# TRANSLATIONAL STATISTICAL ANALYSIS PLAN KT-US-471-0119

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|---|---|
| **Sponsor:** | Kite Pharma, Inc.<br>2400 Broadway<br>Santa Monica, CA 90404<br>United States of America |
| **Product Name:** | KTE-C19 |
| **Protocol:** | KT-US-471-0119 (ZUMA-19)<br>A Phase 1/2 Open-label, Multicenter Study of Lenzilumab and Axicabtagene Ciloleucel in Subjects with Relapsed or Refractory Large B-cell Lymphoma (ZUMA-19) |
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# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AUC | Area under the curve |
| Axicabtagene ciloleucel / KTE-C19 | Autologous T cells transduced with retroviral vector containing anti-CD19 CD28/CD3 zeta chimeric antigen receptor |
| CAR | Chimeric antigen receptor |
| CR | Complete response |
| CRS | Cytokine release syndrome |
| CSF | Cerebrospinal fluid |
| mITT | Modified intent-to-treat |
| NE | Neurologic event |
| ORR | Objective response rate |
| PBMC | Peripheral blood mononuclear cells |
| PD | Progressive disease |
| PR | Partial response |
| SD | Stable disease |
| SOA | Schedule of assessments |
| RP2D | Recommended Phase 2 Dose |
| qPCR | Quantitative PCR |

# 1. INTRODUCTION

This supplemental statistical analysis plan outlines the analyses of pharmacokinetics/ pharmacodynamics, product characteristics, and other biomarkers in support of the end of study for sequenced therapy with lenzilumab and axicabtagene ciloleucel (KTE-C19) in subjects with relapsed or refractory large B-cell lymphoma. The analysis will be conducted for biomarker data within protocol KT-US-471-0119 (ZUMA-19) Amendment 1 on 16 September 2019.

# 2. OBJECTIVES

## 2.1. Objectives

- Characterize the presence, expansion, persistence and clearance of anti-CD19 CAR T cell in blood (cells/μL) (pharmacokinetics), and serum analytes (pharmacodynamics) profiles
- Characterize the KTE-C19 product attributes
- Characterize lenzilumab pharmacokinetics and soluble GM-CSF levels
- Characterize soluble analytes, CAR-T cells and other cell subsets in CSF

## 2.2. Hypothesis

The analyses outlined in this TSAP are exploratory and no formal pre-specified 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 |
|---|---|---|
| Pharmacokinetics data (CAR T) | qPCR/PBMCs | • Number of CAR T cells (/µL)<br>• %PBMC |
| Pharmacokinetics data (lenzilumab) | Immunoassays/serum samples | Serum lenzilumab |
| Pharmacodynamics data (serum analytes) | Serum analyte assays/serum samples | • Proinflammatory, homeostatic, and immune-modulating cytokines: IL-5, IL-6, IL-15, IL-17a, IL-10, tumor necrosis factor-α, GM-CSF, G-CSF, IFN-γ, IL-12p40/p70, and IL-13;<br>• Immune effector molecules: granzymes A and B and perforin;<br>• Correlates of acute phase response: SAA, CRP and ferritin; chemokines MIP-1α, MIP-1β, MCP-1, CXCL-10, and IL-8. In addition, IL-1Ra, IL-2Rα |
| CSF Biomarkers | • Serum analyte assays/CSF samples<br>• Flow cytometry/CSF samples | • Biomarkers listed in the Pharmacodynamics analytes<br>• Infiltration of CAR T cells<br>• Infiltration of myeloid cells (CD14+)<br>Appendix 8.4 |
| Product attributes | Flow cytometry/Product | Total number of T cells, total number of CAR T cells, transduction rate (%), vector copy number, CD3 cells (% and #), CD4 cells (% and #), CD8 cells (% and #), CD4/CD8 ratio, T naïve/CM/EM/EFF cells (% and #), (% Tnaive + % T central memory) / (% T effector memory + % T effector cells), % viability, IFN-gamma production in Co-culture (normalized and not-normalized) |

## 3.2. Endpoints

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

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

All measurable biomarker values at each visit will be used as main 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 anti-CD19 CAR+ cells/µL by visit, peak, Day 0-28 AUC, and time to peak
- Levels of serum analytes by visit, fold change from baseline, fold change from Day 0, peak, Day 0-28 AUC, and time to peak
- Product characteristics measurements after product manufacturing and prior to dosing
- Levels of analytes in CSF pre- and post-infusion
- Levels of CAR-T and other cell subsets in CSF pre- and post-infusion

# 4. DEFINITIONS

## 4.1. General

All definitions are generally applied to pharmacokinetics and pharmacodynamics.

**Study day 0** is defined as the day the subject receives the first KTE-C19 infusion.

**Baseline** is generally defined as the last non-missing value measured on or prior to conditioning chemotherapy (starting at day −5 for serum analyte markers).

## 4.2. Key Measurements of Pharmacokinetics:

### 4.2.1. Anti-CD19 CAR+ T-Cell

The presence, expansion and persistence of anti-CD19 CAR T cells in peripheral blood will be monitored by qPCR analysis.

**Scheduled blood draw for anti-CD19 CAR T cell**

This TSAP will focus on the anti-CD19 CAR T cell data collected as per planned assessment. The schedule of assessments and the analytic visit windows are defined in Appendix 8.1.

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**Baseline number of anti-CD19 CAR T (cells/ µL)** is defined as 0 since the axicabtagene ciloleucel infused in day 0, and number of CAR T (cell/µL) will not be derived.

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

**Time-to-Peak of CAR T cell (days)** is defined as "Peak Date – KTE-C19 Dosing Date + 1".

**Area-Under-Curve (AUC) of levels of anti-CD19 CAR T cell (cells/ µL ▪ days)** 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 overtime. Given the anti-CD19 CAR+ T cell is measured at certain discrete time points, the trapezoidal rule (Appendix 8.5) will be used to estimate the AUCs.

**Anti-CD19 CAR T peak/tumor burden:** ratio of CAR T peak and baseline tumor burden local (investigator's assessment) will be assessed.

$$\frac{\text{Pharmacokinetic anlaytes (nCART, nCAR T Peak, or nCAR T AUC)}}{\text{Baseline Tumor Burden (SPD) (mm\^2) from local lab}}$$

### 4.2.2. Lenzilumab Pharmacokinetics

Serum samples will be assayed for lenzilumab concentration (μg/mL) with the use of a validated analytical method.

Blood draws for lenzilumab pharmacokinetics will be performed at different intervals by study phase (Appendix 8.2).

- **Phase 1**, blood draws will occur at baseline prior to infusion and 30 minutes and 1, 3, 6, 9, and 12 hours after infusion on Day 0, then every 12 hours on Days 1 to 5 and daily on Days 6 and 7, then at Week 2 and Week 4.

## 4.3. Key Measurements of Pharmacodynamics: Serum Analytes

**Scheduled blood draw for serum analytes:** Within approximately 5 days of eligibility confirmation (Enrollment/Leukapheresis) at baseline, Day 0, twice daily from Day 1 to Day 5, daily on Day 6 and Day 7, and Week 2 and Week 4. This TSAP will focus on the serum analyte data collected from baseline to Day 28. The SOA and analytic visit window is defined in Appendix 8.3.

**Baseline of serum analytes** is defined as the last value measured prior to lymphodepleting chemotherapy.

**Fold change from baseline at Day X** is defined as

$$\frac{\text{Analyte level at Day X}}{\text{Analyte level at Baseline}}$$

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

**Time to peak of serum analyte post KTE-C19 infusion** is defined as "Peak Date – KTE-C19 Dosing Date + 1".

**Area-Under-Curve (AUC) of analyte levels from baseline to Day 28**: is defined as the area under the curve in a plot of levels of analyte against scheduled visits from baseline to Day 28. This AUC measures the total levels of analyte overtime. Given the serum analyte is measured at certain discrete time points, the trapezoidal rule will be used to estimate the AUCs.

## 4.4. Key Measurements of CSF Analytes

**CSF analytes** are similar to the serum ones used in pharmacodynamics profiling. Peak and AUC analyses are not applied to CSF analytes.

CSF T cells are listed in Appendix 8.4. The T-cell analyte level normalized to CSF volume or CD45 cells will be used in analysis.

CSF sample collection scheduled assessment visits: Baseline, Day 5, and Day 28 (Month 1)

## 4.5. Key Measurements of Product Characteristics

All product characteristics as listed in Table 3-1 will be summarized individually and also for the correlative analysis with anti-CD19 CAR T levels in blood, serum analyte levels, and clinical outcome endpoints.

# 5. ANALYSIS SETS

## 5.1. Modified Intent-to-treat Analysis Set (mITT)

The modified intent-to-treat set will consist of all subjects enrolled and treated with axicabtagene ciloleucel at a minimum dose of $1.0 \times 10^6$ anti-CD19 CAR T cells/kg (or a minimum dose of $1.0 \times 10^8$ anti-CD19 CAR T cells for subjects who weigh more than 100 kg) prior to axicabtagene ciloleucel infusion. This analysis set will be used for all efficacy analyses.

## 5.2. Safety Analysis Set

The safety set is defined as all subjects treated with any dose of axicabtagene ciloleucel and/or any dose of lenzilumab. This analysis set will be used for all safety analyses except for the primary endpoint analysis.

# 6. STATISTICAL ANALYSIS

## 6.1. General Methods

The following methods will be applied to the data analysis when applicable. All p-values generated will be descriptive.

1) Summary statistics

Summary statistics will be generated in frequency (N, %) and quartile range (Minimum, 1st quartile (Q1), Median, 3rd quartile (Q3), Maximum) in overall and by cohort.

2) Simple linear Regression

Simple linear regression will be conducted to explore relationships between biomarkers with continuous numbers {Gelman 2006}. The estimated slope and its 95% confidence interval with the unadjusted p-value will be reported.

3) Non-parametric Wilcoxon rank sum tests

Non-parametric Wilcoxon rank sum tests {Siegel 1956, Wilcoxon 1945} will be utilized to explore the associations between pharmacokinetics/pharmacodynamics profiles, product characteristics by clinical outcomes subgroups. Unadjusted p-values will be reported. The multiplicity adjustment (Holm-Bonferroni step-down method, {Holm 1979, Hommel 1988} may be implemented when further characterization 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.

4) Non-parametric Kruskal-Wallis test

Non-parametric Kruskal-Wallis test {Kruskal 1952} will be conducted for three or more-group comparison followed by pairwise comparisons using Dunn's test with Holm's adjustment method {Dunn 1964}.

5) Clopper Pearson Method

Will be used to calculate exact 95% confidence intervals for ORR and complete response rate {Brown 2002}.

## 6.2. Analysis

### 6.2.1. Characterize the anti-CD19 CAR T cell expansion (pharmacokinetics) and serum analyte (pharmacodynamics) profiles

- mITT and safety analysis sets will be used

- Individual line plot or median line plot over time with interquartile range will be produced by target doses within each study cohort and overall.

- Anti-CD19 CAR T cell profile (pharmacokinetics) overtime will be summarized using summary statistics described in Section 6.1 by cohort and overall.

- Similarly, pharmacodynamics profile as measured by serum analyte levels overtime will be summarized using summary statistics described in Section 6.1 by cohort and overall.

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

### 6.2.2. Characterize the product attributes

- Safety analysis sets will be used to summarize the product attributes

- Summary statistics for product characteristics will be generated by cohort and overall.

- Additional summaries may be generated by baseline characteristics subgroups, if applicable.

### 6.2.3. Characterize lenzilumab pharmacokinetics and soluble GM-CSF levels

- Safety analysis set will be used for lenzilumab pharmacokinetics and GM-CSF analysis with summary statistics (Section 6.1) in by cohort and overall

- Over time individual line plot or median profile plots will be provided by cohort for serum lenzilumab concentration (µg/mL) both in linear scale

### 6.2.4. Characterize analytes, CAR-T cells and other cell subsets in CSF

- Safety analysis sets will be used to summarize the analytes in CSF

- Summary statistics for CSF biomarkers will be generated for pre- and post-infusion

# 7. REFERENCES

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# 8. APPENDIX

## 8.1. Analytic Visit Windows for CAR T Cells in Blood

### Table 8-1. Visit window for blood draw for PBMC

| Analytic Visit | Baseline | Day 0 | Day 1 | Day 3 | Day 5 | Day 7 | Week 2 | Week 4 | Month 3 |
|---|---|---|---|---|---|---|---|---|---|
| Target Day | Baseline | 0 | 1 | 3 | 5 | 7 | 14 | 28 | 90 |
| Lab Window | ≤ 0 | [0, 0] | [1, 1] | [2, 4] | [5, 6] | [7, 10] | [11, 21] | [22, 59] | [60, 97] |

## 8.2. Analytic Visit Windows for Lenzilumab Pharmacokinetics

### Table 8-2. Visit window for blood draw for Lenzilumab (Phase 1)

| Analytic Visit | Day 0 Baseline | Day 0 0.5 h | Day 0 1 h | Day 0 3 h | Day 0 6 h | Day 0 9 h | Day 0 12 h |
|---|---|---|---|---|---|---|---|
| Target time | 0 | 30 min | 1 h | 3 h | 6 h | 9 h | 12 h |
| Lab Window | < 0 min | [0, 45] min | (45, 120] min | (120, 270] min | (270, 450] min | (450, 630] min | (630, 1080] min |

| Analytic Visit | *Day 1 | | *Day 2 | | *Day 3 | | *Day 4 | | *Day 5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Target Day | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| Lab Window | [0, 12] h | (12, 24] h | [0, 12] h | (12, 24] h | [0, 12] h | (12, 24] h | [0, 12] h | (12, 24] h | [0, 12] h | (12, 24] h |

| Analytic Visit | Day 6 | Day 7 | Week 2 | Week 4 |
|---|---|---|---|---|
| Target Day | 6 | 7 | 14 | 28 |
| Lab Window | [6, 6] day | [7, 10] day | [11, 21] day | [22, 59] day |

*Blood draw twice daily on Day 1 to Day 5

## 8.3. Analytic Visit Windows for Pharmacodynamics Key Measurements (serum analytes)

### Table 8-3. Visit window for blood draw for serum analytes

| Analytic Visit | Baseline | Day 0 | *Day 1 | | *Day 2 | | *Day 3 | | *Day 4 | | *Day 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Target Day | Baseline | 0 | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| Lab Window | ≤ -5 | [0, 0] | [0, 12] h | (12, 24] h | [0, 12] h | (12, 24] h | [0, 12] h | (12, 24] h | [0, 12] h | (12, 24] h | [0, 12] h | (12, 24] h |

| Analytic Visit | Day 6 | Day 7 | Week 2 | Week 4 |
|---|---|---|---|---|
| Target Day | 6 | 7 | 14 | 28 |
| Lab Window | [6, 6] day | [7, 10] day | [11, 21] day | [22, 59] day |

## 8.4. Immune cell subsets in CSF (FLOW)

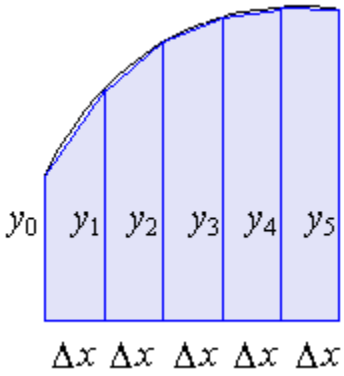
**Table 8-4. Visit window for CSF samples**

| Analytic Visit | Screening/baseline | Day 5 | Week 4 |
|---|---|---|---|
| Target Day | Screening/baseline | 5 | 28 |
| Lab Window | ≤ -5 | [0, 14] day | [15, 45] day |

**Table 8-5. CSF T-cell analytes**

| Number | Name of the analyte (cells/Volume unit) |
|---|---|
| 1 | CD14 (#, gated on CD45+) |
| 2 | CD19 (#, gated on CD45+/66b/14-) |
| 3 | CD3 (#, gated on CD45+/66b/14-) |
| 4 | CD3 CAR+ (#, gated on CD 45+/66b/14-/3+) |
| 5 | CD4 (#, gated of CD45+/66b/14-/3+) |
| 6 | CD4 CAR+ (#, gated on CD45+/66b/14-/3+/4+) |
| 7 | CD45 (#, gated on viable singlets cells) |
| 8 | CD56+CD3- (#, gated on CD45+/66b/14-) |
| 9 | CD56+CD3+(#, gated onCD45+/66b/14-) |
| 10 | CD66b (#, gated on CD45+) |
| 11 | CD8 (#, gated on CD45+/66b/14-/3+) |
| 12 | CD8 CAR+ (#, gated on CD45+/66b/14-/3+/8+) |
| 13 | CSF Volume |
| 14 | Viability (# Total Cells, Gated on Singlets) |
| 15 | Viability (# Viable Cells, Gated on Singlets) |

## 8.5. Using Trapezoidal Rule to Approximate the AUC




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