# TRANSLATIONAL STATISTICAL ANALYSIS PLAN
# KTE-C19-111 END OF PHASE I ANALYSIS

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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: | A Phase 1/2 MulticenterStudy Evaluating the Safety and Efficacy of Axicabtagene Ciloleucel in Combination with Utomilumab in Subjects with Refractory Large B-Cell Lymphoma (ZUMA-11) |
| Protocol Version Number and Date: | Amendment 4.0; 09 August 2021 |
| TSAP Release Date: | 13 September 2021 Final Version 1.0 |
| Replaces Previous Version(s): | |

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA | Anti-drug antibodies |
| 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 |
| CI | Confidence Interval |
| CRP | C-reactive protein |
| CSF | Cerebrospinal fluid |
| mITT | Modified intent-to-treat |
| Nab | Neutralizing antibody |
| ORR | Objective response rate |
| PBMC | Peripheral blood mononuclear cells |
| PK/PD | Pharmacokinetic/pharmacodynamic |
| SAP | Statistical analysis plan |
| Study day 0 | The first day that axicabtagene ciloleucel is administered to the subject |
| TSAP | Translational tatistical analysis plan |

# 1. INTRODUCTION

This translational statistical analysis plan (TSAP) outlines the end of Phase I analyses to be conducted for Pharmacokinetic (levels of anti-CD19 CAR T cells in blood), pharmacodynamics (serum analytes), product characteristics, and other biomarkers in support of end of Phase I analysis for KTE-C19 in combination with Utomilumab in Subjects with Refractory Large B-Cell Lymphoma. The analysis will be conducted for biomarker data within protocol KTE-C19-111 (ZUMA-11), amendment 3 dated 14 July 2020.

# 2. OBJECTIVES

## 2.1. Objectives

- Characterize the anti-CD19 CAR T cell expansion (Axi-cel Pharmacokinetic) and serum analyte (pharmacodynamic) profile
- Characterize the product attributes
- Characterize Utomilumab Pharmacokinetic and immunogenicity (anti-drug antibodies)

## 2.2. Hypothesis

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# 3. ENDPOINTS, SUBGROUPS AND COVARIATES

## 3.1. Biomarker datasets

**Table 1. Data overview on assay methods and biomarker lists for all cohorts**

| Data type | Assay method/ Sample type | Assessment time points | Biomarker set |
|---|---|---|---|
| Pharmacokinetic data (Anti- CD19 CAR T cell levels in blood) | qPCR/PBMC samples | Baseline, Day 1, Day 3, Day 7, Day 10, Week 2, Week 3, Week 4, Day 31, Week 8, Day 59, Week 12, Week 16, Week 20, Month 6, Month 9, Month 12, Month 15,<br>Month 18, Month 24, Month 36, Month 48, Month 60 | number of CAR T cells (/uL), |
| Pharmacodynamic data (levels of serum analytes) | soluble analyte assays/serum samples | Baseline, Day 0, Day 1, Day 3, Day 7, Week 2, Week 3, Week 4, Day 31, Week 8, Day 59, Week 12 | • Serum levels of following key cytokines, chemokines, and immune effector molecules will be reported-<br>• CRP, CXCL10, Ferritin, SAA, Granzyme B, ICAM-1, IFN-gamma, IL-1RA, IL-2, IL-2Ralpha, IL-5, IL-6, IL-7, IL-8, IL-4, IL-10, IL-15, Perforin, TNF-alpha, VCAM-1 and GM-CSF |
| Pharmacokinetic and immunogenicity data (Utomilumab) | Immunoassays/serum samples | • Utomilumab concentrations: Day 1, Day 3, Day 7, Week 2, Week 3, Week 4, Day 31, Week 12, Month 6<br>• Anti-Drug Antibody: Day 1, Week 4, Month 6 | • Anti-Drug Antibody<br>• Utomilumab concentrations (ng/mL) |

| Data type | Assay method/ Sample type | Assessment time points | Biomarker set |
|---|---|---|---|
| Product data | Product characteristics, several assays/ product samples | | Total Number of T Cells, Total Number of CAR T Cells, Total number of Tnaive cells Transduction Rate (%), CD3 (% and number), CD4/CD8 Ratio, T naïve/CM/EM/EFF cells (% and number), (% Tnaive + % T central memory) / (% T effector memory + % T effector cells), IFN-gamma level (pg/ml), Vector Copy Number, % viability, CD4 Cells (% and number ), CD8 Cells (% and number), CCR7+ (Tnaive + Tcm) % and number, CCR7- (Tem + Teff) %, Total number of CCR7+ T cells infused |
| CSF analytes | soluble analyte assays/CSF samples | Baseline, Day 5, Week 4 | Biomarker list are the same with those in the pharmacodynamic serum analytes |
| CSF cell subsets | Flow cytometry/CSF samples | Baseline, Day 5, Week 4 | Analytes are listed in Appendix 2 |

Zuma-11 end of Phase I analysis will include the following data. The analysis will be outlined in the following sections.

- Axi-cel Pharmacokinetic (Anti-CD19 CAR T cell levels in blood)
- Pharmacodynamics (levels of serum analytes)
- Utomilumab pharmacokinetic and immunogenicity (ADA)
- Product attributes

## 3.2. Endpoints

All definitions can be generally applied to anti-CD19 CAR T pharmacokinetic and/or pharmacodynamic endpoints. Detailed definitions can be found in Section 4.

- Change from baseline at Day X
- Fold change
    1) Fold change from baseline at Day X
    2) Fold change from Day 0
- Peak
- Time to peak
- Area-Under-Curve (AUC)

All measurable values at each visit will be used as main endpoints for all biomarkers listed in Table 1 as following

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

# 4. DEFINITIONS

## 4.1. General

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

- **Baseline** is defined as the last non-missing value measured on or prior to conditioning chemotherapy.

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

- The expansion and persistence of anti-CD19 CAR T cells in peripheral blood will be measured 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 1.

- **Number of anti-CD19 CAR T (cells/ uL blood) is defined as:**
  White Blood Cell counts (per uL) x (Monocytes (%) + Lymphocytes (%)) x CAR+ PBMCs (%)

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

- **Time-to-Peak of anti-CD19 CAR T cell (days)** is defined as "Peak Date – KTE-C19 Dosing Date + 1".

- **Area-Under-Curve (AUC) of level of anti-CD19 CAR T cell (cells/ uL ▪ 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 will be used to estimate the AUCs.

## 4.3. Key Measurements of PD: Serum Analytes

- **Scheduled blood draw for serum analytes:** Within approximately 5 days of eligibility confirmation (Enrollment/Leukapheresis) as baseline, Day 0, Day 1, Day 3, Day 7, Week 2 (Day 14) (± 2 days), Week 3 (± 2 days), Week 4 (Day 29), Day 31, Week 8 , and Week 12.

This TSAP will focus on the analyte data collected from baseline to Day 28. The Schedule of Assessment and analytic visit window is defined in Appendix 1.

- **Baseline of analytes** is defined as the last value measured prior to conditioning 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 snalyte post baseline** is defined as the maximum level of cytokine in serum attained after baseline up to Day 28.
- **Time to peak of 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 between baseline and day 28. Given the analyte is measured at certain discrete time points, the trapezoidal rule will be used to estimate the AUCs.

### 4.4. Key Measurements of Product Characteristics

1) All product characteristics as defined in Table 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.
2) Two additional analytes will be derived for exploration:
   - **CD4/CD8 Ratio** is defined as: $\frac{\text{CD4 Cells (\%)}}{\text{CD8 Cells (\%)}}$
   - **CCR7+ in (%) or (#)** is defined as: Naive (%) or (#) + Central Memory (%) or (#), respectively

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### 4.6. Key Measurements of CSF analytes

CSF analytes are similar to those in the pharmacodynamic serum analytes.

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### 4.7. Key Measurements of Utomilumab

- Serum Anti-Drug Antibodies (ADAs)
- Serum utomilumab concentration (ng/mL)
- Maximum serum concentration (Cmax) after first utomilumab dosing and before the second dosing
- Time to maximum serum concentration (Tmax)
- Area-Under-Curve (AUC) from baseline to before the second utomilumab dosing

Serum samples will be assayed for the presence of anti-drug antibodies (ADAs) to utomilumab with the use of validated immunoassays.

Serum samples will be assayed for utomilumab concentrations with the use of a validated analytical method.

Scheduled blood draw for utomilumab PK and ADA: Refer to Appendix 1 for detailed information.

# 5. ANALYSIS SETS

- Safety analysis set (per clinical SAP) will be used if not specified.
- The 'Modified intent-to-treat (mITT)' analysis set will be used to be consistent with Phase 1 efficacy analysis in CSR.

Generally, this TSAP will utilize the same efficacy analysis strategy in CSR, such as analysis sets and related outcome definitions.

# 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** will summarize data in frequency (N, %) and quartile range (Minimum, 1st quartile (Q1), Median, 3rd quartile (Q3), Maximum) in overall and by cohort.

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## 6.2. Analysis

### 6.2.1. Characterize the anti-CD19 CAR T cell expansion (Pharmacokinetic) and serum analyte (pharmacodynamic) profile

- Safety analysis set will be used for analysis
- Anti-CD19 CAR T Cell profile in blood (PK) 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

### 6.2.2. Characterize the product attributes

- Safety analysis set will be used for analysis
- Product characteristics will be summarized using summary statistics described in Section 6.1 by cohort and overall

### 6.2.3. Characterize Utomilumab Pharmacokinetic and Immunogenicity

- Safety analysis set will be used for analysis
- Utomilumab pharmacokinetic will be summarized using summary statistics described in Section 6.1 by cohort and overall
- Over time median profile plots will be provided by cohort for serum utomilumab concentration (ng/mL) in both linear and semi-log scales
- Listing will be provided for subjects with positive ADA and neutralizing antibodies (Nab) against utomilumab

# 7. REFERENCES

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# 8. APPENDIX

## Appendix 1. Analytic Visit Windows

### Table 2. Analysis Visit Windows for Phase 1 Cohort 1, 2, 3 and 4

| Timeline | nCAR T Infusion | UTO IV | UTO Pharmacokinetic Visit Window | UTO ADA Visit Window | CART Pharmacokinetic Visit Window | Pharmacodynamic Visit Window |
|---|---|---|---|---|---|---|
| Baseline | | | | | | APDY < -5 |
| Day 0 | Day 0 | | | | DAY 0 | DAY 0 |
| Day 1 | | D1 (#1) | D1 1 APDY, preUTO1 and posUTO1 (both measurements are taken in same day, use the lab time to identify pre/post UTO measurements) | D1 1 APDY, preUTO1 and posUTO1 (both measurements are taken in same day, use the lab time to identify pre/post UTO measurements) | DAY 1 1 APDY= ADY_uto_dt1, preUTO1 | DAY 1 1 APDY= ADY_uto_dt1, preUTO1 |
| Day 3 | | | D3 3 APDY in [2, 5] | D3 3 APDY in [2, 5] | DAY 3 3 APDY in [ADY_uto_dt1+1, 5], posUTO1 | DAY 3 3 APDY in [ADY_uto_dt1+1, 5], posUTO1 |
| Day 7 | | | D7 7 APDY in [6, 10] | D7 7 APDY in [6, 10] | DAY 7 7 APDY in [6, 8] | DAY 7 7 APDY in [6, 10] |
| Day 10 | | | | | DAY 10 10 APDY in [9, 12] | |
| Week 2 | | | Week 2 14 APDY in [11, 17] | Week 2 14 APDY in [11, 17] | Week 2 14 APDY in [13, 17] | Week 2 14 APDY in [11, 17] |
| Week 3 | | | Week 3 21 APDY in [18, 25] | Week 3 21 APDY in [18, 25] | Week 3 21 APDY in [18, 25] | Week 3 21 APDY in [18, 25] |
| Week 4 | | D29 (#2) | Week 4 29 APDY in [26,57], preUTO2 and posUTO2 (both measurements are taken in same day, use the lab time to identify pre/post UTO measurements) | Week 4 29 APDY in [26,57], preUTO2 and posUTO2 (both measurements are taken in same day, use the lab time to identify pre/post UTO measurements) | Week 4 29 APDY in [26, ADY_uto_dt2], D29preUTO2 | Week 4 29 APDY in [26, ADY_uto_dt2], D29preUTO2 |

| Timeline | nCAR T Infusion | UTO IV | UTO Pharmacokinetic Visit Window | UTO ADA Visit Window | CART Pharmacokinetic Visit Window | Pharmacodynamic Visit Window |
|---|---|---|---|---|---|---|
| Week 4 | | | | Week 4 31 APDY in [ADY_uto_dt2+1, ADY_uto_dt3-1], D31posUTO2 ---- Cohort 4 only | Week 4 31 APDY in [ADY_uto_dt2+1, 44], D31posUTO2 | Week 4 31 APDY in [ADY_uto_dt2+1, 44], D31posUTO2 |
| Week 8 | | D57 (#3) | | | Week 8 57 APDY in [45, ADY_uto_dt3], D57preUTO3 | Week 8 57 APDY in [45, ADY_uto_dt3], D57preUTO3 |
| Week 8 | | | | Week 8 59 APDY in [ADY_uto_dt3+1, 72], D59posUTO3 ----Cohort 4 only | Week 8 59 APDY in [ADY_uto_dt3+1, 72], D59posUTO3 | Week 8 59 APDY >= ADY_uto_dt3+1, D59posUTO3 |
| Week 12 (Month 3) | | D85 (#4) | Week 12 85 APDY in [58, 127], preUTO4 and posUTO4 (both measurements are taken in same day, use the lab time to identify pre/post UTO measurements) | Week 12 85 APDY in [73, 127], preUTO4 and posUTO4 (both measurements are taken in same day, use the lab time to identify pre/post UTO measurements) | Week 12 85 APDY in [73, ADY_uto_dt4], D85preUTO4 | |
| Week 16 (Month 4) | | D113 (#5) | | | Week 16 113 APDY in [ADY_uto_dt4+1, ADY_uto_dt5], D113preUTO5 | |
| Week 20 (Month 5) | | D141 (#6) | | | Week 20 141 APDY in [ADY_uto_dt5+1, ADY_uto_dt6], D141preUTO6 | |
| Week 24 (Month 6) | | | 30 days follow last-UTO 170 APDY >=128 | 30 days follow last-UTO 170 APDY >=128 | 30 days follow last-UTO 170 APDY >= ADY_uto_dt6+1 | |

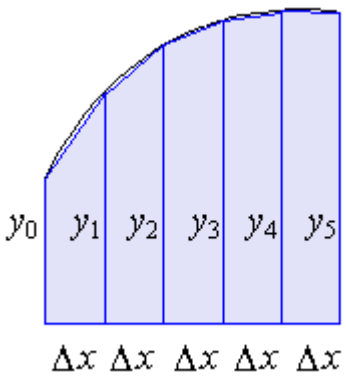
## Appendix 2. CSF T-cell Analytes

Visits: Screening CSF, Post-CSF, Baseline CSF, Unscheduled CSF

### Table 3. 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) |

## Appendix 3. Using Trapezoidal Rule to Approximate the AUC




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