STATISTICAL ANALYSIS PLAN

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Company Code:	KTE-C19 PF-05082566
USAN/INN :	Axicabtagene ciloleucel Utomilumab
Protocol Title	A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination with Utomilumab in Subjects with Refractory Large B-Cell Lymphoma
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-Drug Antibody
ADaM	Analysis data model
AE	Adverse event
ASCT	Autologous stem cell transplant
BSA	Body surface area
CAR	Chimeric antigen receptor
CR	Complete response
CRF	Case report form
CRS	Cytokine release syndrome
CTCAE	Common terminology criteria for adverse event
DLT	Dose-limiting toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
HLGT	High-level group term
IPD	Important protocol deviations
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PT	Prefer term
RCR	Replication-competent retrovirus
OS	Overall survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable disease
SDTM	Study data tabulation model
SMQ	Standardized MedDRA query
SOC	System organ class
SOP	Standard operating procedure
SPD	Sum of the product of the diameters
SRT	Safety review team
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) sets forth prospectively the details of statistical analyses that are outlined in protocol KTE-C19-111 entitled "A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination with Utomilumab in Subjects with Refractory Large B-Cell Lymphoma (ZUMA-11)".

2. OBJECTIVES

The primary objective of Phase 1 is to evaluate the safety of axicabtagene ciloleucel in combination with utomilumab and to identify the most appropriate dose and timing of utomilumab to carry forward into Phase 2.

The primary objective of Phase 2 is to evaluate the efficacy of axicabtagene ciloleucel and utomilumab, as measured by complete response (CR) rate, in subjects with refractory large B-cell lymphoma.

The secondary objectives of Phase 1 and Phase 2 are to assess the safety and tolerability of axicabtagene ciloleucel and utomilumab, additional efficacy endpoints, and levels of axicabtagene ciloleucel in blood (pharmacokinetics [PK]) and levels of cytokines in serum (pharmacodynamics [PD]).

3. STUDY DESIGN

3.1. Overview

This is a phase 1/2, open-label, multicenter study evaluating the safety and efficacy of axicabtagene ciloleucel in combination with utomilumab administration in subjects with refractory large B-Cell lymphoma. The trial will be separated into 2 distinct phases designated as Phase 1 and Phase 2.

During Phase 1, up to 36 subjects with refractory large B-cell lymphoma will be enrolled in a 3+3 design in up to 6 of 10 possible cohorts to evaluate the safety of axicabtagene ciloleucel and utomilumab treatment regimens as depicted in Figure 1. Axicabtagene ciloleucel will be administered as a single dose, and utomilumab will be administered at escalating doses. Subjects will be enrolled and treated one at a time during the Phase 1 portion of the study. Subject treatment with axicabtagene ciloleucel will be staggered by at least 2 weeks.

Axicabtagene ciloleucel will be administered at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg (range 1 x 10^6 anti-CD19 CAR T cells/kg to 2.4 x 10^6 anti-CD19 CAR T cells/kg) on Day 0. Utomilumab will begin at a fixed dose of 10 mg on Day 1 in Cohort 1. An internal safety review team (SRT), comprising the study sponsor and at least one Phase 1 investigator, will review safety data after all subjects in Cohort 1 complete the dose-limiting toxicity (DLT) window (28 days after the last subject in a cohort received the first utomilumab infusion). If Cohort 1 passes DLT criteria, then the study will proceed to Cohort 2. CCI [redacted] The same rules will apply to all the rest of cohorts.

In Phase 2, approximately 24 subjects will be enrolled to receive axicabtagene ciloleucel and utomilumab based on the dose and schedule selected to move forward from the Phase 1 portion of the study as recommended by the SRT.

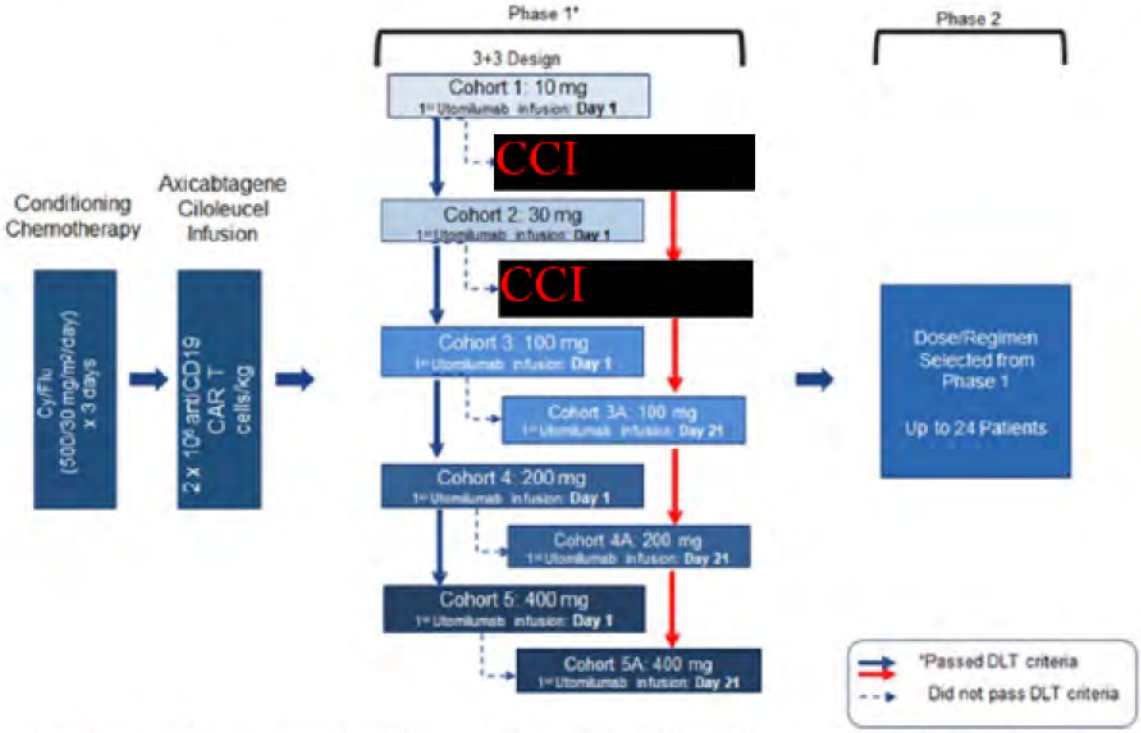
Independent of the cohort or phase of the study, each subject will proceed through the following study periods as depicted in Figure 2:

- Screening
- Enrollment/Leukapheresis
- CCI [redacted]
- Conditioning chemotherapy
- Investigational product treatment (axicabtagene ciloleucel and utomilumab)

- Post-treatment assessment
- Long-term follow-up (LTFU)

Subjects who achieve a PR or CR and subsequently experience disease progression may have an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel.

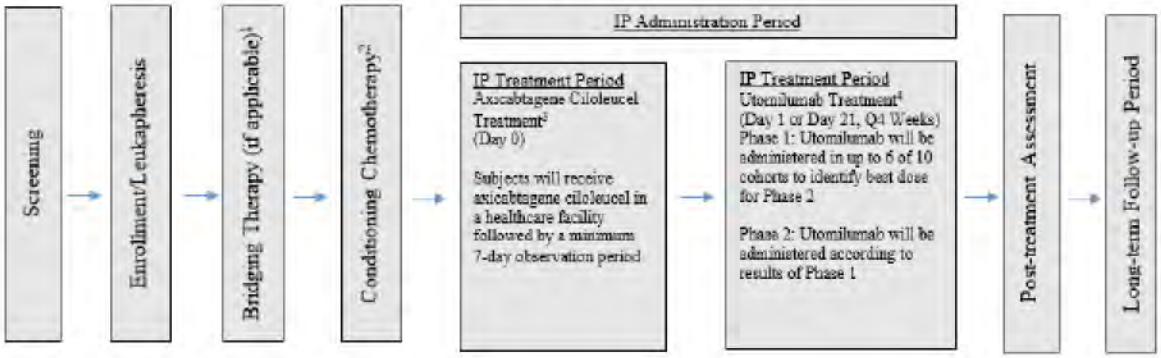
Figure 1. Study Schema of 3+3 Design



* Utomilumab will be administered at total doses of 10 mg, 30 mg, 100 mg, 200 mg, and 400 mg Q4W for 6 months unless there is disease progression.

Abbreviations: DLT, dose-limiting toxicity.

Figure 2. Study Schema in Phase 1 and Phase 2



[1] Non-chemotherapy bridging therapy will be administered at the discretion of the investigator. For subjects receiving bridging therapy, refer to protocol Section 6.1.2 for bridging therapy details.
[2] Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2/day and fludarabine 30 mg/m^2/day, administered x 3 days. Refer to Section 6 for chemotherapy treatment details.
[3] Axicabtagene ciloleucel treatment consists of a single infusion of CAR transduced autologous T cells administered intravenously on Day 0 at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg (maximum 2 x 10^8 anti-CD19 CAR T cells).
[4] Utomilumab treatment consists of an intravenous infusion started on Day 1 or Day 21 and continuing Q4 weeks for 6 months or until PD, whichever comes first. The SRT will make recommendations on further study conduct of Phase 1. Additional axicabtagene ciloleucel and utomilumab regimens may be explored in Phase 1
Utomilumab treatment in Phase 2 will follow the dosing regimen from Phase 1 agreed upon by the study sponsors and the SRT.
Abbreviations: IP, investigational product.

3.2. Hypothesis

No formal hypothesis will be tested in this study. The Phase 2 portion of the study is designed to estimate the true CR rate in subjects with refractory large B-cell lymphoma treated with axicabtagene ciloleucel followed by utomilumab.

3.3. Sample Size Consideration

The anticipated enrollment in this study is approximately 3 to 60 subjects. Phase 1 will enroll approximately 3 to 36 subjects. If the study proceeds to Phase 2, a total of up to 24 additional subjects will be enrolled.

This study uses a single-arm design to estimate the true CR rate in subjects with refractory large B-cell lymphoma treated with axicabtagene ciloleucel and utomilumab at the dosing schedule tested in Phase 1 and deemed safe by the SRT. With a total sample size of approximately 27 subjects at a given dosing schedule, of which at least 3 will have been treated in the Phase 1 portion, an observed CR rate of 70% will yield an exact 95% confidence interval (CI) of (50%, 86%). This target CR rate, and the lower limit of the 70% CI for the CR rate, is meaningful because it would represent a significant improvement in the response rate for the subjects with relapsed/refractory large B-cell lymphoma over existing therapies.. Additional assumptions and corresponding two-sided 95% and 80% exact confidence intervals are provided in Table 1.

Table 1. Exact Confidence Intervals (95% and 80%) Corresponding to Observed CR Rate based on 27 Subjects

Subjects with CR	Observed CR Rate	95% Confidence Interval	80% Confidence Interval
15	56%	[35%, 75%]	[42%, 69%]
17	63%	[42%, 81%]	[49%, 76%]
19	70%	[50%, 86%]	[56%, 82%]
21	78%	[58%, 91%]	[64%, 88%]
23	85%	[66%, 96%]	[73%, 93%]

Abbreviations: CR, complete response

4. STUDY ENDPOINTS AND COVARIATES

4.1. Endpoints

4.1.1. Primary Endpoint

- Phase 1: Incidence of AEs defined as DLTs
- Phase 2: Complete response (CR) rate per the Lugano Classification (Cheson et al, 2014), as determined by the study investigators

4.1.2. Secondary Endpoints

Secondary endpoints are applicable to both Phase 1 and Phase 2:

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

4.2. Subgroups and Covariates

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

- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1)
- Age at baseline (<65 years, ≥65 years)
- Race
- Gender
- Histologically proven DLBCL type

- Cell of origin (GCB, ABC, or Other)
- Double/Triple hit status
- Disease stage at study entry
- International Prognostic Index (IPI) total score at baseline
- Refractory subgroup (primary refractory, refractory to second line or greater, relapse post ASCT)
- Number of prior chemotherapy regimens
- Prior transplant (autologous stem cell transplant [ASCT]) (Y/N)
- Bulky disease (at least one lesion 10 cm in diameter))
- Tumor burden at baseline, as measured by the sum of the product of the diameters (SPD) of target lesions at baseline (≤ median vs. > median value)
- Received bridging chemotherapy

5. DEFINITIONS

5.1. General

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

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

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

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

Refractory Subgroup at Baseline:

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

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

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

5.2. Safety

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

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

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

Identified risks:

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

Potential risks:

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

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

Neurologic Event: Neurologic 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 or concomitant conditions (e.g. CRS). Additionally, the MedDRA system organ classes (SOCs) of Psychiatric Disorders and Nervous System Disorders will be reviewed for additional events; these events will then be evaluated for potential inclusion as neurologic AEs.

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

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

Infections: Infections are identified as AEs within the MedDRA SOC of Infections and Infestations that occur after treatment with anti-CD19 CAR T cells. Subtypes of infections are identified using MedDRA high level group terms (HLGT) that capture events of:

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

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

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

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

Autoimmune disorders: Autoimmune disorders are identified via collection on a CRF in which the investigator classifies the event as an autoimmune disorder. Additionally, adverse events that are coded into the MedDRA HLGT of auto-immune disorders within the immune system disorders SOC will be reviewed to identify other potential events.

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

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

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

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

The cumulative dose of utomilumab is defined as the sum of all doses (in mg) administered across the treatment period.

5.3. Efficacy

Complete Response Rate (CRR): The proportion of subjects with a CR while after treatment with axicabtagene ciloleucel and utomilumab and prior to any subsequent anti-cancer therapy. Subjects who do not meet the criteria for CR by the analysis cutoff date will be considered non-CR. The derivation of this endpoint will only include response assessments obtained after at least one dose of utomilumab administration after axicabtagene ciloleucel infusion, and prior to any subsequent anti-cancer therapies (including stem cell transplant [SCT]). Responses will be assessed per the Lugano Classification {Cheson 2014}, as determined by the study investigators.

Objective Response Rate (ORR): The proportion of subjects with a CR or PR while after treatment with axicabtagene ciloleucel and utomilumab and prior to any subsequent anti-cancer

therapy. Subjects who do not meet the criteria by the analysis cutoff date will be considered non-responders. The derivation of this endpoint will only include response assessments obtained after at least one dose of utomilumab administration after axicabtagene ciloleucel infusion, and prior to any subsequent anti-cancer therapies (including SCT). Responses will be assessed per the Lugano Classification {Cheson 2014}, as determined by the study investigators.

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

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

Overall Survival (OS): OS is defined as the time from the axicabtagene ciloleucel infusion date to the date of death. Subjects who have not died by the analysis data cutoff date will be censored at their last date known to be alive or the data cutoff date, whichever is earlier. Further details on the derivation of OS and the specific data modules that will be used to derive the last date known to be alive are provided in Appendix 2.

6. ANALYSIS SETS

The following analyses sets are defined for this study.

6.1. Full Analysis Set

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

6.2. Modified Intent-to-treat Analysis Set

The modified intent-to-treat (mITT) analysis set consists of all subjects enrolled and treated with the target dose of axicabtagene ciloleucel at 2×10^6 anti CD19 CAR T cells/kg (range 1.0×10^6 to 2.4×10^6) and at least one dose of utomilumab after axicabtagene ciloleucel infusion, as determined upon completion of the Phase 1 and Phase 2 portions of the study. This analysis set will be used for all efficacy analyses.

6.3. Safety Analysis Set

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

6.4. DLT Analysis Set

The DLT evaluable set consists of all subjects in each Phase 1 cohort who are treated with axicabtagene ciloleucel and at least one dose of utomilumab who either:

- Received the target axicabtagene ciloleucel dose and were followed for at least 28 days after the first utomilumab infusion, or
- Received a dose of axicabtagene ciloleucel lower than the target for that cohort and a subsequent utomilumab infusion and experienced a DLT during the 28-day, post-utomilumab infusion period

6.5. Safety retreatment analysis set

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

6.6. mITT Retreatment Analysis Set

The mITT retreatment analysis set will consist of all subjects who undergo retreatment with target dose of axicabtagene ciloleucel. This set will be used for all retreatment efficacy analyses.

7. INTERIM ANALYSIS AND EARLY STOPPING GUIDELINES

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

7.1. Safety Interim Analysis

An internal SRT, comprising the study sponsor medical monitor, drug safety physician, study statistician, and at least one active investigator, will be chartered to review safety during Phase 1 of the study and to make recommendations on further study conduct in Phase 1 and progression to Phase 2 based on the incidence of investigational product related dose-limiting toxicities (DLTs) and review of serious adverse events (SAEs).

The SRT will meet to review the safety data following the accrual and completion of the DLT assessment period of each Phase 1 cohort, i.e. for each Phase 1 cohort after all subjects in that cohort have had the opportunity to complete the DLT window (28 days after the last subject in a cohort received the first utomilumab infusion).

The SRT will additionally meet on at least one occasion during the Phase 2 portion of the study after 6 subjects have completed their 1-month disease assessment. The SRT will review safety and efficacy data and will make trial conduct recommendations based on an analysis of benefit vs risk.

The SRT may meet more often as needed.

8. DATA SCREENING AND ACCEPTANCE

8.1. General Principles

The database will be subject to the edit checks outlined in the Data Management Plan and additional manual data reviews defined by the study team. Data inconsistencies will be reviewed and resolved before the database snapshot for the primary analysis and the final database lock.

8.2. Electronic Transfer and Archiving of Data

The Medidata Rave system will be used to collect the data in this study. Raw data extracted from Medidata Rave will be archived prior to further dataset creation, maintenance, and analysis. Datasets (raw data, study data tabulation model [SDTM] data, and/or analysis data model [ADaM] data) for planned analyses will be archived. Any additional unplanned analyses that occur after the primary analysis and prior to the final analysis will also be archived. Key data external to the clinical study database will be included in the relevant SDTM and ADaM modules when the external data are available.

8.3. Handling of Missing and Incomplete Data

8.3.1. Efficacy

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

8.3.2. Safety

Partial AE start dates will be imputed. If dates are missing or incomplete for AE start dates, the algorithm defined in Appendix 1 (Section 12) will be used. Completely missing death dates or death dates with only a year reported will not be imputed.

8.4. Detection of Bias

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

8.5. Outliers

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

8.6. Distributional Characteristics

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

8.7. Validation and Configuration Management

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

9. STATISTICAL METHODS OF ANALYSIS

9.1. General Principles

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

The primary efficacy analysis will be performed when the last treated subject in the mITT set has had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment.

All subjects will be followed for survival for up to approximately 15 years after the last subject receives axicabtagene ciloleucel. No formal hypothesis testing will be performed based on data obtained after the cutoff for the primary analysis. Descriptive estimates of key efficacy and safety analyses may be updated to assess the overall treatment profile.

The final analysis will occur when all subjects have completed the study. Additional analyses for internal review or publication may occur after the primary analysis.

9.2. Subject Accountability

The number of subjects screened, enrolled (i.e. leukapheresed), treated with conditioning chemotherapy, treated and re-treated with investigational treatments will be summarized. The reasons for discontinuing treatment and discontinuing study will be summarized.

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

The number of subjects enrolled by site will be summarized.

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

9.3. Important Protocol Deviations

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

9.4. Demographic and Baseline Characteristics

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

- Age (in years) at baseline and by category (< 65, ≥ 65)
- Sex
- Ethnicity and race
- Weight at leukapheresis
- ECOG performance status at baseline
- Number of prior chemotherapy regimens and best overall response to the last prior regimen
- Prior ASCT and best overall response corresponding to the ASCT
- Refractory subgroup (primary refractory, second line or greater, relapse post-ASCT)
- Tumor burden, as measured by the SPD of selected nodes or lesions at baseline
- Disease stage at study entry (I, II, III, IV)
- Cell of origin
- Histologically proven DLBCL type
- Disease extent (presence of B symptoms, S [splenic involvement], E [extranodal disease], X [bulky disease], bone marrow involvement) as determined by the investigator at screening
- Double/Triple Hit Status
- International Prognostic Index Total Score at baseline
- For subjects with cytogenetics testing performed:
  - BCL-2 alternations/over-expressions (Y/N)
  - BCL-6 alternations/over-expressions (Y/N)
  - C-MYC alternations/over-expressions (Y/N)

9.5. Medical and Surgical History

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

9.6. Prior Therapy for Primary Study Disease and Prior Radiotherapy

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

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

9.7. Efficacy Analyses

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

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

9.7.1. Complete Response and Objective Response

9.7.1.1. Analyses of Response Rate

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

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

9.7.1.2. Subgroup Analyses

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

9.7.2. Duration of Response

The number of subjects censored or having events, and the reasons for censoring or type of events (PD or death) will be summarized. The Kaplan-Meier approach will be used to estimate DOR and its quartiles' 2-sided 95% confidence interval, as well as estimates of the proportion of subjects alive and in response at 3-month intervals. The reverse Kaplan-Meier approach {Schemper 1996} will be used to estimate the follow-up time for DOR.

A sensitivity analysis of DOR will be conducted in which disease assessments obtained after SCT (for subjects who undergo SCT while in an axicabtagene ciloleucel-induced response) are used in the derivation of DOR.

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

9.7.3. Progression Free Survival

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

A sensitivity analysis of PFS will be conducted in which the disease assessments obtained after SCT will be included in the derivation of PFS. Subgroup analyses of the PFS rate at 6 months may be generated in subgroups defined by the covariates in Section 4.2.

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

9.7.4. Overall Survival

The analysis of OS will use the same methods as the analysis of PFS.

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

9.7.5. Tumor Burden

The change in tumor burden, as measured by the SPD of the selected lesions, from baseline to post-baseline nadir will be summarized in absolute numbers (mm^2) and percentage change. Summary statistics will be provided for this change. Data collected after new anti-cancer therapy (including SCT) will not be included for the analyses.

9.8. Safety Analyses

Safety analyses will be conducted on the safety analysis set, with the exception that Phase 1 DLT will be summarized in the DLT analysis set. The primary analysis of safety data will summarize all TEAEs and laboratory values.

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

Subjects enrolled, but not received investigational treatments, will be followed for AEs for 30 days after the last study procedure. AEs reported in these subjects will be archived in the study database and available in SDTM and ADaM datasets, but will not be tabulated in AE summaries.

9.8.1. Adverse Events

DLTs observed in the Phase 1 subject's DLT window will be listed and tabulated by SOC and PT in the DLT analysis set.

The subject incidence of the following TEAEs will be tabulated in the safety analysis set:

- Summary of AEs (any, worst severity, serious, related, fatal)
- All AEs by SOC and PT
- All SAEs by SOC and PT
- All axicabtagene ciloleucel and/or utomilumab related AEs/SAEs
- All Grade 3 or higher AEs
- All Grade 3 or higher axicabtagene ciloleucel and/or utomilumab related AEs
- AEs of interest, including identified risks and potential risks
- AEs leading to study treatment discontinuation
- Other clinically important adverse reactions
- Fatal AE and death (through the long term follow-up period)

Subjects with prolonged cytopenias (neutropenia or thrombocytopenia or anemia) will be identified with cytopenias (neutropenia or thrombocytopenia or anemia) present on or after Day 30 post axicabtagene ciloleucel infusion

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

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

9.8.2. Laboratory Test Results

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

9.8.3. Anti-drug Antibody

The subject incidence of any anti-axicabtagene ciloleucel, anti-utomilumab and neutralizing antibodies will be tabulated. For subjects testing positive for antibodies, the persistence (in magnitude [titer] over time, time of onset, and duration) of the antibody will be summarized.

9.8.4. Replication Competent Retrovirus

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

9.9. Exposure to Study Treatments and Product Characteristics

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

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

9.10. Exposure to Concomitant Medications and Procedures

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

9.11. Subsequent Anti-Cancer Therapy

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

9.12. Duration Metrics

Summary statistics will be provided for the following durations:

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

9.13. Axicabtagene Ciloleucel Delivery Time

Summary statistics will be provided for the following delivery time:

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

9.14. Pharmacokinetics

Refer to separate PK/PD SAP.

9.15. Pharmacodynamics

Refer to separate PK/PD SAP.

10. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Not applicable.

11. REFERENCES

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.

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.

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

Topp MS, Gokbuget 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 Oncol 2015;16 (1):57-66.

12. APPENDICES

Appendix 1. Conventions for Clinical Data That Require Imputation for Partial or Missing Dates
Appendix 2. Derivation of Time to Event Endpoints
Appendix 3. Derivation of Last date known to be alive

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

The following data will be imputed using the algorithm shown in Table 2 below:

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

Table 2. Imputation Rules for Partial or Missing Start Dates

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

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

Imputation rules for partial or missing death dates:

1) If death year and month are available but day is missing:

- If mmyyyy for the last contact date = mmyyyy for death date, set death date to the day after the last date known to be alive.
- If mmyyyy for the last date known to be alive < mmyyyy for death date, set death date to the first day of the death month.
- If mmyyyy for last date known to be alive > mmyyyy for death date, data error and do not impute.

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

Imputation rules for original date of diagnosis:

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

Appendix 2. Derivation of Time to Event Endpoints

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

Duration of Response (DOR):

Table 3. Primary Analysis of DOR

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

Table 4. Sensitivity Analysis of DOR

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

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

Progression-free Survival (PFS):

Table 5. Primary Analysis of PFS

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

Table 6. Sensitivity Analysis of PFS

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

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

Overall Survival (OS):

Table 7. Imputation Rule of OS Event/Censoring Date

Circumstance	Event / Censored	Date of Event / Censoring
Death before data cutoff date for analysis	Event	Date of death
Death after data cutoff date for analysis	Censored	Data cutoff date
Known to be alive after data cutoff date for analysis	Censored	Data cutoff date
Alive up through the discontinuation of study or data cutoff date and no further information available afterwards	Censored	last date known to be alive up through the date of discontinuation of study, or data cutoff date, whichever is earlier

Appendix 3. Derivation of Last date known to be alive

The last date known to be alive will be derived by obtaining the maximum complete date among the following data modules:

- Start date of AE (including targeted AE)
- Leukapheresis date
- Conditioning chemotherapy admin date
- Axicabtagene ciloleucel infusion date
- Utomilumab infusion date
- CT scan date
- PET scan date
- Target lesion assessment date
- Non-target lesion assessment date
- New lesion assessment date
- Disease response assessment date
- Long term follow-up subject status date where status = 'alive'
- End of treatment disposition where status is not equal to death or lost to follow up
- End of post-treatment assessment period where status is not equal to death or lost to follow up
- End of study data where end of study reason is not equal to death or lost to follow up