Seattle Children's Hospital and Research Institute

Statistical Analysis Plan

Pediatric and Young Adult **L**eukemia **A**doptive **T**herapy (**PLAT**)-**02**: A Phase 1/2 Feasibility and Safety Study of CD19-CAR T Cell Immunotherapy for $CD19^{+}$ Leukemia

Protocol Number:	PLAT-02
Investigational Product:	Defined Composition CD4 and CD8 T Cells Lentivirally Transduced to Express a Second Generation 4-1BB:zeta CD19 CAR and EGFRt
IND Number:	BB IND# 15829
NCT Number	NCT02028455
Development Phase:	Phase 1/2
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Statistical Analysis Plan for PLAT-02 Phase II

Protocol Title: Pediatric and Young Adult Leukemia Adoptive Therapy (PLAT)-02: A Phase 1/2 Feasibility and Safety Study of CD19-CAR T Cell Immunotherapy for CD19+ Leukemia

Prepared for: Immunotherapy Coordinating Center

Version: 1.0

Date: February 9, 2021

SIGNATURE PAGE

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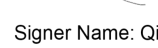
Qian (Vicky) Wu, PhD Assistant Member, FHCRC	DocuSigned by:  Signer Name: Qian (Vicky) Wu Signing Reason: I approve this document Signing Time: 2/8/2021 | 7:27:34 PM PST 9514CED841704135ADAF9CF1B0A57299
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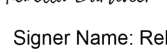
Rebecca Gardner, MD Study Chair	DocuSigned by:  Signer Name: Rebecca Gardner Signing Reason: I approve this document Signing Time: 2/9/2021 | 4:58:50 PM PST 2E320D1B3F034EB49254810B82BE7675

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REVISION HISTORY

Version Number	Date	Details
v0.1	02/09/2021	\\childrens\research\ImmunotherapyCons\PLAT-02\SAP
v0.2		
v0.3		

This document is edited and maintained via Microsoft Word and resides in the folder indicated above. Formal and approved versions will be "frozen" in PDF and will receive a version number. Revisions will be listed here.

The final statistical report(s) will describe and justify any deviations from the final version of the SAP. Such deviations will be explicitly presented as post-hoc analyses.

ABBREVIATIONS

AE	Adverse Event
ITT	Intent-to-treat
QC	Quality control
SD	Standard deviation

1 SCOPE AND PURPOSE

This Statistical Analysis Plan (SAP) describes the framework for analysis and related procedures of Phase II of the PLAT-02 study (including Phase I subjects treated at the RP2D). This includes:

- Analysis of data to assess the attainment of the study's primary and secondary endpoints, as defined in the Protocol and below in Section 3.
- Comprehensive safety analyses for all B-ALL subjects who received flu/cy LD chemo followed by infused with CD19-CAR T Cells (SCRI-CAR19v1 and v1.5).
- Describe the descriptive analysis of ALL subjects in cohort 2B and the subjects with a diagnosis of NHL
- Descriptive analysis of repeat infusions of CAR T cells on this protocol.

This SAP does <u>not:</u>

- Describe the protocol-defined analysis of Phase I data. This analysis has already been performed.
- Describe the protocol-defined analysis of the ALL subjects in cohort 2E. This analysis has already been performed.

2 STUDY OVERVIEW

2.1 PLAT-02 Summary

This phase 1/2, open-label, non-randomized study will enroll pediatric and young adult research participants with relapsed or refractory CD19+ leukemia with and without prior history of allogeneic stem cell transplant, to examine the safety, feasibility, and efficacy of administering T cell products derived from subject peripheral blood mononuclear cells (PBMC) that have been genetically modified using a self-inactivating SIN lentiviral vector to express a CD19-specific chimeric antigen receptor (CAR) and the selection-suicide marker EGFRt.

Phase I has completed and achieved its objective of identifying a recommended dose for Phase II (RP2D). Statistical outputs for Phase I have already been produced and reported.

Two cohorts of subjects will enroll in Phase II, those receiving fludarabine/cyclophosphamide lymphodepletion (Cohort 2A) and those receiving alternative lymphodepletion (Cohort 2B). During Phase II, CD19+ Non-Hodgkin lymphoma subjects will also be eligible to enroll, but they will be analyzed

separately for both toxicity and efficacy. Twenty-seven subjects had products manufactured as SCRI-CAR19v2 during Phase II and are excluded from all primary and secondary analyses.

2.2 Phase II Treatment Summary

Phase II subjects receive one CAR T-cell infusion (can receive more than one if eligible): a nominal dose of one million EGFRt+ T cells per kg of body weight (allowed range: $>7.5x10^5$ to $1x10^6$ per kg). The infusion day is designated as "Day 0".

In addition, during the week prior to Day 0, subjects receive a conditioning lymphodepletion treatment:

- The default lymphodepletion is Fludarabine 30mg/m2 BSA, via IV once daily x4 days, and Cyclophosphamide 500mg/m2 BSA, via IV once daily during the last 2 of these 4 days; hereafter, "Flu/Cy". Subjects receiving this treatment belong to Cohort 2A. In terms of treatment, it is equivalent to Phase I Cohort 1F2.
- Subjects contraindicated against Flu/Cy, or receiving a different lymphodepletion for any other reason, followed by the standard Phase II infusion, will belong to Cohort 2B.

CD4 and CD8 T cell subsets will be isolated from apheresis products obtained from the research participant. The CD4 and CD8 CD19 CAR modified T cells will be administered as two separate infusions. Once the subject has recovered from any acute toxicity from re-induction/salvage chemotherapy, the T cell product will be infused via an indwelling catheter or peripheral IV. Subjects who experience significant and potentially life-threatening toxicities (other than clinically manageable cytokine storm/engraftment syndrome) will receive infusions of cetuximab to assess the ability of the EGFRt transgene to be an effective suicide mechanism for the ablation of transferred T cell products.

3 STATISTICAL ANALYSIS

3.1 Cohort Definitions:

Below are the cohort definitions referred to in this SAP

- 1F2 – Phase 1 subjects who were treated with fludarabine/cyclophosphamide lymphodepletion at the recommended phase 2 dose
- 2A – phase 2 subjects who were treated with fludarabine/cyclophosphamide lymphodepletion
- 2B – phase 2 subjects who were treated with alternative lymphodepletion.
- 2E – phase 2 subjects who were treated with SCRI-CAR19v2 products (manufactured with ExpAct expansion beads) or had SCRI_CAR19v2 product manufactured but never underwent infusion

- ND – phase 2 subjects who were unassigned to cohort A or B because they never proceeded with CAR T cell infusion. This does not include subjects who enrolled on PLAT-02 but then received CAR T cells on PLAT-03

3.2 Analysis Sets

Below are the definitions of analysis sets to be used in the analyses.

- **Enrolled Set**: all subjects with B-ALL in cohort 1F2, 2A, 2B, and ND
- **Feasibility Set**: all subjects with B-ALL in the enrolled set for whom a CAR T cell manufacturing attempt was made
- **Treated Set**: all subjects with B-ALL in cohort 1F2 and 2A
- **Efficacy Evaluable Set**: all subjects in the treated set who are evaluable for efficacy per Protocol Section 10.9
- **Intent to treat Efficacy Evaluable set**: subjects with B-ALL in cohort 1F2, 2A, and ND. Includes subjects in the Efficacy Evaluable set plus subjects who enrolled but weren't treated due to manufacturing failure or death. Subjects who enrolled on PLAT-03 to receive their CAR T cell infusion are not included
- **Functional persistence set**: all subjects in the treated set who achieved B cell aplasia due to CAR T infusion
- **Leukemia-Free Set**: all subjects in the efficacy evaluable set who achieved an MRD negative complete remission by Day 63 and prior to receiving alternative therapy
- **Cetuximab Ablation Set**: all subjects in the treated set who received cetuximab for the purpose of ablating CAR T cells
- G**VHD Set**: Treated set with a prior history of hematopoietic cell transplant
- **Descriptive Lymphoma Set**: all subjects with lymphoma from cohort 2A, 2B, 2U
- **Descriptive Leukemia Set:** all subjects with B-ALL from cohort 2B
- **Descriptive Re-infusion set**: all subjects with B-ALL or lymphoma who received a 2nd or greater infusion of SCRI-CAR19

3.3 Analysis Objectives

3.3.1 Primary Objectives

The primary objectives are to determine the feasibility of deriving therapeutic product, the safety of the T cell product infusion, the full toxicity profile, the response rate and persistence of T cell product past day +63.

- **Feasibility** will be assessed by looking at the number of products successfully manufactured versus those that were unsuccessful. Feasibility criteria will be defined as follows: No therapeutic product could be generated for the patient after two attempts using a single apheresis product for starting material. Unsuccessful products will be defined as:
  - Cell product did not meet QC release criteria and could not be released for infusion
  - Cell product that was not manufactured due to expansion failure
- **Safety and toxicity profile** of the infusion will be analyzed using the following data (the evaluation within 24 hours before the initial T cell infusion will serve as baseline):
  - Adverse events according to CTCAE grade 4 with exception of CRS which was graded according to modified Lee criteria

Grade	Description of Symptoms
1: Mild	Not life-threatening, require only symptomatic treatment such as antipyretics and anti-emetics (e.g., fever, nausea, fatigue, headache, myalgia, malaise)
2: Moderate	Require and respond to moderate intervention: Oxygen requirement for nasal cannula or simple face mask, or Hypotension responsive to fluids or low dose of a single vasopressor, or Grade 2 organ toxicity (by CTCAE v4.0) attributed to CRS
3: Severe	Require and respond to aggressive intervention: Oxygen requirement for non-rebreather or CPAP/BiPAP, or Hypotension requiring high dose of a single vasopressor (e.g., norepinephrine ≥ 20 μg/min, dopamine ≥ 10 μg/kg/min, phenylephrine ≥ 200 μg/min, or epinephrine ≥ 10 μg/min), or Hypotension requiring multiple vasopressors (e.g., vasopressin + one of the above agents, or combination vasopressors equivalent to ≥ 20 μg/min norepinephrine), or Grade 3 organ toxicity or Grade 4 transaminitis (by CTCAE v4.0) attributed to CRS
4: Life-threatening	Life-threatening: Requirement for ventilator support, or Grade 4 organ toxicity (excluding transaminitis)
5: Fatal	Death

Adapted from (Lee 2014)

- **Response rates** for leukemia subjects will be analyzed using bone marrow aspirates taken at Day 21 and Day 63 with responses graded per standard ALL criteria per Protocol Section 11.2. Response rates for NHL subjects will be analyzed separately with bone marrow aspirates and PET scan taken at Day 21 and Day 63 and graded per standard NHL criteria per Protocol Section 11.3.
- **Functional Persistence** of CAR+ T cells will be analyzed with peripheral blood and bone marrow samples, and is defined as B cell aplasia (defined as <1% CD19+ cells in the lymphocyte subset as determined by flow cytometry) that cannot be attributed to other B cell targeting agents.

3.3.2 Secondary Objectives

The secondary objectives are to assess the duration and magnitude of the in vivo persistence of the adoptively transferred T cells, the accumulation of the transferred T cells in the bone marrow and cerebral spinal fluid, to quantitate the anti-leukemia responses by measuring changes in leukemia burden using flow cytometry, IgH deep sequencing, or induction of CD19+ B cell aplasia and look at the overall survival, leukemia free survival, and event free survival, the development of GVHD in those who have a history of HCT, the efficacy of cetuximab to ablate EGFRt+ T cells, to determine response rates and toxicity rates separately in the MRD+ group and the refractory group, to assess the impact of CD19

antigen load/disease burden and conditioning regimen on the persistence of CAR+ T cells, overall survival, leukemia free survival, event-free survival, and non-relapse mortality.

- **Magnitude and in vivo persistence and accumulation in bone marrow** of transferred T cells will be analyzed using bone marrow, cerebral spinal fluid and peripheral blood from MPF.
- **B cell aplasia** will be analyzed with MPF from bone marrow and peripheral blood.
- **GVHD** will be analyzed among subjects who received post-infusion HCT
- **Response rates/toxicity rate** will be separately analyzed in CR, MRD+ group and refractory group
- **Efficacy of cetuximab to ablate EGFRt+ T cells** will be analyzed using pre and post cetuximab T cell persistence data
- **Associations between CAR T persistence and CD19 antigen load/disease burden and conditioning regimen** will be analyzed using baseline disease assessments and persistence follow up data
- **Overall survival** will be analyzed using all available follow up data
- **Leukemia-free survival** will be analyzed using all available follow-up data in conjunction with disease responses per standard ALL criteria for leukemia subjects
- **Event-free survival** will be analyzed using all available follow-up data in conjunction with disease responses per standard ALL criteria for leukemia subjects

3.3.3 Exploratory Objectives

- feasibility, response rates, engraftment of CAR T-cells and safety will be described for lymphoma subjects
- feasibility, response rates, engraftment of CAR T-cells and safety will be described for cohort 2B leukemia subjects

3.4 Endpoints

3.4.1 Primary Endpoints

- **Feasibility (Feasibility Set)**: the number and percent of subjects with at least one successfully manufactured product out of the number of subjects for whom a manufacturing attempt was made.
- **Safety and toxicity profile:**
  - Medical history **(Treated Set)**: the number and percent of subjects experiencing each baseline toxicity, presented by highest grade

- B cell reconstitution **(B Cell Aplasia Set)**: descriptive statistics summarizing the distribution at selected study time points
- Serum immunoglobulin levels **(Treated Set)**: descriptive statistics summarizing the distribution at selected study time points
- Graft versus host disease assessments **(GVHD Set)**: the number and percent of treated subjects who experience GVHD after a post-infusion HCT and prior to loss of T cell persistence
- Adverse events **(Treated Set)** the number and percent of treated subjects who experience at least one adverse event within 30 days of CAR T infusion by body system organ class, CTCAE term and highest grade will be presented for the following:
  - Related Adverse events: possibly, probably or definitely related to CAR T infusion **(Treated Set)**
  - Treatment Emergent Non-hematologic adverse events **(Treated Set)**
  - Treatment Emergent Hematologic adverse events **(Treated Set)**
  - Serious adverse events **(Treated Set)**
  - Adverse events of special interest, i.e., cytokine release syndrome and neurotoxicities **(Treated Set)**

- **Response rates (Efficacy Evaluable Set)**: the number and percent of treated leukemia subjects who achieve a disease response of MRD-CR (per standard ALL criteria) by day 63, defined as the disease assessment done following CAR T cell infusion and prior to Day 77 and occurring before receiving alternative anti-cancer therapy. Subjects who receive alternative anti-cancer therapy prior to the Day 63 assessment and did not achieve MRD-CR prior to alternative therapy will be considered a non-responder. A supplemental summary of the number and percent achieving MRD-CR in the **Intent to treat Efficacy Evaluable set** will also be generated, with subjects who didn't receive CAR T cells due to manufacturing failure or death considered non-responders.
- **Persistence at Day 63 (Efficacy Evaluable Set)**: the number and percent of treated leukemia subjects who have ongoing persistence at Day 63, defined as the assessment between Day 49 and Day 77 in the peripheral blood or bone marrow. Persistence is defined as either detection of CAR+ T cells by flow or PCR or B cell aplasia that cannot be attributed to other B cell targeting agents. Subjects who exited prior to day 63 for cohort B on PLAT-03 will be considered as loss of CAR T cell persistence at day 63.
- **Primary Efficacy Endpoint (Efficacy Evaluable Set)**: a composite endpoint of MRD-CR status by Day 63 and persistence status at Day 63. All treated leukemia subjects in the Efficacy Evaluable Set will be included in the analysis and receive either 0, 1 or 2 points. A subject receives 1 point if they achieve MRD-CR by Day 63, and prior to receiving alternative therapy. Subjects who

achieve MRD-CR by Day 63 receive a second point if they also have persistence at Day 63. Persistence is defined by either having detectable EGFRt+ CAR T cells on the Day 63 visit or ongoing B cell aplasia attributed to the PLAT-02 CAR T cell infusion (e.g., before receiving other treatments which can also cause B cell aplasia). The study will have demonstrated the efficacy of CAR T cell infusions if the total efficacy score is 83 points out of 72 evaluable subjects with at least 25 subjects experiencing both MRD-CR by Day 63 and ongoing persistence at Day 63. Further details are in Section 3.6 of this SAP.

3.4.2 Secondary Endpoints

- **Magnitude and in vivo persistence**: descriptive statistics summarizing the distribution of selected measures of CAR T cell persistence (T_{max}, C_{max}, AUC). **In vivo functional persistence B cell aplasia (B Cell Aplasia Set)**: time to loss of B cell aplasia, defined as the time from infusion to first loss of B cell aplasia. Only subjects who achieve B cell aplasia attributed to infusion will be included in the analysis. Loss of B cell aplasia is defined as the earliest MPF/PCR result showing detectable CD19+ cells with a later, confirmatory result also showing detectable CD19+ cells. If there is no later, confirmatory result available, a last result showing detectable CD19+ cells will also be considered a loss of B cell aplasia. Subjects who do not lose B cell aplasia will be censored at time of last MPF/PCR result. Subjects who receive alternative therapy which could also cause B cell aplasia will be censored on the last MPF/PCR result prior to receiving alternative therapy. If a subject dies, experiences a CD19- relapse, receives a 2nd infusion or receives a stem cell transplant and is known to have ongoing B cell aplasia at the time of the event, such events will be treated as competing events in the analysis.
- **GVHD (GVHD Set):** The number and percent of subjects who experience GVHD following a post-CAR T infusion HCT.
- **Response rates (Efficacy Evaluable Set): estimates stratified by disease status at CAR T treatment (MRD+CR, refractory)**
- **Efficacy of cetuximab to ablate EGFRt+ T cells (Cetuximab Ablation Set)**: the number of percent of subjects given cetuximab to ablate EGFRt+ T cells who exhibit absence of detectable EGFRt+ T cells 28 days after initiation of cetuximab.
- **Associations between CAR T persistence and CD19 antigen load/disease burden** will be analyzed using a logistic regression model where the outcome is whether the subject had persistence at Day 63. Baseline CD19 antigen load/disease burden will be included as main effects (univariately).

- **Overall survival (Treated Set)**: time from CAR T infusion to death from any cause. Subjects not known to have died will be censored at time of last follow-up or correlative studies draw date, whichever occurred later.
- **Leukemia-free survival (Leukemia-Free Set)**: time from achievement of MRD negative complete remission on protocol (or time from first CAR T infusion, if subject is in MRD negative complete remission at infusion) to the first occurrence of relapse or death; Subjects not known to have relapsed or died will be censored at time of last follow up. An MRD relapse is not considered an event for the main analysis. Subjects who have an MRD relapse will be summarized descriptively. Analyses that include MRD relapse as an additional event type may also be explored as a supplement to the main leukemia-free survival analysis.
- **Event-free survival (Treated Set)**: time from CAR T infusion to earliest occurrence of relapse, death or determination of nonresponse. For subjects who do not achieve complete remission, the determination of nonresponse shall be based on the day 63 visit data, unless the subject goes off protocol prior to the day 63 visit in order to receive other salvage therapy or palliative care. In that case, the determination of nonresponse will be the off-protocol date. (Note that a subject going off-protocol to receive consolidation HCT while in remission is not considered an event in the EFS or LFS analyses. Follow-up for relapse and death events continues for these subjects.) Subjects who achieve CR but relapse on or before the day 63 visit are counted as relapse events on the date the relapse was diagnosed. Subjects achieving complete remission and not known to have relapsed or died will be censored at time of last follow up. An MRD relapse is not considered an event for the main EFS analysis. Subjects who have an MRD relapse will be summarized descriptively. Analyses that include MRD relapse as an additional event type may also be explored as a supplement to the main EFS analysis.

3.5 Descriptive Statistics

Summary statistics for continuous variables will include the sample size, mean, standard deviation, quartiles, minimum and maximum. Summary statistics for categorical variables will include the sample size, frequency and percentage. Analyses will use one of the analysis sets defined in Section 3.2 of this SAP. Analyses may be repeated for multiple analysis sets and subgroups of analysis sets. The number of missing values for each analysis will be reported.

3.6 Primary Efficacy Analysis

The primary efficacy analysis will be based on the composite endpoint of MRD-CR status and CAR T cell persistence status by Day 63. Subjects will receive 0, 1 or 2 points as follows:

- 0 points: subjects who do not achieve MRD-CR status by Day 63
- 1 point: subjects who achieve MRD-CR status by Day 63, and prior to receiving alternative anti-cancer therapy, but do not have ongoing CAR T cell persistence at Day 63
- 2 points: subjects who achieve both MRD-CR by Day 63 and ongoing CAR T cell persistence at Day 63

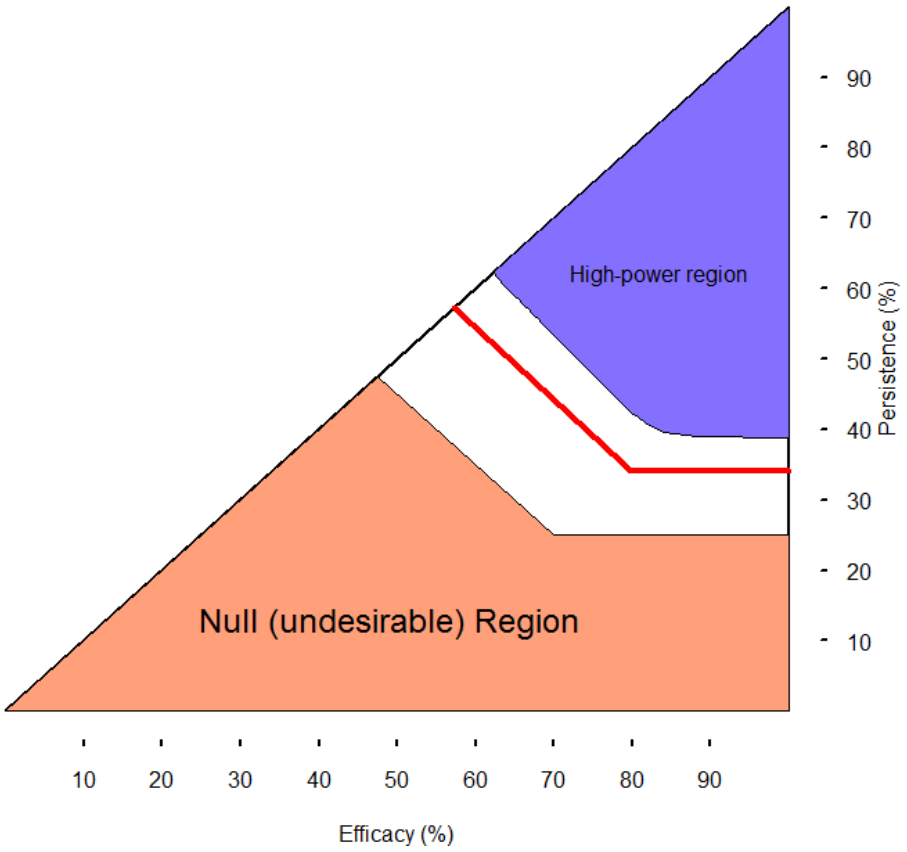
The hypothesis test for efficacy based on the composite endpoint described above is defined as an acceptable combination of efficacy and persistence. The Null hypothesis, representing insufficient response is:

Persistence beyond Day 63 ≤ 25% OR composite endpoint of persistence + efficacy ≤ 0.95 points per subject

A successful response rate for Phase II will be declared if the Null is rejected at $\alpha < 0.05$, using a one-sided Multinomial test. With exactly n=72 subjects, efficacy will be achieved with > 80% power, given any of the scenarios below:

- Percent of subjects achieving MRD-CR by Day 63 and ongoing persistence at Day 63 is 62.5% or greater, even with no additional subjects achieving MRD-CR
- True MRD-CR by Day 63 rate is ≥ 88% (including persisting subjects), and true persistence at Day 63 rate is ≥ 39%
- Other scenarios shaded in blue in the below figure.

The decision rule is outlined by a bold red line in the figure below with favorable areas in blue and unfavorable areas in orange.



The x and y axes indicate the true underlying proportions of efficacy and persistence responses, respectively. The orange region indicates conditions included under the definition of the Null hypothesis. The red line demarcates the observed proportions lying on the decision boundary. The purple-blue region consists of conditions under which successful trial completion is expected with probability 80% or greater.

3.7 Primary Safety Analysis

There is no formal success criterion for Phase II safety. Summaries of Hematologic and Non-Hematologic adverse events will also be presented by body system organ class, toxicity, cohort and highest grade per subject using the Treated Set. Listings of all serious adverse events (SAEs) and adverse events of special interest (Cytokine release syndrome and neurotoxicity) will also be presented by highest grade per subject using the Treated Set.

3.8 Analysis of Secondary and Exploratory Objectives

Besides summary statistics in section 3.4, for the association testing model, we will build flexible regression framework between each endpoint and covariate of interest.

For binary endpoints, such as response, persistence, a logistic regression model will be given to access the association between variable of interest (e.g., CD19 disease burden) and outcome of interest (e.g., persistence), respectively.

$$logit\big(\pi(\boldsymbol{X}_i)\big) = \boldsymbol{X}_i^T\boldsymbol{\beta} \qquad (1)$$

where π denotes the probability of response, $\boldsymbol{X}_i$ are the ith subject's covariate vector, $\boldsymbol{\beta}$ is the coefficient vector for the covariate vector. Similarly, for categorical endpoints, such as composite endpoint for primary efficacy, an ordinal proportional odds logistic regression model will be given. For continuous endpoints, a linear regression model will be given if applicable. Note that other demographic variables that are found to be of interest in clinical studies may be evaluated and be included in all statistical models based on statistical and clinical evidence.

3.8.1 Survival Analysis

For survival analysis with endpoints such as overall survival, leukemia-free survival and event-free survival, we will build Cox proportional hazard regression to access the association between each time to event outcome and variable of interest. The Kaplan-Meier method and survival curves, survival estimates, and 95% confidence intervals (CIs) will be presented. For competing risk data, such as analysis for B cell aplasia, we will use Fine and Gray model to assess the association between each outcome and variable of interest, and cumulative incidence plots with 95% CIs will be presented unless there are no competing events in the data. Other survival analyses may be conducted in an exploratory manner.

3.8.2 Statistical Tests and Confidence Intervals

All statistical tests, except the primary efficacy analysis in Section 3.5 of this SAP, will be exploratory and conducted at the 0.05 level of significance. Confidence intervals will be constructed at the 95% level, unless otherwise specified. Confidence intervals for proportions will be constructed using the Clopper-Pearson method. Statistical tests for Kaplan-Meier-based methods will use the log rank test while tests for cumulative incidence-based methods will use the Gray test for sub-distribution hazards.

4 DATA PROCEDURES

4.1 Statistical Quality Control

The final statistical report outputs will each define the set of subjects used for the analysis according to the definitions provided in Section 3.1 of this SAP. All programs used to produce the outputs will be documented and archived in a dedicated shared folder. The statistical outputs will be prepared by the study team and validated internally.

4.2 Statistical Software

All statistical outputs will be prepared using SAS v9.4 or R (> 3.6) if appropriate.

4.3 Handling Exceptions

4.3.1 Outliers

The study team will identify data values that appear to be potential outliers. These values will be verified against source documents by study investigators. Decisions on handling each outlier will be based on medical judgment as well as on statistical grounds. The three possible decisions are:

a) Exclude the outlier: only with documented evidence that the outlier represents a data error, or when the outlier is a physically infeasible value and the original value cannot be recovered by the study team.
b) Conduct sensitivity analyses that examine the outlier's effect via exclusion, or mitigate it via adjustment, stratification, or a more robust analysis method. This will take place when the outlier is suspected of being an error (but lacking solid evidence), of representing a different subpopulation, or of resulting from additional processes besides ordinary disease and treatment-response dynamics.
c) If the outlier is deemed to represent part of the expected ordinary variability, the analysis will continue using the planned approach with no sensitivity analyses.

4.3.2 Values Outside Quantification Limits

For values below the lower detection limit ("<LOD") we will substitute one-half the LOD. For values above the upper quantification limit, we will substitute the upper limit plus the LOD.

4.3.3 Missing Data

In general, analyses will follow the definitions of the analysis sets described in Section 3.1 of this SAP. Subjects missing data for baseline characteristics and disease status will be excluded from analyses of variables from which they are missing data. An explanation will be provided for each analysis where the number of subjects included in the analysis differs from the definition of the analysis set.

4.3.4 Protocol Violations

Subjects experiencing at least one major protocol violation will be identified by the study team.

REFERENCE:

1. Fine, J. P., & Gray, R. J. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association*, *94*(446), 496-509.