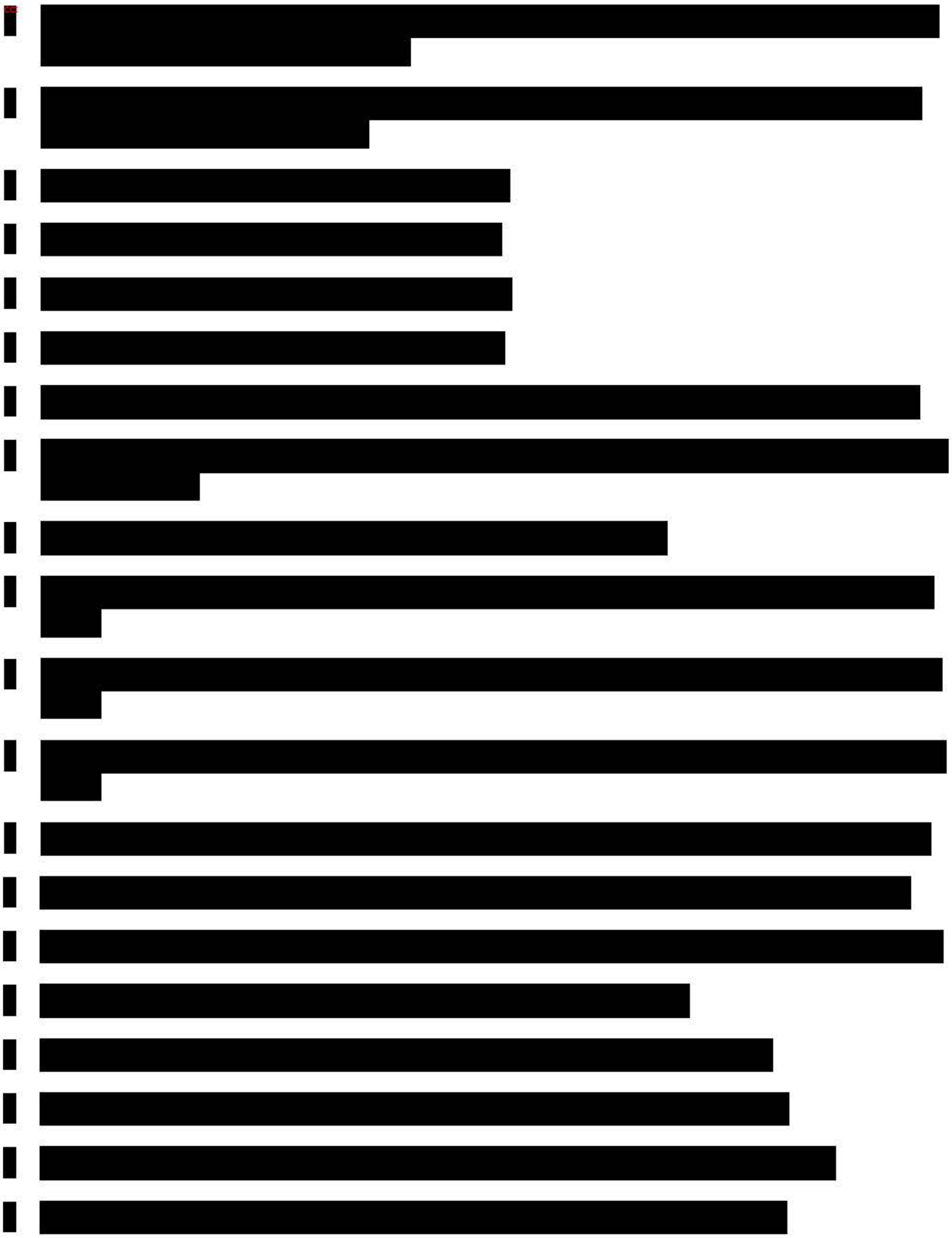
The following baseline covariates may be used to examine efficacy in subgroups or covariate analyses:

- Race
- Sex
- [redacted]

- Age at baseline (< 65, ≥ 65)

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

- Age at baseline (< 65, ≥ 65)
- Sex (male, female)



CCI

5. DEFINITIONS

5.1. General

Study enrollment: Study enrollment occurs at the commencement of leukapheresis.

Study day 0: Study day 0 is defined as the day the subject received the first axicabtagene ciloleucel infusion. The day prior to study day 0 will be study day -1. The day of enrollment and any days after enrollment and before study day -1 will be sequential and negative integer-valued.

Baseline: The baseline value is defined as the last value measured prior to conditioning chemotherapy. For subjects in phase 2 SMS (e.g. Cohort 5), if conditioning chemotherapy was not administered per protocol, the baseline value is defined as the last value measured prior to axicabtagene ciloleucel infusion.

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

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

End of study: This will occur after all subjects have been followed for 15 years post axicabtagene ciloleucel infusion, have withdrawn consent, been lost to follow-up, experienced an AE that precluded further follow up, or have died.

Refractory Subgroup at baseline: Refractory subgroups are defined below. A subject may meet the criteria for multiple refractory subgroups. In this event, any subject who meets the criteria for relapse post ASCT will be categorized as such. If a subject meets more than one refractory subgroup other than relapse post ASCT, the refractory subgroup defined by the subject's last line of therapy prior to study entry will be used to categorize the subject into a refractory subgroup. Note that bridging or debulking therapies should not be included for defining the Relapsed/Refractory subgroups.

- Primary refractory: CCI [redacted]
- Refractory to 2nd or greater line therapy: CCI [redacted]

- Relapsed to 2nd or greater line therapy: CCI [redacted]
- Relapse post ASCT: CCI [redacted]

Bulky disease: bulky disease is defined as the presence of a single lesion with largest diameter 10 cm or larger or mediastinum wider than 1/3 of the chest on a chest x-ray. The presence of bulky disease will be determined by the investigator when baseline disease extent is evaluated.

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

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

5.2. Safety

Treatment-emergent adverse event (TEAE): Any AE with onset on or after the first dose of conditioning chemotherapy. For subjects taking retreatment of axicabtagene ciloleucel, TEAEs during retreatment period may be summarized separately.

Deaths: All deaths that occur after study enrollment up through the end of study will be summarized. Deaths that occur from axicabtagene ciloleucel infusion up through 30 days after the infusion will also be summarized. For subjects taking retreatment of axicabtagene ciloleucel, deaths occurred during retreatment period may also be summarized separately.

AEs of interest: Adverse events of special interest for axicabtagene ciloleucel treatment include identified risks (CRS, neurologic toxicity, infections, cytopenias, hypogammaglobulinemia) and potential risks (secondary malignancies, tumor lysis syndrome, bone marrow failure, graft-versus-host-disease, replication competent retrovirus, immunogenicity).

Neurologic toxicity (neurotoxicity): Neurotoxicity 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 relatedness, temporal relationshipor concomitant conditions (eg CRS). Events are identified with a search list of MedDRA preferred terms. Additionally, the MedDRA system organ classes (SOCs) of Psychiatric Disorders and Nervous System Disorders will be reviewed for additional events; these events will then be evaluated for potential inclusion as neurologic AEs.

CRS: CRS is identified via collection of the syndrome on a case report specifically designed to collect CRS. Specific symptoms of the CRS collected on the AEs log are coded using Medicinal Dictionary for Regulatory Activities (MedDRA) and are linked to the corresponding CRS

episode. Individual symptoms of CRS will be graded per Common Terminology Criteria for Adverse Events (CTCAE) v4.03, and CRS syndrome severity is graded according to a modification of the grading system proposed by Lee and colleagues {Lee 2014}. In the modified grading scale, neurologic AEs are not reported as part of the CRS syndrome and will be reported separately and summarized separately.

Immunogenicity (anti-axicabtagene ciloleucel antibody): Immunogenicity are identified by the development of antibodies against CAR expressing cells by flow cytometry. In addition, a manual review of the AE terms indicative of autoimmunity, inclusive of infusion-related events and anaphylactic reactions among subjects who test positive for anti-axicabtagene ciloleucel antibodies, will be performed.

For other AEs of special interest, specific adverse events may be mapped to these categories using dictionary coded event term and standardized MedDRA queries (SMQs) or other search strategies. Specific definitions of these events and the coded terms to which they correspond will be provided in the Program Safety Analysis Plan.

Duration of an AE of special interest: Duration of an AE of special interest is defined as the time from the earliest onset date of the AEs in the event class of interest through the resolution date of the last AEs in the event class, regardless of the gaps of the days between multiple events, i.e., the resolution date of the last AE in the event class – the start date of the first AE in the event class + 1. The duration may only be calculated on subjects for whom all AEs in the event class have been resolved by the data cutoff date.

5.3. Efficacy

ORR: proportion of subjects with either a CR or PR while on study. All subjects who do not meet the criteria for objective response by the analysis data cutoff date will be considered non-responders. The derivation of this endpoint will only include response assessments obtained prior to any other additional therapy (e.g. SCT or retreatment with axicabtagene ciloleucel). Response may be defined per Investigator read – {Cheson 2007} or Central Read – {Cheson 2007}.

DOR: DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or death from any cause. Response and progression may be defined per Investigator read – {Cheson 2007} or Central Read – {Cheson 2007}. Subjects not meeting the criteria for progression or death from any cause 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 initiation of new anticancer therapy (excluding SCT). Disease assessments obtained after SCT will be used in the derivation of DOR. CCI

PFS: PFS is defined as the time from axicabtagene ciloleucel infusion date to the date of disease progression or death from any cause. Progression may be defined per Investigator read – {Cheson 2007} or Central Read – {Cheson 2007}. 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 initiation of new anti-cancer therapy (excluding SCT). Disease assessments after SCT will be used in the derivation of PFS. CCI [redacted]

OS: OS is defined as the time from axicabtagene ciloleucel infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date for each analysis will be censored at the data cutoff date. CCI [redacted]

CCI [redacted]

6. ANALYSIS SETS

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

6.1. Modified Intent-to-Treat (mITT) (defined for Phase 2)

The mITT analysis set will consist of all subjects treated with at least 1.0 x 10^6 anti-CD19 CAR T cells/kg. The mITT analysis set will be used for efficacy analyses of Phase 2.

6.2. Safety Analysis Set

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

For interim analyses, the safety set will be focused only on those subjects who have had the opportunity to be followed for one month after the axicabtagene ciloleucel infusion.

6.3. Full Analysis Set (FAS)

The FAS will consist of all enrolled patients and will be used for the summary of subject disposition, sensitivity analyses of ORR and DOR, and subject listings of deaths.

6.4. mITT Re-treatment Analysis Set (defined for Phase 2)

The mITT Re-treatment Analysis Set will consist of the set of all subjects who undergo re-treatment with axicabtagene ciloleucel at a dose of at least 1.0 x 10^6 anti-CD19 CAR T cells/kg. This set will be used for all re-treatment efficacy analyses.

6.5. Safety Re-treatment Analysis Set

The Safety Re-treatment Analysis Set will consist of all subjects who undergo re-treatment with axicabtagene ciloleucel.

For interim analyses, the Safety Re-treatment set will be focused only on those subjects who have had the opportunity to be followed for one month after the re-treatment axicabtagene ciloleucel infusion.

6.6. Subgroup Analysis Sets

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

6.7. Interim Analysis Sets

The **DLT evaluable Set(s)** (Phase 1 only), defined for each dosing Cohort in Phase 1, will include subjects treated in the Phase 1 dosing Cohort who:

- Received the target and were followed for at least 30 days after the axicabtagene ciloleucel infusion; or
- Received a dose of anti-CD19 CAR T cells (axicabtagene ciloleucel) lower than the target for that Cohort and experienced a DLT during the 30 day post-infusion period.

If needed, more subjects will be enrolled to achieve 6 DLT evaluable subjects at the target dose for each Cohort.

CCI [redacted]

[redacted]

[redacted]

Phase 2 SMS

The SMS Interim Analysis Sets will consist of the first 20 subjects treated in Phase 2 Cohort 3, Cohort 4, Cohort 5 and Cohort 6 respectively who have had the opportunity to be followed for 30 days after the axicabtagene ciloleucel infusion.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

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

The DSMB will meet 2 times during the Phase 2 Cohort 1 of the study. The DSMB will review safety and efficacy data and will be chartered to make trial conduct recommendations based on the risk versus benefit of treatment with axicabtagene ciloleucel. The DSMB will also meet to review safety data after 20 subjects in Phase 2 Cohorts 3, 4, 5 and 6 have been dosed with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days, respectively.

Additionally, as part of its oversight of the study, the DSMB will also assess criteria to pause enrollment after 10, 20, 30, and 50 subjects in the Phase 2 pivotal portion have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days. Enrollment will be paused if any of the following criteria are met:

1) subject incidence of grade 5 axicabtagene ciloleucel related AEs within 30 days is > 10%

   OR

2) subject incidence of the following grade 4 axicabtagene ciloleucel-related AEs lasting more than 7 days is > 33%:

   - Neurotoxicity
   - CRS (per Lee 2014 criteria)
   - Other non-hematologic SAE
   - Infection (treatment-related)

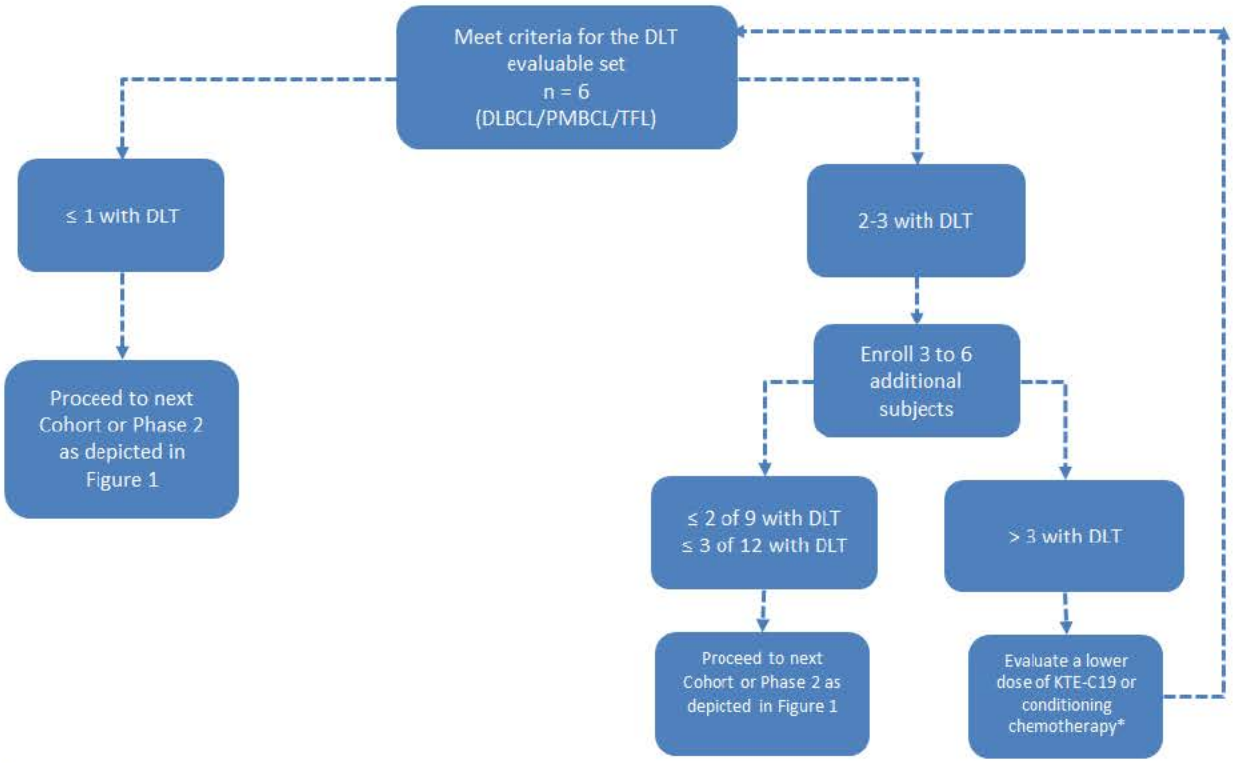
These DSMB reviews will be based on SAE reports.

The DSMB may meet more often as needed.

7.1. Phase 1 – Safety Interim Analyses

The SRT will evaluate the incidence of DLTs and SAEs after 6 subjects, 9 subjects (if applicable), and 12 subjects (if applicable) have met the criteria for the DLT evaluable set. The SRT may recommend progression to the Phase 2 portion of the trial according to the schema in Figure 3.

Figure 3. Phase 1 DLT Evaluation Scheme



*or proceed to Phase 2 with the dose previously tested in the NCI study, as depicted in Figure 1.

7.2. Phase 2 – Interim Safety and Efficacy Analyses

An independent DSMB will be chartered to make recommendations on study conduct during the Phase 2 portion of the study. Details may be found in the DSMB Charter. CCI [redacted] Safety analyses will present data from both study Phases and all Cohorts.

CCI [redacted]

CCI [redacted]

CCI [redacted] interim analyses are for safety and will be conducted when 20 subjects in Phase 2 Cohort 3, Cohort 4, Cohort 5 and Cohort 6 have been treated with axicabtagene ciloleucel and have had the opportunity to be followed for 30 days, respectively.

After the planned primary analysis of Cohort 1 and the planned primary analysis of the Cohorts 1 and 2 combined, additional efficacy and safety analyses of Cohorts 1 and 2 may be performed to support regulatory interaction or publications. These analyses will be descriptive. Additional descriptive analyses of Cohorts 3, 4, 5 and 6 data may also be conducted after the primary analyses of these Cohorts have been completed.

7.3. Access to Aggregate and Subject Level Data and Individual Subject Treatment Assignments

This study is open-label. Subjects, the study sponsor, and investigators will be aware that each subject is planned to be treated with axicabtagene ciloleucel. Data handling procedures designed to maintain the trial credibility and validity in this open-label single arm study are described in the Trial Integrity Document.

An independent statistician will perform the interim safety and efficacy analyses for the Phase 2 portion of the study 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 Pharma 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 has not passed all data cleaning procedures at the time the data are extracted for snapshot.

8.2. Electronic Transfer and Archival of Data

The Medidata Rave system will be used to collect the data in this study. Raw data extracted from Medidata Rave will be archived prior to further dataset creation, maintenance, and analysis. Raw data, SDTM data, and ADaM datasets 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 (see below) will be included in the relevant SDTM and ADAM modules when the external data are available. For the SRT analyses, raw data may be archived and used in data review.

Data from the central pathology laboratory (including tumor pathology, tumor genetic, and molecular characteristics), the product manufacturing (total T cells, CAR T cells [transduction ratio], duration of manufacturing time), central laboratory assessment of subject serum samples (including CAR T cell levels in the peripheral blood, antibody assays, RCR testing), and central radiology review will be generated from contract laboratories and Kite Pharma. These data will be transferred to Kite and held in a peripheral directory and not built into the clinical trial database. At the time analyses require these data, they may be merged with the SDTM and ADAM datasets.

The source and disposition of all data sources obtained from imaging vendors or laboratories is described in Appendix 2.

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 3 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 3 will be used. Completely missing death dates or death dates with only a year reported will not be imputed.

8.4. Detection of Bias

A listing of subjects with important protocol deviations will be generated. The deviations included in this list will include, but not be limited to, violations of eligibility criteria and use of exclusionary medication during the study. Lack of protocol compliance will be evaluated by summarizing the subject incidence of 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 bias; 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

The primary analysis of the primary endpoint is an exact binomial test used to compare the observed response rate in the Phase 2 Cohort 1 and Cohort 1 and 2 combined to a response rate of 20%. This test assumes only the independence of the individual subject responses. The validity of the assumption of a 20% historical response rate is described in Section 3.4.

An exact 95% confidence interval will be generated about the response rate. The Clopper-Pearson method will be used to generate this interval. While the Clopper-Pearson interval provides adequate coverage probability, it is commonly wider than necessary {Brown 2002}, leading to overly conservative estimates of the lower bound of ORR. Sensitivity analyses will be conducted in which the interval is calculated with different methods (Section 9.5.1).

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 CCI [redacted] Standard Operating Procedures (SOPs) and Kite SOPs if applicable. The software and version used to generate analyses will be indicated in the archived documentation.

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

The goal of the primary statistical analysis is to compare the observed response rate in Phase 2 Cohort 1 and in Cohorts 1 and 2 combined per investigator read – {Cheson 2007} to a historical control rate of 20% with an exact binomial test. Hypothesis testing will be one-sided, and all 95% confidence intervals will be 2–sided. At the time of planned analyses, 95% confidence intervals for the response rate in each study Cohort will be presented.

The timing of the interim and primary analyses will be based on subject accrual and disease assessment milestones. The primary analysis clinical study report (CSR) will be written at the primary analysis of Phase 2 Cohorts 1 and 2 combined. CCI [redacted]
Additionally, the CSR will be amended with the primary analyses of Phase 2 SMS Cohort 3, Cohort 4, Cohort 5 and Cohort 6, and may be amended with additional subject safety and survival follow up after the planned primary analysis.

CCI [redacted] Safety data from all subjects treated will be included in the primary analysis.

Analyses of the Phase 1 and Phase 2 portions of the study will be presented separately. Within the Phase 1 summaries, each dose Cohort will be presented separately. For data presented over time, assessments may be grouped into "windows" based on the actual assessment times.

9.2. Subject Accountability

The number of subjects screened, enrolled, leukapheresed, treated with conditioning chemotherapy, treated with axicabtagene ciloleucel, and re-treated with axicabtagene ciloleucel will be summarized. The reasons for discontinuing treatment and discontinuing study 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 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 (e.g. 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:

- ECOG performance status at baseline
- Sex (male, female)
- Height
- Weight
- Age at baseline (< 65, ≥ 65)
- Ethnicity
- Race: white, black, Asian, other (categories may be collapsed or expanded based on accrual)
- Country
- Disease type (DLBCL, PMBCL, TFL, HGBCL)
- Disease subtype (DLBCL associated with chronic inflammation, EBV + DLBCL, T cell / histiocyte rich large B cell lymphoma, primary cutaneous DLBCL (leg type), DLBCL not otherwise specified, primary mediastinal (thymic) large B cell lymphoma, transformation of follicular lymphoma to DLBCL, other)
- Number of prior chemotherapy regimens
- Response to last chemotherapy regimen (among subjects who are not relapsed post ASCT)
- Refractory subgroup
- Prior autologous stem cell transplant (ASCT)
- Prior anti-CD20 treatment

- Prior anthracycline treatment
- Prior platinum treatment
- Tumor burden, as measured by the SPD of selected nodes or lesions at baseline
- Morphologic characteristics (centroblastic, immunoblastic, anaplastic, other)
- CD19 expression in tumors at baseline
- Molecular subgroup (germinal center B cell-like (GBC), activated B-cell like (ABC))
- BCL-2 alterations / overexpression (Y/N)
- BCL-6 alterations / overexpression (Y/N)
- C-MYC alterations / overexpression (Y/N)
- Double hit (C-MYC alteration/overexpression and either BCL-2 or BCL-6 alteration/overexpression) status
- Triple hit (3 of 3 recurrent chromosome translocations) status
- Disease stage (I, II, III, IV) and extent (presence of B symptoms, splenic involvement, bulky disease, extranodal disease)
- International prognostics index (IPI) risk category
- History of bone marrow involvement

9.5. Efficacy Analyses

Efficacy analyses will be conducted on the mITT analysis set. For the primary analysis, the investigator assessment of disease status per {Cheson 2007} will be used. Sensitivity analyses will be conducted that use the central radiology review of disease assessments per {Cheson 2007}. The investigator and central radiology reviewer will provide the determination of disease status (CR, PR, SD, PD, NE) at each time point. SAS programs developed by Kite Pharma and CCI will derive the best overall response, DOR, and PFS based on these assessments.

The primary efficacy analysis will be presented in the following analysis populations:

- mITT set
- [redacted]
- [redacted]

[redacted]

For subjects re-treated 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 and best response, DOR, PFS, and summaries of change in tumor burden. For such subjects, disease assessments obtained after re-treatment will be included in the summaries of objective and best response to retreatment with axicabtagene ciloleucel and DOR after re-treatment with axicabtagene ciloleucel. The subject's OS time will be derived from the last date known alive regardless of re-treatment time.

[redacted]

9.5.1. Objective Response and Best Response

9.5.1.1. Primary Analyses of Objective Response

The subject incidence of objective response will be calculated. An exact binomial test will be used to compare the observed response rate to the hypothesized historical control rate of 20%. The subject incidence of best response (CR, PR, SD, PD, NE, ND) will be calculated. Confidence intervals will be provided about the ORR, calculated with the following methods:

- Clopper-Pearson (an exact interval)

[redacted]

The primary analysis of objective response and best response will include subjects from the Phase 2 pivotal portion and will be conducted for subjects by Cohort and for Cohorts 1 and 2 combined. Analyses of Cohort 2 alone and individual Cohorts 3, 4, 5 and 6 in the Phase 2 SMS will be descriptive. The exact binomial test will not be presented for Cohorts 3, 4, 5 and 6. Sensitivity analyses of objective response will be conducted in the FAS set.

The number and percent of subjects who initially attain a partial response and subsequently attain a complete response will be summarized.

9.5.1.2. Analyses of Objective Response and Best Response per Central Read

The analyses of objective response and best response specified above will be repeated for objective response and best response per central read – {Cheson 2007}.

The concordance of objective response and best objective response per investigator read – {Cheson 2007} and central read – {Cheson 2007} will be evaluated. A summary table of concordance, concordance rate, a kappa statistic, and a 2-sided 95% confidence interval about the kappa statistic will be provided.

Further analyses between the investigator and central reads may be described in a supplemental SAP.

CCI [redacted]

- CCI [redacted].

9.5.1.4. Analyses of Objective Response – Phase 1

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

At minimum, ORRs and 95% confidence intervals will be generated for each dose Cohort in Phase 1.

9.5.2. DOR

The Kaplan-Meier approach will be used to estimate DOR. Disease assessments obtained after SCT while in study treatment induced remission will be used in the derivation of DOR. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for DOR per investigator read – {Cheson 2007}, as well as per central read – {Cheson 2007}. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR.

CCI [redacted]

9.5.3. PFS

Kaplan-Meier plots, estimates and 2-sided 95% confidence intervals will be generated for PFS. Disease assessments obtained after SCT while in study treatment induced remission will be used in the derivation of PFS. Estimates of the proportion of subjects alive and progression-free at 3 month intervals will be provided. The number of subjects censored and the reasons for censoring will be summarized. Analyses will be generated for PFS per investigator read – {Cheson 2007} and PFS per central read – {Cheson 2007}.

CCI [redacted]

CCI [redacted]

[redacted]

9.5.4. OS

The analysis of OS will use the same methods as the analysis of PFS. A graphical summary of the time to response, DOR, retreatment, progression, and death times from the time of axicabtagene ciloleucel infusion depicted on a horizontal time axis for each patient ("swim lane plot") will be provided.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

9.5.9. European Quality of Life-5 Dimensions and Visual Analogue Scale Scores

EQ-5D and VAS scores will be collected and summarized at baseline and post study treatment visits for Phase 2 SMS Cohorts 3, 4, 5 and 6. Changes in the EQ-5D-5L and VAS scores from baseline at post-study treatment visits will also be summarized with descriptive statistics.

CCI [redacted]

[redacted]

9.6. Safety Analyses

Safety analyses will be conducted on the safety analysis set. The primary analysis of safety data will summarize all TEAEs and laboratory values. Additional summary tables will present all TEAEs, as well as AEs with onset time categorized by study treatment period (conditioning chemotherapy treatment period, axicabtagene ciloleucel treatment period, primary post-treatment follow up period, and secondary post-treatment follow up period). For subjects who undergo retreatment with axicabtagene ciloleucel, AEs occurring in the axicabtagene ciloleucel re-treatment period may be summarized in an additional separate summary that presents only the AEs occurring during the retreatment period. Sample table layouts are provided in Appendix 3.

AEs will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) at the time of each analysis. The version of the MedDRA may vary over time as the current version in use is updated. The severity of AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Cytokine release syndrome (CRS) will be graded using a revised CRS grading scale developed by Lee et al {Lee 2014} and per CTCAE 4.03. 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.

Fatal AEs that are attributed to disease progression may be included in the death summary with a primary death reason of 'disease progression' regardless of the coded CTCAE version 4.03 preferred term.

Subjects enrolled but not dosed with axicabtagene ciloleucel will be followed for AEs for 30 days after the last study procedure. AEs reported in these patients will be archived in the study database and available in SDTM and ADAM datasets, but will not be tabulated in AE summaries.

Safety summaries will be presented separately for each Phase 1 dosing Cohort and for Phase 2 by Cohort and overall.

9.6.1. Adverse Events

The subject incidence of the following treatment-emergent AEs will be tabulated for the:

- Summary of AEs (any, worst severity, serious, related)
- All AEs

- All SAEs
- All leukapheresis-related AEs
- All conditioning-chemotherapy-related AEs
- All axicabtagene ciloleucel-related AEs
- All conditioning chemotherapy-related SAEs
- All axicabtagene ciloleucel-related SAEs
- All grade 3 or higher AEs
- All grade 3 or higher conditioning chemotherapy-related AEs
- All grade 3 or higher axicabtagene ciloleucel-related AEs
- Fatal AEs
- AEs of interest, including identified risks and potential risks

Summary statistics for the onset time (Kaplan-Meier estimates) and duration of AEs of interest will be provided.

The subject incidence of deaths by treatment period will be provided.

A subject listing of deaths and SAEs (including narratives) will be provided overall and by treatment period.

A summary of demographics and baseline characteristics among subjects who experience CRS and who do not experience CRS may be provided.

CCI [redacted]

9.6.3. Laboratory Test Results

Laboratory results will be graded according to NCI Common Toxicity Criteria (CTCAE version 4.03). The incidence of worst grade CTCAE toxicities post axicabtagene ciloleucel infusion for all analytes will be provided. Laboratory data collected at baseline and through the axicabtagene ciloleucel Treatment Period will be summarized. Shifts from baseline to minimum post-baseline and / or maximum post-baseline may be presented for select analytes.

9.6.4. Anti-axicabtagene Ciloleucel Antibodies

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

9.6.5. Replication Competent Retrovirus (RCR)

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

9.6.6. Exposure to Study Treatment and Product Characteristics

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

- Total 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 ratio
- Percentages of CD4 and CD8 T cells
- Percentages of T cell memory phenotypes
- IFN-gamma production in co-cultures of axicabtagene ciloleucel product and $CD19^+$ target cells
- Vector copy number of axicabtagene ciloleucel product

Separate summaries will be presented for the 2nd administration of conditioning chemotherapy for subjects in the Re-treatment Analysis Set.

CCI [redacted]

9.9. CAR T cells Measured in Peripheral Blood

Summary statistics for the level of CAR T cells in serum post axicabtagene ciloleucel infusion will be provided for CAR T cells measured at intervals outlined in the Schedule of Assessment of the protocol. The area under the concentration over time curve may be summarized from day 0 to day 28.

9.10. B-cell Aplasia

The subject incidence of B-cell aplasia, and the subject incidence of recovery after B-cell aplasia will be provided for each subject based on B cells measured by flow cytometry prior to conditioning chemotherapy, on the day of the axicabtagene ciloleucel infusion, week 4, month 3, month 6, month 9, month 12, month 15, month 18, and month 24. The use of IVIG treatment will be summarized.

10. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

None.

11. REFERENCES

Ardeshna KM, Kakouros N, Qian W, Powell MG, Saini N, D'Sa S, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. Br J Haematol 2005;130 (3):363-72.

Brown LD, Cai TT, DasGupta A. Interval Estimation for a Binomial Proportion. Statistical Science 2001;16 (2):101-33.

Brown LD, Cai TT, DasGupta A. Confidence Intervals for a Binomial Proportion and Asymptotic Expansions. The Annals of Statistics 2002;30 (1):160-201.

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32 (27):3059-68.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25 (5):579-86.

Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130 (16):1800-8.

Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999;94 (446):496-509.

Hitz F, Connors JM, Gascoyne RD, Hoskins P, Moccia A, Savage KJ, et al. Outcome of Patients with Chemotherapy Refractory and Early Progressive Diffuse Large B Cell Lymphoma After R-CHOP Treatment. Blood (ASH Annual Meeting Abstracts, Poster Session) 2010;116 (Abstract #1751).

Josting A, Rueffer U, Franklin J, Sieber M, Diehl V, Engert A. Prognostic factors and treatment outcome in primary progressive Hodgkin lymphoma: a report from the German Hodgkin Lymphoma Study Group. Blood 2000;96 (4):1280-6.

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

Matasar MJ, Czuczman MS, Rodriguez MA, Fennessy M, Shea TC, Spitzer G, et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. Blood 2013;122 (4):499-506.

Moskowitz CH, Bertino JR, Glassman JR, Hedrick EE, Hunte S, Coady-Lyons N, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol 1999;17 (12):3776-85.

Nagle SJ, Woo K, Schuster SJ, Nasta SD, Stadtmauer E, Mick R, et al. Outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma with progression of lymphoma after autologous stem cell transplantation in the rituximab era. American Journal of Hematology 2013;88 (10):890-4.

Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Statistics in Medicine 1993;12 (8):737-51.

Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333 (23):1540-5.

Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Statistics in Medicine 2007;26 (11):2389-430.

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

Seshadri T, Kuruvilla J, Crump M, Keating A. Salvage Therapy for Relapsed/Refractory Diffuse Large B Cell Lymphoma. Biology of Blood and Marrow Transplantation 2008;14 (3):259-67.

Song Y, Chi GY. A method for testing a prespecified subgroup in clinical trials. Stat Med 2007;26 (19):3535-49.

Telio D, Fernandes K, Ma C, Tsang R, Keating A, Crump M, et al. Salvage chemotherapy and autologous stem cell transplant in primary refractory diffuse large B-cell lymphoma: outcomes and prognostic factors. Leukemia & Lymphoma 2012;53 (5):836-41.

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

Wang SJ, O'Neill RT, Hung HM. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. Pharm Stat 2007;6 (3):227-44.

12. APPENDICES

CCI [redacted]

Appendix 2. Source and Disposition of Non-Clinical Database Data
Appendix 3. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates
Appendix 4. Sample Adverse Event Table Layouts
Appendix 5. Derivation of Time to Event Endpoints and Last Date Known to Be Alive


CCI

Appendix 2. Source and Disposition of Non-Clinical Database Data

Sample Type	Analysis / Data Element	Testing Lab / Source	Responsible to transfer to TCR	Include in Clinical Data Submitted to FDA	Analysis Plan
Product cells	Total T cells	Batch record	Kite/TCR	Yes	Primary SAP
Product cells	Transduction ratio	Batch record	Kite/TCR	Yes	Primary SAP
Product cells	Total CARCAR T cells	Batch record	Kite/TCR	Yes	Primary SAP
Product cells	Total T Cells	Batch record	Kite/TCR	Yes	Primary SAP
Product cells	Days of manufacture	PCT / Batch record	Kite/TCR	Yes	Primary SAP
Product cells	CD4/CD8 Ratio, Memory phenotypes	Kite	Kite	No	Primary SAP and supplemental translational research SAP
Product cells	Cytokines (co culture)	Kite	Kite	No	Supplemental translational research SAP
Biospecimen (post KTE-C19 infusion samples)	Cell differentiation and phenotype	Kite	Kite	No	Supplemental translational research SAP
Biospecimen	Cytokines	Kite	Kite	No	Supplemental translational research SAP
Biospecimen	CAR PCR	CCI	CCI	Yes	Primary SAP and Supplemental translational research SAP
Biospecimen	Antibody	CCI	CCI	Yes	Primary SAP
Biospecimen	RCR	CCI	CCI	Yes	Primary SAP
Tissue blocks	Pathology	CCI	CCI	Yes	Primary SAP
Independent Radiology Review	{Cheson 2007}	CCI	CCI	Yes	Primary SAP
CCI					

All data will be archived at CCI Kite Pharma. Data indicated as 'Yes' for inclusion in the clinical data submitted to FDA will be merged with the clinical data. Data indicated as 'No' for inclusion in the clinical data submitted to FDA will be archived at CCI or Kite but may not merged with the clinical data.

Appendix 3. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates

The following data will be imputed using the following algorithm:

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

Table 4. Imputation Rules for Partial or Missing Start Dates

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

1 = impute the date of day 0
2 = impute the first of the month
3 = impute January 1 of the year
4 = impute January 1 of the stop year
Note: if the start date imputation leads to a start date that is after the stop date, then do not impute the start date.
Imputation rules for partial or missing death dates:

1) If death year and month are available but day is missing:
   - If mmyyyy for the last date known to be alive = mmyyyy for death date, set death date to the day after the last date known to be alive.
   - If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.
   - If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.
2) If both month and day are missing for death date or a death date is completely missing, do not impute and censor the subject survival time at the last date known to be alive.

Appendix 4. Sample Adverse Event Table Layouts

All treatment emergent adverse events will be summarized in the AE Summary Table format below. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, Phase 2 Cohort3, Phase 2 Cohort 4, Phase 2 Cohort 5, and Phase 2 Cohort 6.

AE Summary Table Format

	(N =)
Any TEAE	X (XX)
Worst Grade 1	
Worst Grade 2	
Worst Grade 3	
Worst Grade 4	
Worst Grade 5	
Worst Grade ≥ 3	
Any Serious TEAE	
<Worst Grades as above>	
Any Conditioning Chemotherapy Related TEAE	
<Worst Grades as above>	
Any Serious Conditioning Chemotherapy Related TEAE	
<Worst Grades as above>	

Adverse Event Summary Layout 1: All AE summaries and AE subgroup analyses will be provided in format 1. The preferred terms will be sorted by descending order of frequency of the All, Any column. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, Phase 2 Cohort 3, Phase 2 Cohort 4, Phase 2 Cohort 5, and Phase 2 Cohort 6.

Subject Incidence of <AE Descriptor> Adverse Events in Descending Order of Preferred Term by Worst Severity

(N =)

MedDRA Preferred Term n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Any						
Preferred Term 1						
Preferred Term 2						

Adverse Event Summary Layout 2: All AE summaries and AE subgroup analyses will be provided in format 2. The preferred terms will be sorted by descending order of frequency of the All, Any column. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, Phase 2 Cohort 3, Phase 2 Cohort 4, Phase 2 Cohort 5, and Phase 2 Cohort 6.

Subject Incidence of Grade 3 or Higher <AE Descriptor> Adverse Events in Descending Order of Preferred Term by Worst Severity

(N =)

MedDRA Preferred Term n (%)	Any	Worst Grade 3	Worst Grade 4	Worst Grade 5
Any				
Preferred Term 1				
Preferred Term 2				

Adverse Event Summary Layout 3: All treatment emergent adverse events will be presented in the format below. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, Phase 2 Cohort 3, Phase 2 Cohort 4, Phase 2 Cohort 5, and Phase 2 Cohort 6.

Subject Incidence of <AE Descriptor> Adverse events in Descending Order of Preferred Term by System Organ Class and Worst Severity

(N =)

	Any	Gr 3	Gr 4	Gr 5
Any <AE Descriptor> Adverse Event n(%)	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 1	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 1	XX (X)	XX (X)	XX (X)	XX (X)
Preferred Term 2	XX (X)	XX (X)	XX (X)	XX (X)
System Organ Class 2				
…				

Adverse Event Summary Layout 4: Fatal adverse events will be summarized in the format below. Tables will be generated for Phase 1, Phase 2 Cohort 1, Phase 2 Cohort 2, Phase 2 Cohort 1 and 2 combined, Phase 2 Cohort 3, Phase 2 Cohort 4, Phase 2 Cohort 5, and Phase 2 Cohort 6.

Subject Incidence of Fatal Adverse Events

(N =)

MedDRA Preferred Term n (%)	
Any	
Preferred Term 1	
Preferred Term 2	

Appendix 5. Derivation of Time to Event Endpoints and Last Date Known to Be Alive

CCI [redacted]

1. DOR

DOR is defined only for subjects who experience an objective response and is the time from the first objective response to disease progression or death due to any cause. Response and progression may be defined per Investigator read – {Cheson 2007} or Central Read – {Cheson 2007}. CCI [redacted]

CCI [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

CCI [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3. PFS

PFS is defined as the time from axicabtagene ciloleucel infusion date to the date of disease progression or death from any cause. Progression may be defined per Investigator read – {Cheson 2007} or Central Read – {Cheson 2007}. 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 initiation of new anti-cancer therapy (excluding SCT). Disease assessments after SCT will be used in the derivation of PFS. CCI [redacted]

CCI

[redacted]

CCI [redacted]

4. OS

OS is defined as the time from axicabtagene ciloleucel infusion to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date for each analysis will be censored at the data cutoff date.

CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

CCI [redacted]

[redacted]

13. HISTORY OF REVISIONS

Version	Date	Description of Changes
Original (1.0)	11MAY2015	N/A
2.0	28AUG2016	• Added Phase 2 Cohort 3 and the corresponding objectives, sample size, endpoints, interim analysis and primary analyses of the cohort • Updated overall study sample size • Added the definition of Study Day 0 • Updated the timing of primary clinical study report generation CCI [redacted] CCI [redacted] • Replaced lymphocyte subsets section with B-cell aplasia • Removed All Leukapheresed Analysis Set (ALS)
3.0	08JUL2019	• Added Cohort 4, Cohort 5 and Cohort 6 to Phase 2 safety management study (SMS) and the corresponding objectives, sample size, endpoints, interim analysis and primary analyses of each of the cohorts • Clarified central read of tumor assessment data are collected for Phase 2 pivotal study only • Added EQ-5D scale score and VAS score to Phase 2 SMS CCI [redacted] • Updated the section of definitions (including identified and potential risks) • Updated electronic transfer and archival of data • Updated the list of demographic and baseline characteristics CCI [redacted] • Updated imputation rules for partial or missing start dates CCI [redacted] • Made other changes to improve document consistency with the study protocol