TRANSLATIONAL STATISTICAL ANALYSIS PLAN

KTE-C19-112 TRANSLATIONAL PRIMARY ANALYSIS (PA)

Sponsor:	Kite Pharma, Inc. 2400 Broadway Santa Monica, CA 90404 United States of America
Product Name:	Axicabtagene ciloleucel
Protocol:	A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma (ZUMA-12)
Protocol Version:	Amendment 1, 14 August 2019
TSAP Release Date:	25 February 2021
Replaces Previous Version(s):	

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AUC	area under the curve
CAR	chimeric antigen receptor
CCR7	C-C motif chemokine receptor 7
CR	complete response
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
IPI	International Prognostic Index
NE	neurologic event
OR	objective response
ORR	objective response rate
PA	primary analysis
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PK	pharmacokinetics
PR	partial response
SD	stable disease
TNF	tumor necrosis factor
TSAP	translational statistical analysis plan

1. INTRODUCTION

This translational statistical analysis plan (TSAP) outlines the primary analyses (PA) to be conducted for translational data within protocol KTE-C19-112 Amendment 1 titled "A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma", dated on 14 August 2019.

2. OBJECTIVES

2.1. Objectives

- Characterize the presence, expansion, persistence and clearance of anti-CD19 chimeric antigen receptor (CAR) T cell in blood (cells/µL) (pharmacokinetics [PK]), and serum cytokine (pharmacodynamics) profiles
- Explore associations between anti-CD19 CAR T cell PK/pharmacodynamics and clinical efficacy and safety outcomes
- Characterize levels of serum cytokines at baseline, after conditioning chemotherapy, and prior to and after infusion of KTE-C19
- Explore association between serum cytokine profile (e.g. peak, area under the curve [AUC]) versus safety outcomes
- Characterize the key KTE-C19 product attributes
- Explore association between key product attributes and anti-CD19 CAR T cell PK, clinical efficacy, and safety outcomes

2.2. Hypothesis

The analyses outlined in this TSAP are descriptive summaries, and no formal prespecified hypothesis will be tested.

3. ENDPOINTS, SUBGROUPS AND COVARIATES

3.1. Biomarker datasets

Table 3-1. Data overview on assay methods and biomarker lists

Data type	Assay method/ Sample type	Biomarker set	Time points of scheduled assessment
PK data (Anti-CD19 CAR T cell levels in blood)	qPCR/PBMC	Number of CAR T cells (cells/µL)	Outlined in Appendix 1
Pharmacodynamic data (levels of cytokines in serum)	Cytokine assay/serum sample	• Homeostatic, pro-inflammatory and immune modulating cytokines IL-2, IL-6, IL-10, IL-12p40/p70, IL-15, IL-17a, TNF-α, IFN-γ and GM-CSF • acute phase reactants, such as CRP • chemokines IL-8, MCP-1 and MIP-1α and IP-10 • HLH related markers ferritin and IL-2Rα	Outlined in Appendix 2
Product characteristics	Flow cytometry/investigational products	• Total number of T cells • Total number of CAR T cells • CD4/CD8 ratio • % Tnaive • % T central memory • % T effector memory • % T effector cells • (% Tnaive + % T central memory)/ (% T effector memory + % T effector cells) • IFN-gamma level (pg/ml) • % CD4 • % CD8 • Viability • % transduction rate • Vector copy number • CCR7	

Abbreviations: CAR, chimeric antigen receptor; CCR, C-C chemokine receptor; CD, cluster of differentiation; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLH, hemophagocytic lymphohistiocytosis; IFN, interferon; IL, interleukin; IL-2Rα, interleukin-2 receptor α; IP, interferon gamma-induced protein; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; PBMC, peripheral blood mononuclear cells; PK, pharmacokinetics; qPCR, quantitative polymerase chain reaction; TNF, tumor necrosis factor.

3.2. Endpoints

All definitions are generally applied to PK and/or pharmacodynamics endpoints. Detailed definitions can be found in Section 4.

- Peak
- Time to peak
- AUC
- Fold change from baseline at Day X
- Fold change from Day 0 at Day X

All measurable biomarker values at each visit will be used in calculating endpoints for all biomarkers listed in Table 3-1 as follows:

- Levels of anti-CD19 CAR T cells in blood samples measured as number of CAR T cells in blood (cells/µL) by visit, peak value, Day 0-28 AUC, and time to peak (details for the derivations are included in Section 4, the definition section)
- Levels of cytokines in serum by scheduled visit, fold change from baseline, fold change from Day 0, peak value, Day 0-28 AUC, and time to peak
- Product attributes measurements after product manufacturing and prior to dosing

3.3. Outcomes, Subgroup, and Key Covariates

All of the covariates from clinical Statistical Analysis Plan will be investigated if applicable to translational data analysis, including:

- Worst neurologic event (NE) grade: Grade 3 or higher versus Grade 2 or lower
- Worst NE grade: Grade 2 or higher versus Grade 1 or lower
- Worst cytokine release syndrome (CRS) grade: Grade 3 or higher versus Grade 2 or lower
- Worst CRS grade: Grade 2 or higher versus Grade 1 or lower
- Complete response (CR) vs. non-CR (partial response [PR] + stable disease [SD] + progressive disease [PD]) per study investigator assessment
- Objective response (OR; CR + PR) vs. nonresponder (SD + PD) per study investigator assessment

- Ongoing response (ongoing vs. relapsed vs. nonresponder) by data cutoff date
- Baseline covariates
  - Age at baseline (< 65 years, ≥ 65 years)
  - Sex (male, female)
  - Race (categories may be collapsed or expanded based on accrual)
- Tocilizumab use (Yes, No)
- Systemic Steroids used
  - Yes vs. No
  - Steroids alone, Tocilizumab alone, Both Steroids and Tocilizumab, Neither Steroids nor Tocilizumab
- Diagnosis category per central lab (Double-/Triple-hit Lymphomas, Double-/Triple-hit with International Prognostic Index (IPI) score ≥ 3, Double-/Triple-hit with IPI score < 3, Non-double-/triple-hit with IPI score ≥ 3, Overall)
- Diagnosis category per study investigator assessment (Double-/Triple-hit Lymphomas, Double-/Triple-hit with IPI score ≥ 3, Double-/Triple-hit with IPI score < 3, Non-double-/triple-hit with IPI score ≥ 3, Overall)
- Baseline tumor burden (sum of product of diameters in mm^2 by median or quartiles)
- CD19 immunohistochemistry (IHC) test H-Score at baseline (≤ 5 vs. > 5) by central pathology
- Other baseline covariates if applicable

4. DEFINITION

4.1. General

All definitions are generally applied to PK and pharmacodynamics endpoints and analyses.

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. Any days after enrollment and prior to Study Day -1 will be sequential and negative integer valued.

4.2. Key Measurements of Pharmacokinetics: Anti-CD19 CAR+ T Cell

The presence, expansion, persistence of anti-CD19 CAR T cells in peripheral blood will be measured by quantitative polymerase chain reaction (qPCR) analysis.

Scheduled blood draw for anti-CD19 CAR T cells: Enrollment/Leukapheresis, Day 7, Week 2 (Day 14 ± 3 days), Week 4 (Day 28 ± 3 days), Month 3 (Day 90 ± 1 week), Month 6, Month 9, Month 12, and Month 24. This TSAP will focus on blood anti-CD19 CAR T cell PK data collected per planned assessment. The analytic visit window is defined in Appendix 1.

Number of anti-CD19 CAR T (cells/µL) derivation:

$$White\ Blood\ Cell\ counts\ (/\mu L) \times (Monocytes(\%) + Lymphocytes(\%)) \times\ PBMCs(\%)$$

Baseline anti-CD19 CAR T (cells/µL) is defined as 0 since KTE-C19 is infused on Day 0.

Peak anti-CD19 CAR T cell (cells/µL) is defined as the maximum absolute number of CAR T cells in blood attained after Day 0.

Time to Peak of anti-CD19 CAR T cells (days) is defined as "Peak date – KTE-C19 dosing date +1".

AUC of anti-CD19 CAR T cell (cells/ mL*Days) from Day 0 to Day 28 is defined as the area under the curve in a plot of levels of anti-CD19 CAR T cells against scheduled visits from Day 0 to Day 28. This AUC measures the total levels of anti-CD19 CAR T cells over time. Given that anti-CD19 CAR T cells are measured at certain discrete time points, the trapezoidal rule (see Appendix 3) will be used to estimate the AUC.

4.3. Key Measurements of Pharmacodynamics: Serum Cytokines, Chemokines, and Other Blood Biomarkers

Scheduled blood draws for cytokines: Enrollment/Leukapheresis, Day 0, Day 1, Day 3, Day 7, Week 2 (Day 14 ± 3 days), and Week 4 (Day 28 ± 3 days). This TSAP will focus on the cytokine data collected from baseline to Day 28. The analytic visit window is defined in Appendix 2.

Baseline is defined as the last value measured prior to conditioning chemotherapy.

Fold change from baseline at Day X is defined as

$$\frac{\text{Cytokine level at Day X}}{\text{Cytokine level at baseline}}$$

Fold change from Day 0 at Day X is defined as

$$\frac{\text{Cytokine level at Day X}}{\text{Cytokine level at Day 0}}$$

Change from baseline at Day X is defined as

Analyte level at Day X – Analyte level at baseline

Peak post baseline is defined as the maximum level of analytes in serum attained after baseline up to Day 28.

Time to peak of serum biomarker is defined as the number of days from Day 0 to the day when the peak level was attained, "Peak date – KTE-C19 dosing date + 1".

AUC from baseline to Day 28 is defined as the area under the curve in a plot of levels of serum analytes against scheduled visits from baseline to Day 28. This AUC measures the total levels of serum analytes overtime. Given the measurements are made at certain discrete time points, the trapezoidal rule will be used to estimate the AUC (see Appendix 3).

4.4. Product Characteristics

- All product characteristics as defined in Table 3-1 will be summarized individually and also for the correlative analysis with anti-CD19 CAR T levels and clinical outcome endpoints.
- Two additional covariates will be derived for exploration:
  - **CD4/CD8 ratio** is defined as: $\frac{\text{CD4 Cells (\%)}}{\text{CD8 Cells (\%)}}$
  - **CCR7$^+$ in (%) or (#)** is defined as naïve (%) or (#) + central memory (%) or (#), respectively

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is defined as all subjects treated with any dose of axicabtagene ciloleucel. The safety analysis set will be used to summarize translational data and association analysis between translational data and safety outcomes.

5.2. Response Evaluable Analysis Set

The response evaluable analysis set will consist of the subjects who are enrolled and treated with axicabtagene ciloleucel at a dose of at least 1×10^6 anti-CD19 CAR T cells/kg and centrally confirmed disease type (double-/triple- hit lymphomas) or IPI score ≥ 3. This analysis set will be used for all association analysis between translational data and efficacy outcomes including CR rate, objective response rate (ORR), and ongoing response.

5.3. Safety Re-treatment Analysis Set

The safety retreatment analysis set will consist of all subjects who undergo retreatment with axicabtagene ciloleucel. This set will be used to summarize translational data in the retreatment period.

6. STATISTICAL ANALYSIS

6.1. General Methods

The following methods will be applied to the data analysis when applicable.

- Summary statistics

Summary statistics refers to number of subjects, median, first quartile (Q1), third quartile (Q3), minimum and maximum for continuous measurements by appropriate subgroups and covariates, and summary analysis in quartile range ([Min , Q1), [Q1, Median), [Median, Q3), [Q3, Max]) by appropriate subgroup and covariates.

- Simple Linear Regression

Simple Linear Regression (SLR) may be conducted to explore relationships between biomarkers and continuous numbers (Gelman and Hill, 2006). The estimated slope and its 95% confidence interval with the unadjusted p-value will be reported.

- Non-parametric Wilcoxon rank sum tests

Non-parametric Wilcoxon rank sum tests (Wilcoxon, 1945; Siegel, 1956) will be utilized to explore the associations between PK/pharmacodynamics, product characteristics, and outcomes. Unadjusted p-values will be reported. The multiplicity adjustment (Holm-Bonferroni step-down method, Holm 1979; Hommel 1988) may be implemented when further characterizations of potential association are identified, and adjusted p-values will be reported. Median fold change will be utilized to describe the differences in the outcome.

- Non-parametric Kruskal-Wallis test

Non-parametric Kruskal-Wallis test (Kruskal; Wallis, 1952) will be conducted for 3 or more group comparison followed by pairwise comparisons using Dunn's test with Holm's adjustment method (Dunn, 1964).

6.2. Analysis

6.2.1. 6.2.1 Characterize the anti-CD19 CAR T cell expansion (PK) and serum cytokine (pharmacodynamics) profile

- Safety Analysis Sets will be used
- The Median Line plot over time with interquartile range (IQR) will be produced
- Anti-CD19 CAR T cell profile (PK) over time will be summarized using summary statistics described in section 6.1 by subgroup and baseline covariates specified in section 3.3.

- Similarly, pharmacodynamics profile as measured by serum cytokine levels over time will be summarized by subgroup and baseline covariates using summary statistics described in section 6.1.

  — Pre-selected key analytes as listed in Table 3-1 will be presented in the Clinical Pharmacology report

  — Number (%) of subjects with a 2-fold or higher change from baseline at peak and week 4 will be summarized.

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6.2.4. 6.2.4 Characterize product attributes

- Safety analysis set will be used

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[redacted]

7. REFERENCE

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8. APPENDICES

Appendix 1. Definition of Analytic Visit Windows for CAR T Cells in Blood Measurements

To define the analytic visit for scheduled measurements of CAR T cell in blood, given the real lab data, for each analytic visit, say 'Day 7', search through the records with lab day in window of Day [1, 10], then assign analytic visit 'Day 7' to the record whose lab day is closest to 'Target Day', ie, Day 7. If there are 2 records being same closest to target day, choose the earlier one.

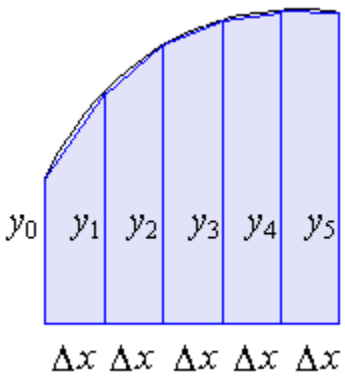
Analytic Visit	Baseline	Day 7	Week 2	Week 4	Month 3	Month 6	Month 9	Month 12	Month 24
Target Day	0	7	14	28	90	180	270	360	720
Lab Window	≤ 0	[1, 10]	[11, 21]	[22, 59]	[60, 135]	[136, 225]	[226, 314]	[315, 540]	>=541

Appendix 2. Definition of Analytic Visit Windows for Cytokines in Serum Measurements

To define the analytic visit for scheduled measurements of cytokines in serum, given the real lab data, for each analytic visit, say 'Day 7', search through the records with lab day in window of Day [5, 10], then assign analytic visit 'Day 7' to the record whose lab day is closest to 'Target Day', ie, Day 7. If there are 2 records being same closest to target day, choose the earlier one.

Analytic Visit	Baseline	Day 0	Day 1	Day 3	Day 7	Week 2	Week 4
Target Day	-5	0	1	3	7	14	28
Lab Window	≤ -5	0	1	[2, 4]	[5, 10]	[11, 21]	[22, 59]

Appendix 3. Trapezoidal Rule to Approximate the Area Under the Curve



$$\text{AUC} \approx \frac{1}{2}(y_0 + y_1) \cdot \Delta x + \frac{1}{2}(y_1 + y_2) \cdot \Delta x + \frac{1}{2}(y_2 + y_3) \cdot \Delta x + \ldots$$

KTE_C19_112_TSAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	21-Jun-2021 18:24:11