Janssen Research & Development *

Statistical Analysis Plan

An Open-label, Multicenter, Phase 2 Study Evaluating the Efficacy and Safety of Daratumumab in Pediatric and Young Adult Subjects ≥1 and ≤30 Years of Age with Relapsed/Refractory Precursor B-cell or T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma

Protocol 54767414ALL2005; Phase 2

JNJ-54767414 (daratumumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ARA-C	cytarabine
AST	aspartate aminotransferase
CI	confidence interval
CCO	clinical cutoff
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRi	complete response with only partial hematological recovery
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicities
ECG	electrocardiogram
EFS	event-free survival
HC	hydrocortisone
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
IRR	Infusion-related reaction
LL	lymphoblastic lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MTX	methotrexate
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PK	pharmacokinetic(s)
RBC	red blood cell
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SET	safety evaluation team
SMQ	Standardized MedDRA Queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for planned analyses for study 54767414ALL2005.

1.1. Trial Objectives

Primary Objective

The primary objective is to evaluate the efficacy of daratumumab in combination with standard chemotherapy in pediatric subjects with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) and T-cell ALL as measured by the complete response (CR) rate.

Secondary Objectives

The secondary objectives are:

- To assess the efficacy of daratumumab in addition to standard chemometry, including overall response rate (ORR), relapse-free survival (RFS), event-free survival (EFS), and overall survival (OS) in pediatric subjects with B-cell and T-cell ALL, and minimal residual disease (MRD) negative rate in subjects with B-cell and T-cell ALL
- To assess the safety and tolerability of daratumumab in addition to standard chemometry in pediatric subjects with B-cell and T-cell ALL
- To assess the pharmacokinetics (PK) of daratumumab in pediatric subjects with B-cell and T-cell ALL
- To assess daratumumab immunogenicity in pediatric subjects with B-cell ALL and T-cell ALL
- To assess daratumumab concentration in cerebrospinal fluid (CSF)

Exploratory Objectives

The exploratory objectives are:

- To explore biomarkers predictive of response or resistance to therapy
- To assess expression of CD38 at study entry and at relapse

1.2. Trial Design

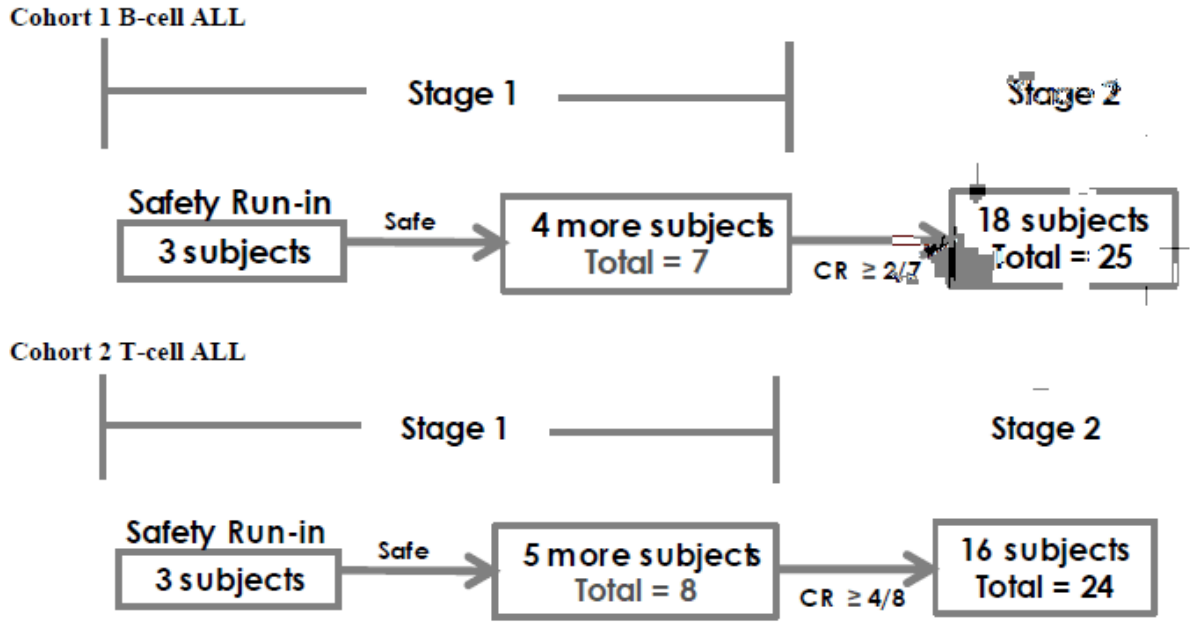
This open-label, multicenter, Phase 2 study will enroll approximately 49 subjects aged ≥1 to <18 years with relapsed/refractory ALL and a maximum of 69 total subjects ≥1 and ≤30 years of age with relapsed/refractory ALL/LL. Cohort 1 will evaluate the safety and efficacy of daratumumab in combination with vincristine and prednisone in subjects with B-cell ALL/LL in second relapse or greater. Cohort 2 will evaluate the safety and efficacy of daratumumab in combination with a standard 4-drug re-induction regimen (prednisone, vincristine, doxorubicin, and PEG-asparaginase) in subjects with T-cell ALL/LL in first relapse.

Subject participation will include a Screening Period, a Treatment Period, and a Post-treatment Period. The Screening Period will be up to 21 days before first dose. During the Treatment Period, cycles are 28 days. Subjects with B-cell ALL/LL will receive treatment until disease progression or unacceptable toxicity. Subjects with T-cell ALL/LL will receive treatment for up to 2 cycles (induction and consolidation). There is an optional maintenance phase for all subjects who achieve CR and need to bridge therapy until an allogeneic hematopoietic stem cell transplant (HSCT). The Post-treatment Period begins immediately following the End-of-Treatment Visit, and will continue until death, loss to follow-up, or consent withdrawal for study participation, whichever occurs first.

A diagram of the study design is provided below in Figure 1. The study has 2 stages. Stage 1 will evaluate the initial safety and efficacy in each cohort. Only B-cell or T-cell ALL subjects aged 1 to <18 years will be enrolled in their respective cohorts in Stage 1. Stage 1 will include a safety run-in which will evaluate the initial 3 subjects with B-cell ALL and initial 3 subjects with T-cell ALL. Enrollment will continue after safety is confirmed in each cohort separately. After confirming safety, Cohort 1 (B-cell ALL) will enroll an additional 4 subjects aged 1 to <18 years in Stage 1 and Cohort 2 (T-cell ALL) will enroll an additional 5 subjects aged 1 to <18 years in Stage 1. During Stage 1, the dose of daratumumab will be evaluated with ongoing PK analysis to confirm the therapeutic dose of daratumumab to be used in Stage 2 of the study. The study will have a futility analysis for each cohort after Stage 1 is completed before enrolling subjects to Stage 2. All subjects enrolled into Stage 1, including subjects in the safety run-in at the confirmed safe dosing regimen will be included in the futility analysis.

In Stage 2, an additional 18 subjects with B-cell ALL and 16 subjects with T-cell ALL aged 1 to <18 years will be enrolled for a total of 25 subjects with B-cell ALL and 24 subjects with T-cell ALL aged 1 to <18 years. The sponsor plans to enroll a minimum of 3 subjects with ALL in each of the following age groups in both cohorts if an individual cohort proceeds to Stage 2: 1 to 6, 7 to 12, and 13 to <18 years. In Stage 2 subjects with LL and young adults with ALL will also be enrolled. A maximum of 10 subjects aged 1 to 30 years with LL and a maximum of 10 subjects aged 18 to 30 years with ALL will be enrolled to the respective B-cell and T-cell cohorts. The data from these subjects with LL (pediatric and young adult) and young adult subjects aged 18 to 30 years with ALL will be descriptively summarized.

Figure 1: Schematic Overview of the Study



Abbreviations: ALL=acute lymphoblastic leukemia; CR=complete response; LL=lymphoblastic lymphoma.
Note: In addition to the pediatric subjects with ALL included in this study, young adult subjects with ALL, aged 18 to 30 years, and subjects with LL, aged 1 to 30 years, will be enrolled in Stage 2.

Subjects with B-cell ALL/LL will receive treatment continuously in 28-day cycles until disease progression or unacceptable toxicity. Treatment will consist of daratumumab 16 mg/kg IV weekly for 8 doses, then every 2 weeks for 8 doses, then every 28 days thereafter; vincristine 1.5 mg/m^2 (maximum 2 mg) IV weekly for 4 doses, then every 2 weeks for 2 doses, then every 28 days thereafter; and prednisone 40 mg/m^2 orally daily for 28 days, then pulses on the first 5 days of each cycle thereafter.

Subjects with T-cell ALL/LL will receive up to two 28-day cycles of therapy. Subjects who achieve CR should proceed to allogeneic hematopoietic stem cell transplant off study. Cycle 1 treatment consists of daratumumab 16 mg/kg IV weekly for 4 doses, vincristine 1.5 mg/m^2 (maximum 2 mg) IV weekly for 4 doses, prednisone 40 mg/m^2 orally daily for 28 days, doxorubicin 60 mg/m^2 IV once, and peg-asparaginase 2500 U/m^2 IM or IV twice. Cycle 2 treatment consists of daratumumab 16 mg/kg IV weekly for 4 doses, cyclophosphamide IV 1 g/m^2 once, cytarabine 75 mg/m^2 IV/subcutaneous for 8 doses, 6-mercaptopurine 60 mg/m^2 orally daily for 14 doses, and methotrexate 5 g/m^2 IV once.

Subjects in both cohorts will also receive age-adjusted treatment with intrathecal methotrexate (for subjects without central nervous system [CNS] involvement) or intrathecal methotrexate-hydrocortisone-cytarabine (for subjects with CNS involvement).

During the safety run-in, 3 subjects in each cohort will be evaluated for dose-limiting toxicities (DLTs). A Safety Evaluation Team (SET) will review the DLT data and determine whether a modification to the dose or schedule of study drugs is needed for any of the treatment cohorts. The DLT Evaluation Period is defined as the first 28 days from the start of the first dose of daratumumab. DLTs will be evaluated in each cohort separately at the end of Cycle 1. Only toxicities that occur during the DLT evaluation period will be used for the purpose of defining DLT and for subsequent dose or dosing schedule modifications or safety-run in expansion. However, toxicities that occur in all cycles will be considered in the overall decisions of the SET. If a subject receives less than 75% of the planned dose of daratumumab for reasons other than toxicity (e.g., disease progression, subject withdrawal, etc.), that subject will be considered non-evaluable for DLTs and may be replaced, but the safety profiles of these subjects will be included in the SET review. Additional safety reviews will be conducted by the SET after Stage 1 of the study in each cohort and as deemed necessary during the conduct of the study.

If 1 or more subjects in a cohort experience a DLT, then the safety run-in for that cohort will be expanded to 6 subjects. After the additional 3 subjects complete 1 cycle of therapy, safety will be re-evaluated. If 2/6 or more subjects experience a DLT, the dose or schedule of study drugs may be adjusted in the remaining treatment cycles, and an additional 3 subjects may be treated at a lower dose or adjusted schedule for a given combination regimen. A new safety evaluation will begin with 3 new subjects with the adjusted dosing regimen and will follow the guidelines noted below.

1.3. Statistical Hypotheses for Trial Objectives

The primary objective is to evaluate the efficacy of daratumumab in addition to standard chemotherapy in relapsed/refractory B-cell ALL and T-cell ALL as measured by the CR rate.

The primary hypothesis for each ALL subtype is as follows:

For the B-cell ALL cohort, treatment with daratumumab in combination with vincristine and prednisone will result in a CR rate of 40% or higher. The following hypotheses will be tested:

- H_0: CR rate ≤15% vs.
- H_a: CR rate ≥40%

For the T-cell ALL cohort, treatment with daratumumab in combination with doxorubicin, prednisone, vincristine, and asparaginase will result in a CR rate of 60% or higher. The following hypotheses will be tested:

- H0: CR rate ≤30% vs.
- Ha: CR rate ≥60%

1.4. Sample Size Justification

The study utilizes a Simon's 2-stage design for subjects aged less than 18 years. The B-cell ALL cohort will enroll 7 subjects in the first stage. If there is more than 1 responder after these subjects have received 2 cycles of treatment, then an additional 18 subjects will be enrolled in Stage 2. If 6

or fewer subjects in the B-cell ALL arm respond, then the drug will be considered ineffective and further development in this disease will be stopped. If 25 subjects are enrolled, then there is 80% power to show that the true CR rate is >15% at a one-sided alpha of 5%. The T-cell ALL cohort will enroll 8 subjects in the first stage. If there are more than 3 responders after these subjects have received at least 1 cycle of treatment, then an additional 16 subjects will be enrolled in Stage 2. This cohort will be considered ineffective if 10 or fewer subjects respond at the end of Stage 2. If 24 pediatric subjects are enrolled, then there is 80% power to show that the true CR rate is >30% at a one-sided alpha of 5%.

In addition, a maximum of 10 young adult subjects (aged 18 to 30 years) with ALL and a maximum of 10 subjects with LL (aged 1 to 30 years) will be included to evaluate the safety and efficacy in this subject population and their data will be summarized descriptively.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Cohorts

In general, outputs will be displayed by the 4 cohorts listed unless otherwise specified. B-cell cohort terminated after futility analysis at the end of stage 1 and thus only has 1 cohort. T-cell ALL total will also be presented where applicable.

- B-cell ALL (1-17 Yrs)
- T-cell ALL (1-17 Yrs)
- T-cell ALL (18-30 Yrs)
- T-cell LL (1-30 Yrs)

2.2. Visit Windows

For analyses of data by cycle, if data are collected by date (e.g., AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study treatment administration data. The start date of a particular cycle is defined as the date of the first actual dose of any component of the study treatment, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or the minimum of last study treatment date plus 30 days or subsequent anticancer therapy minus 1 day, if the end of treatment visit date is not available.

In general, if data (e.g., laboratory and vital sign etc.) are collected by cycle, the nominal cycle will be used to summarize data.

2.3. Pooling Algorithm for Analysis Centers

All participating centers in the study will be pooled together for analyses.

2.4. Study Treatment and Study Drug

In this study, study treatment refers to intrathecal MTX/ Triple Intrathecal Therapy (both T and B cell cohorts), vincristine (both T and B cell cohorts), prednisone (both T and B cell cohorts), doxorubicin (T-cell only), asparaginase (Pegaspargase [PEG-Asparaginase] or Erwinia – T-cell only), high dose methotrexate (T-cell only), cyclophosphamide (T-cell only), cytarabine (ARA-C) (T-cell only), 6-mercaptopurine (T-cell only) and daratumumab.

Study drug refers to daratumumab.

2.5. Study Treatment Dosing Date

Study treatment dosing date is the date on which a subject received study treatment (partial or complete) and will be recorded in the study treatment administration dataset.

For subjects in the B-cell ALL cohort, the first study treatment date is defined as the earliest date of non-zero dose of the following administration: intrathecal MTX, intrathecal MTX/HC/ARA-C, vincristine, prednisone or daratumumab. The last study treatment date is defined as the latest date of non-zero dose of the administration mentioned above.

For subjects in the T-cell ALL/LL cohort, the first study treatment date is defined as the earliest date of non-zero dose of the following administration: intrathecal MTX, intrathecal MTX/HC/ARA-C, doxorubicin, vincristine, prednisone, peg-asparaginase, high dose methotrexate, cyclophosphamide, cytarabine, 6-mercaptopurine, mesna, erwinia asparaginase or daratumumab. The last study treatment date is defined as the latest date of non-zero dose of the administration mentioned above.

2.6. Treatment Cycle

A subject is considered as treated in a cycle if he/she receives any nonzero dose of intrathecal MTX, intrathecal MTX/HC/ARA-C, vincristine, prednisone, doxorubicin, peg-asparaginase, high dose methotrexate, cyclophosphamide, cytarabine, 6-mercaptopurine, mesna, erwinia asparaginase or daratumumab in that cycle.

2.7. Study Day

Day 1 refers to the start of the first study drug administration. All efficacy, PK, immunogenicity, and safety assessments at all visits will be assigned a day relative to this date.

Study day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'.

2.8. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study drug administration.

2.9. Unique Lab Value

In general, in instances when there are multiple records at a given visit date for lab parameters associated with disease assessment, the following rules will be applied to select the unique lab value for analysis: a) multiple records from both central and local lab, central lab value always takes precedence over local lab value; b) multiple records from central lab, select the latest value as the unique lab value; c) multiple records from local lab, select the latest lab value as the unique lab value.

2.10. Imputation of Partial Dates

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purpose, missing or partial date in adverse event (AE) (AE onset date; AE end date), death date, concomitant therapies (start date; end date), B-cell ALL/T-cell ALL/LL initial diagnosis (date of diagnosis), and subsequent systemic therapy (start date) data domain will be imputed. Date as collected (missing or partial) rather than imputed date will be displayed in listings where applicable.

2.10.1. Missing/Partial AE Onset Date

If the onset date of an AE is missing completely or partially, the following imputation rules will be used.

- When month and year are present and the day is missing,
  - If the onset month and year are the same as the month and year of first study treatment, the day of first study treatment or the day-component of the AE end date (possibly imputed), whichever is earlier is imputed.
  - If the onset month and year are not the same as the month and year of first study treatment, then the first day of the month is imputed.
- When only a year is present,
  - If the onset year is the same as the year of first study treatment
    - If AE end date is available and is prior to first study treatment, the day and month of AE end date are imputed.
    - Otherwise, the day and month of first study treatment are imputed.
  - If the onset year is different from the year of first study treatment, the 1st of January is imputed.
- If the onset date is completely missing, the date of first study treatment is imputed as the onset date.

No imputation will be done for partial or missing AE onset time.

If AE onset date needs imputation, but the AE onset time is available, the AE onset time will be dropped in the imputed AE onset date/time variable.

2.10.2. Missing/Partial AE End Date

If the end date of an AE is partially missing, the following imputation rules will be used.

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.
- If the imputed date is later than the date of death (if available), the date of death will be used as the imputed date instead.

If the end date is completely missing the AE will be considered as ongoing at the end of study and no imputation will be done.

No imputation will be done for partial or missing AE end time.

If AE end date needs imputation, but the AE end time is available, the AE end time will be dropped in the imputed AE end date/time variable.

2.10.3. Missing/Partial Death Date

If the death date is completely missing or the month is missing, no imputation will be performed. If only the day of death date is missing, the following imputation rules will be applied:

- The first day of the month is imputed.
- If it has the same year and month as the date of the last known alive, then the date of the last known alive + 1 will be used as the imputed date instead.

2.10.4. Partial Concomitant Medication Start/End Date

In case of partially missing concomitant medication start/end dates, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed.

- If only the day is missing, the 15th day of the month will be used
- If both the day and month are missing, the 30th of June will be used

If the medication was taken prior to study start, and the imputed start date is after first treatment date, further adjust of the imputed start date as the day prior to first dosing date; If the medication was taken after study start, and the imputed start date is prior to the first dosing date, the imputed start date will be adjusted to be the first dosing date. The imputed medication end date will also be adjusted so that it is on or after first dosing date.

After applying above adjusting method, if it results in medication start date that is after medication end date, the medication start date needs re-adjustment as follows:

If medication start date was imputed then adjust as follows:

- Impute the same month and year as medication end date if the non-imputed date parts are the same
- Impute the first day of the month as medication start day

If medication end date was imputed then re-adjust medication end date to be the same as the medication start date if the corresponding non-imputed date parts match the medication start date.

Also adjust the imputed medication end date so that it is on or after first dosing date.

2.10.5. Partial B-Cell ALL/T-Cell ALL/LL Diagnosis Date

If the B-cell ALL/T-cell ALL/LL diagnosis date is completely missing, no imputation will be applied. For the partial date of B-cell ALL /T-cell ALL/LL initial diagnosis, the following imputation rules will apply:

- If only the day of the diagnosis date is missing:
    - If the month and year of the diagnosis date are the same as the month and year of the start date of the first line of prior B-cell ALL/T-cell ALL/LL therapy, and day of the start date of the first line of prior B-cell ALL/T-cell ALL/LL therapy is available, impute day of the diagnosis date with the day of the start date of the first line of prior B-cell ALL/T-cell ALL/LL therapy;
    - Otherwise, impute day of diagnosis date with 15;
- If both month and day of the diagnosis date are missing:
    - If the year of the diagnosis date is the same as the year of the start date of the first line of prior B-cell ALL/T-cell ALL/LL, and the month of the start date of the first line of prior B-cell ALL/T-cell ALL/LL therapy is available:
        - if both month and day of the start date of the first line of prior B-cell ALL/T-cell ALL/LL therapy are available, impute diagnosis month and day with the month and day of the start date of the first line of prior B-cell ALL/T-cell ALL/LL therapy;
        - if only the month of the start date of the first line of prior B-cell ALL/T-cell ALL/LL therapy is available, impute the month of diagnosis date with the month of the start date of the first line of prior B-cell ALL/T-cell ALL/LL therapy and the day of the diagnosis date with 15;
    - Otherwise, impute the month and day of the diagnosis date with June 30.

2.10.6. Partial Subsequent Systemic Therapy Start Date

If the year or month of subsequent anticancer therapy start date is missing or no components of the start date are present, no imputation will be performed.

If only the day-component is missing, the following steps apply:

- If the month and year of the start date are the same as the month and the year of last dosing date, the day of last dosing date or the day-component of the stop date of subsequent anticancer therapy is imputed, whichever is earlier.
- If the start month and year are not the same as the month and year of last dosing date, the first day of the month is imputed.

After applying above adjusting method, if it results in that medication start date is after medication end date, the medication start date needs to be re-adjusted to be the same as the end date.

No imputation will be applied for missing or partial subsequent anticancer therapy end date.

2.11. General Analysis Method

In general, summary statistics for continuous variables include mean, standard deviation, median, minimum, and maximum unless otherwise specified. Categorical data will be presented as frequencies and percentages. The Kaplan-Meier method will be used for descriptive summaries for time-to-event variables. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus 1 day will be used.

2.12. Analysis Sets

The following analysis sets are defined for conducting planned analyses.

2.12.1. Response Evaluable Analysis Set

The response evaluable analysis set includes all enrolled subjects who receive at least 1 dose of daratumumab and have at least 1 adequate post-baseline disease assessment. Sensitivity analyses of CR rate and ORR will be based on response evaluable analysis set.

2.12.2. All treated Analysis Set

The all treated analysis set includes all enrolled subjects who receive at least 1 dose of daratumumab. This analysis set will be used for all safety analyses, analyses of the primary efficacy endpoint CR rate, and major secondary endpoints, such as ORR, MRD negative rate, HSCT rate, time-to-event variables (e.g., EFS, RFS, and OS), and subject information summaries that described in Section 4.

2.12.3. Serum Pharmacokinetics Evaluable Analysis Set

The serum PK evaluable analysis set includes all enrolled subjects who receive at least 1 dose of daratumumab and provide at least 1 post-infusion blood sample for serum daratumumab concentrations. This analysis set will be used for daratumumab serum concentrations summary.

2.12.4. CSF Pharmacokinetics Evaluable Analysis Set

The CSF PK evaluable analysis set includes all enrolled subjects who receive at least 1 dose of daratumumab and provide at least 1 post-infusion CSF sample for daratumumab concentrations. This analysis set will be used for CSF daratumumab concentrations summary.

2.12.5. Immunogenicity Evaluable Analysis Set

The immunogenicity evaluable analysis set includes all enrolled subjects who receive at least 1 dose of daratumumab and have at least 1 post-infusion sample for detection of anti-daratumumab antibodies. This analysis set will be used for daratumumab immunogenicity analysis.

2.12.6. Dose Limiting Toxicity (DLT) Evaluable Analysis Set

The DLT-evaluable analysis set includes any subject in the safety run-in phase who has a DLT regardless of dose received or who completed the first 28 days from the start of the first dose of Daratumumab and received at least 75% of the planned dose during the DLT evaluation period, which is the first 28 days starting from the day of the first dose of study drug.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Non-binding futility analysis (based on a Simon two-stage design) will be performed for Cohorts 1 and 2.

A SET consisting of the participating principal investigators, the sponsor's responsible medical officer, sponsor's statistician, sponsor's clinical pharmacologist and sponsor's safety management team chair will monitor safety in the run-in of the first 3 subjects in each cohort separately. Additional safety reviews will be conducted by the SET after Stage 1 of the study in each cohort and as deemed necessary during the conduct of the study. The details will be provided in a separate SET charter.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Unless specified otherwise, all demographic and baseline characteristics variables will be summarized for the all treated analysis set. All interested baseline disease characteristics variables that are listed in Table 2 will also be summarized for the all treated analysis set.

The distribution of subject's enrollment will be presented for each cohort according to region, country, and site.

Table 1 presents a list of demographic and baseline characteristics variables that will be summarized by cohort.

Table 2 presents a list of baseline disease characteristics variables that will be summarized by cohort.

Table 1: Demographic and Baseline Characteristics Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum).
Weight (kg)	
Height (cm)	
BMI (kg/m^2)	
BSA (Body surface area) (m^2)	

Categorical Variables	
Age (1-6, 7-12, 13-17, 18-30)	Frequency distribution with the number and percentage of subjects in each category.
Sex (Male, Female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Not reported, Multiple)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 2: Baseline Disease Characteristics Variables

Continuous Variables:	**Summary Type**
Time from initial diagnosis to first dose (days)	Descriptive statistics (N, mean, SD, median, minimum and maximum).
Lines of prior systemic therapy	
Time since last progression of prior systemic therapy to first dose (days)	
Baseline tumorous leukemia/lymphoma cells (%) by bone marrow aspirate/biopsy	
Categorical Variables	
	Frequency distribution with the number and percentage of subjects in each category.
Lines of prior systemic therapy (=1, >1)	
Evidence of extramedullary disease at study entry (Yes, No)	
Presence of testicular involvement at study entry (Yes, No)	
CNS disease status at study entry (CNS Negative, CNS Positive)	

4.2. Medical History

Medical history will be summarized by system-organ class (SOC) and preferred term for each cohort and overall. A subject is counted only once within a category. Percentages are based on the number of subjects in the all treated analysis set within each cohort.

4.3. Disposition Information

The number and percentage of subjects in the following disposition categories will be summarized for all treated subjects throughout the study by cohort:

- subjects in each of the study analysis sets
- subjects completing the study
- subjects discontinued from daratumumab
- primary reason for daratumumab discontinuation
- subjects discontinued from backbone therapies
- primary reason for backbone therapies discontinuation
- subjects discontinued from the study

- primary reason for study discontinuation

All percentages will be based on the number of all treated subjects within each cohort.

Listings for treatment disposition and study disposition will be provided for the DLT-evaluable analysis set.

4.4. Extent of Exposure

Extent of exposure to study treatments will be summarized through the following variables: number of treatment cycles, duration of study treatment, total dose administered, dose intensity, relative dose intensity, and number of subjects with cycle delay and dose modification etc. These summaries will be based on the all treated analysis set and presented by cohort.

The number and percentage of subjects treated within each cycle will be summarized. The maximum number of treatment cycles received for each subject will be summarized by frequency and descriptive statistics.

Duration of study treatment, defined as the number of days from the date of the first administration of study treatment to the date of the last administration of study treatment, will be summarized.

Exposure occurring after the subject switched to Daratumumab continuation phase will be considered separately and the last cycle number will be presented for these subjects.

Descriptive statistics for the number of daratumumab administrations will be provided for each cohort. The total dose administered for each study treatment (i.e., daratumumab (mg/kg) for both T and B cell cohorts, MTX (mg) for both T and B cell cohorts, vincristine (mg/m^2) for both T and B cell cohorts, prednisone (mg/m^2) for both T and B cell cohorts, doxorubicin (mg/m^2) for T-cell only, peg-asparaginase (IU/m^2) or erwinia asparaginase (IU/m^2) for T-cell only , high dose MTX (g/m^2) for T-cell only, cyclophosphamide (g/m^2) for T-cell only, cytarabine (ARA-C) (mg/m^2) for T-cell only and 6-mercaptopurine (mg/m^2) for T-cell only will be summarized overall, and by treatment cycle.

The dose intensity, which is defined as the sum of the total dose administered in specified cycles divided by the number of cycles, will be calculated for each study treatment and summarized accordingly. The dose intensity will be summarized based on the treatment schedule, for each study treatment.

The relative dose intensity (%), defined as the ratio of total actually received dose and total planned dose will be calculated for each study treatment and summarized using descriptive statistics and categories (<80%, 80%-100%, >100%).

Duration of Daratumumab infusion in minutes for first, second and all subsequent infusions will be summarized.

The number of subjects with cycle delays and the number of subjects with dose modifications (dose delays, dose interruption, dose skipping, or dose reduction) for each study treatment

including reasons (AE, awaiting count recovery or other) for cycle delays and reasons for dose modifications, will be reported.

Listings for study agent administration and batch lot number will also be provided.

4.5. Protocol Deviation

Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized for the all treated analysis set by the following categories of deviation for each cohort:

- Entered but did not satisfy criteria
- Developed withdrawal criteria but not withdrawn
- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment
- Other (Overall and COVID-19 related)

A list of subjects with major protocol deviations including subject ID, type of deviation, and reasons for deviation will be provided.

A list of minor protocol deviations related to COVID-19 for T-cell Subjects will be provided.

4.6. Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant medications are defined as those medications taken on or after the first study treatment dose date through 30 days after the last study treatment dose date and will be summarized by therapeutic class, pharmacologic class, and preferred term for each cohort based on the all treated analysis set.

A similar summary of pre-infusion medications and post-infusion medications will be provided based on the all treated analysis set.

4.7. Prior and Subsequent Systemic Therapy

Subsequent systemic therapy, conditioning therapy and bridging therapy recorded during the study will be summarized and presented by therapeutic class, pharmacologic class and preferred term for each cohort based on the all treated analysis set.

For subjects who received at least one line of prior therapy, the number of lines of prior therapy will be calculated for each subject and summarized by cohort through frequency and descriptive statistics. In addition, their overall best response to the first prior therapy, relationship with allogenic transplant, progress/relapse on or after the first therapy will be summarized.

Listings of subsequent systemic therapy, conditioning and bridging therapy and prior systemic therapy will be provided.

5. EFFICACY

Assessments of disease response and progression for subjects with ALL will be based on the modified National Comprehensive Cancer Network (NCCN) criteria[1]. Response criteria for subjects with LL will be based on response criteria in adult non-Hodgkin's lymphomas (NHL)[2].

Efficacy endpoints will be conducted using the all treated analysis set unless otherwise specified.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical testing will be performed using a 1-sided test at the 5% level of significance, unless otherwise noted. All interval estimation will be reported using 2-sided 90% confidence intervals (CIs).

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

5.2. Primary Efficacy Endpoint(s)

The primary endpoint is the CR rate prior to the start of subsequent anti-cancer therapy or allogeneic HSCT within 2 cycles of therapy for B-cell ALL and at the end of Cycle 1 for T-cell ALL/LL.

5.2.1. Definition

A CR is defined as:

- Less than 5% blasts in the bone marrow
- No evidence of circulating blasts or extramedullary disease
- Full recovery of peripheral blood counts:
    - Platelets >$100x10^9$/L
    - Absolute neutrophil count (ANC) >$1.0x10^9$/L

5.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

- Population:
    - B-cell ALL (1-17 Yrs) cohort: subjects with B-cell ALL aged from 1 to <18 years old;
    - T-cell ALL (1-17 Yrs) cohort: subjects with T-cell ALL aged from 1 to <18 years old;
- Variable: CR prior to the start of subsequent anti-cancer therapy or allogeneic HSCT within 2 cycles of therapy for B-cell ALL cohort and at the end of Cycle 1 for T-cell ALL/LL cohorts;
- Intercurrent event: Treatment discontinuation is considered as an intercurrent event for overall response and treatment policy strategy will be implemented, i.e., disease assessments ignoring the treatment discontinuation will be implemented;
- Population-level summary: CR rate.

5.2.3. Analysis Methods

The analysis of CR rate will be performed based on the all treated analysis set. The number and percentage of subjects who achieve a CR including a two-sided 90% Clopper-Pearson exact CI will be calculated. The exact p-value to test the hypothesis, H0: CR rate ≤15% in the pediatric B cell ALL cohort and H0: CR rate ≤30% in the pediatric T-cell ALL cohort, will also be calculated.

Besides, sensitivity analyses of CR rate based on the response-evaluable analysis set will be performed in a similar manner.

In addition data gathered for ALL subjects aged 18 to 30 years of age and subjects with LL will be summarized descriptively; the number and percentage of subjects who achieve a CR including a two-sided 90% Clopper-Pearson exact CI will be calculated.

5.3. Major Secondary Endpoints

The major secondary endpoints include ORR, EFS, RFS, OS, MRD negative rate in subjects with B-cell and T-cell ALL, and allogeneic HSCT rate.

5.3.1. Overall Response Rate (ORR)

5.3.1.1. Definition

The ORR is defined as the proportion of ALL subjects who have a CR or CRi according to modified NCCN criteria, during or after treatment administration but prior to the start of subsequent anti-cancer therapy or allogeneic HSCT.

- CR for ALL is defined as above
- CRi for ALL is defined as:
    - Less than 5% blasts in the bone marrow
    - No evidence of circulating blasts or extramedullary disease
    - Partial recovery of peripheral blood counts not meeting criteria for CR noted above

For LL subjects, the ORR is defined as the proportion of subjects who have CR or PR during or after treatment administration but prior to the start of subsequent anti-cancer therapy or allogeneic HSCT.

5.3.1.2. Analysis Methods

The number and percentage of subjects with the corresponding best overall response categories will be summarized for each of B-cell and T-cell ALL cohorts. The number and percentage of subjects who have an overall response (CR + CRi) and a two-sided 90% Clopper-Pearson exact CI will be calculated for each of the three ALL cohorts. These analyses will be performed based on the all treated analysis set.

A sensitivity analyses of ORR will be performed in a similar manner based on the response-evaluable analysis set only.

Besides, the number and percentage of subjects with the corresponding best overall response categories will be summarized for the T-cell LL cohort.

5.3.2. Event-Free Survival (EFS)

5.3.2.1. Definition

EFS is defined as the time from the date of first study drug administration to the first documented treatment failure (i.e., disease progression) or date of relapse from CR or death due to any cause, whichever occurs first. Relapse from CR is defined as reappearance of leukemia blasts in the peripheral blood or >5% blasts in the bone marrow, or reappearance of extramedullary disease or new extramedullary disease. Disease progression or relapse from CR reported in disease evaluation CRFs or in subsequent therapy CRFs will be used to identify the first disease progression/relapse date.

Subjects who withdrew consent from the study or lost to follow-up before disease progression/relapse from CR will be censored at the last disease assessment before withdrawal of consent from the study or lost to follow-up.

Subjects who died after consent withdrawal will be censored at the date of consent withdrawal.

For subjects who have not progressed and are alive, data will be censored at the last disease assessment before the start of any subsequent systemic therapy. Conditioning, bridging and allogeneic HSCT therapies should not be considered as subsequent systemic therapy. Survival follow-up will also be considered as disease assessment for subjects who received allogeneic HSCT.

Subjects without any post-baseline bone marrow or peripheral blood counts assessment will be censored at first study drug administration.

Determination of dates of EFS event and dates for censoring is summarized in Table 3 as follows.

Table 3: EFS Event and Censoring Method

Situation	Date of Event or Censoring	Outcome
Disease progression/relapse from CR	Date of disease progression	EFS event
Death prior to disease progression	Date of death	EFS event
No post-baseline bone marrow or peripheral blood counts assessment	Date of first study drug administration	Censored
No EFS events	Date of last adequate disease evaluation (including survival follow-up for subjects who received allogeneic HSCT)	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up etc.)	Date of last adequate disease evaluation. Date of consent withdrawal if died after consent withdrawal.	Censored

5.3.2.2. Analysis Methods

Analysis of EFS will be performed based on the all treated analysis set. The Kaplan-Meier method will be used to estimate the distribution of overall EFS for each cohort. The median EFS with 90% CI will be provided. In addition, the number and percentage of subjects who had an EFS event or were censored will be reported. The Kaplan-Meier EFS curve will also be plotted by cohort.

Besides, reasons for EFS and censoring will be summarized for the all treated analysis set.

5.3.3. Relapse-Free Survival (RFS)

5.3.3.1. Definition

RFS is defined as the time from CR to relapse from CR or disease progression or death due to any cause, whichever occurs first. Relapse from CR or disease progression reported in disease evaluation CRFs or in subsequent therapy CRFs will be used to identify the first relapse date or disease progression date.

Subjects who withdrew consent from the study or lost to follow-up before relapse from CR will be censored at the last disease assessment before withdrawal of consent to study or lost to follow-up.

Subjects who died after consent withdrawal will be censored at the date of consent withdrawal.

Subjects who don't have RFS event and are still alive will be censored at the last disease assessment.

Survival follow-up will also be considered as disease assessment for subjects who received allogeneic HSCT.

Determination of dates of RFS event and dates for censoring is summarized in Table 4 as follows.

Table 4: RFS Event and Censoring Method

Situation	Date of Event or Censoring	Outcome
Relapse from CR / disease progression	Date of relapse from CR / disease progression	RFS event
Death prior to relapse	Date of death	RFS event
No RFS events	Date of last adequate disease evaluation (including survival follow-up for subjects who received allogeneic HSCT)	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up etc.)	Date of last disease adequate evaluation. Date of consent withdrawal if died after consent withdrawal.	Censored

5.3.3.2. Analysis Methods

Analysis of RFS will be performed based on the all treated subjects who achieve a complete response analysis set. The Kaplan-Meier method will be used to estimate the distribution of overall RFS for each cohort. The median RFS with 90% CI will be provided. In addition, the number and percentage of subjects who had a RFS event or were censored will be reported. The Kaplan-Meier RFS curve will also be plotted by cohort.

Besides, reasons for RFS and censoring will be summarized for the all treated analysis set.

5.3.4. Overall Survival (OS)

5.3.4.1. Definition

OS is measured from the date of first study drug administration to the date of death due to any cause. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subjects who died after consent withdrawal will be considered as having an OS event. If the subject is alive or the survival status is unknown, then the subject's data will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.3.4.2. Analysis Methods

Analysis of OS will be performed based on the all treated analysis set. The Kaplan-Meier method will be used to estimate the distribution of OS for each cohort. Median OS with 90% CI will be provided. In addition, the number and percentage of subjects who had died or were censored will be reported. The Kaplan-Meier OS curve will also be plotted by cohort.

5.3.5. MRD Negative Rate

5.3.5.1. Definition

MRD negativity is defined as <0.01% abnormal population counts to nucleated mononuclear cell counts when measured by flow cytometry.

MRD negativity rate is defined as the proportion of subjects who are considered MRD negative after MRD testing by bone marrow aspirate at any timepoint after first study treatment administration and before disease progression or starting subsequent anti-cancer therapy or allogeneic HSCT. MRD positive subjects include subjects of which all tested samples were found to be MRD positive or ambiguous. Subjects with missing or unevaluable MRD status will be considered as MRD positive.

5.3.5.2. Analysis Methods

Analysis of MRD negative rate will be performed based on the all treated analysis set. The proportion of subjects who are MRD negative and a two-sided 90% Clopper-Pearson exact CI will be calculated.

5.3.6. Allogeneic Hematopoietic Stem Cell Transplant Rate

5.3.6.1. Definition

The allogeneic HSCT rate is defined as the proportion of subjects who receive an allogeneic HSCT after treatment with daratumumab.

5.3.6.2. Analysis Methods

Analysis of the allogeneic HSCT rate will be performed based on the all treated analysis set. The proportion of subjects who received an allogeneic HSCT after treatment with daratumumab will be calculated. A two-sided 90% Clopper-Pearson exact CI will also be calculated.

Descriptive statistics for number of CD34+ cells transplanted (10^6/kg), the number and percentage of subjects in each source of CD34+ cells transplanted (chord blood, peripheral blood, bone marrow), the number and percentage of subjects with hematopoietic reconstruction, descriptive statistics for time to engraftment (days) and the number and percentage of subjects have graft failure will also be summarized by cohort.

5.4. Other Efficacy Endpoints

Not Applicable

6. PHARMACOKINETIC AND IMMUNOGENICITY

6.1. Pharmacokinetic

Serum samples to assess both the serum concentration (PK) of daratumumab and the generation of anti-daratumumab antibodies (immunogenicity) will be obtained from all subjects; analysis will be performed using validated immunoassay methods by or under the supervision of the sponsor's bioanalytical facility. Up to 1 mL of CSF will also be collected for assessment of daratumumab concentrations using a validated assay method by or under the supervision of the sponsor's bioanalytical facility.

PK analyses will be performed on the serum PK evaluable analysis set for daratumumab serum concentration and CSF PK evaluable analysis set for daratumumab CSF concentration. Descriptive statistics (N, mean, SD, median, range, CV (%), geometric mean) will be provided for serum daratumumab and CSF concentrations at each sampling timepoint. PK parameters of daratumumab are defined by the assigned timepoint: C_{min} (minimum observed concentration) is the predose concentration and C_{max} (maximum observed concentration) is the end of infusion concentration. Concentrations for each individual and mean concentration of each cohort will be presented in figures with linear. Concentrations below the lowest quantifiable concentration in a sample will be treated as zero in the summary statistics.

Besides, by age (1 to 6 Yrs, 7 to 12 Yrs, 13 to 17 Yrs) summaries will be provided for pediatric subjects for serum daratumumab and CSF concentrations based on serum PK evaluable analysis set and CSF PK evaluable analysis set, respectively if the number of subjects in the subgroups is sufficient. Corresponding figures will be provided. Also, by baseline body weight quartiles summaries will be provided for pediatric subjects for serum daratumumab and CSF concentrations based on serum PK evaluable analysis set and CSF PK evaluable analysis set, respectively.

Additionally, a summary of serum daratumumab concentrations by anti-daratumumab antibodies (negative, positive) for each cohort will be provided based on serum PK evaluable analysis set.

Corresponding data listings will be provided. All serum concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration data listing.

The population PK details will be specified in an analysis plan and the results will be presented in a separate report. If an exposure-response analysis is performed, it will also be detailed in a separate analysis plan and report.

6.2. Immunogenicity

For the immunogenicity assessments, serum samples will be screened for antibodies binding to daratumumab and serum titer will also be determined from confirmed positive samples. Other immunogenicity analyses (e.g., assessment of neutralizing capabilities) may be performed to further characterize the immune responses that are generated.

Immunogenicity analyses will be performed on the immunogenicity evaluable analysis set. The incidence of anti-daratumumab antibodies will be summarized by cohort and listings will be provided of sample anti-daratumumab antibody status and the concurrent serum daratumumab concentration for immunogenicity evaluable analysis set and for the subset of subjects with IRR within this analysis set.

7. BIOMARKER

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information. Results of biomarker analyses may be presented in a separate report.

7.1. Minimal Residual Disease (MRD)

MRD will be monitored using validated flow cytometry assay at the central lab, University of Washington on bone marrow aspirate.

7.1.1. Sampling Timepoints

MRD assessments will be done by flow cytometry with baseline bone marrow aspirate to define tumor burden, posttreatment samples to determine MRD negativity (end of both Cycle 1 and Cycle 2 for T-cell cohort), and End of Treatment.

7.1.2. Analysis Methods

Details on MRD negativity rate analyses are described in Section 0. For this study, threshold value of 10^{-4} will be used for the MRD negativity analysis. In addition, the relationship between MRD negativity and clinical outcome (CR + CRi rate) could be evaluated.

7.2. CD38 Expression on Lymphoblasts

Proportion of CD38+ lymphoblasts and CD38 receptor density on lymphoblasts will be measured on residual bone marrow aspirate samples after MRD analysis by flow cytometry ay University of Washington.

A figure of CD38 expression on blasts (MESF) over time by subjects will be provided.

7.3. Other Biomarker

Figures with median and Interquartile range of NK absolute counts (CD16CD56) in peripheral blood over time, CDX27NMN (for B-cell) over time and CDX27PMN (for-T-cell) over time will be provided.

8. SAFETY

Safety assessment will be evaluated through AEs, clinical laboratory tests, vital signs measurements, physical examination findings, Karnofsky and Lansky performance status, and ECG assessment. Safety analyses will be based on the all treated analysis set and presented by cohort.

8.1. Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug, unless the subject withdraws consent for study participation, or starts subsequent anticancer therapy. For subjects who have received additional treatment with therapeutic intent for ALL/LL during the AE reporting period, only study treatment-related AEs must be reported (unless the subject has been withdrawn from the study). An AE is considered study treatment-related if the attribution is possible, probable, or very likely. AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 or later.

The verbatim terms used in the case report form (CRF) by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAE is defined as any AE with onset date and time on or after that of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent therapy or HSCT, whichever is earlier; or the follow-up AE (linked to an existing TEAE) with onset date and time beyond 30 days after the last study treatment but prior to the start of subsequent therapy or HSCT whichever is earlier; or any AE that is considered study agent related regardless of the start date of the event. AEs with missing or partial onset date and time will be considered as treatment-emergent unless the onset date and time of an AE can be determined as earlier than that of the first study treatment, or later than 30 days after last study treatment. All summaries of AEs will be based on treatment-emergent adverse events (TEAEs). For each TEAE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by cohort.

Unless otherwise specified, at each level (e.g., SOC and/or preferred term) of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded. For summarizing new onset events, all event records of the same preferred term from the same subject are to be linked by the onset date and the end date. If an event is followed by another event of the same preferred term with an onset date (or date/time) the same as or 1 day (or 1 minute if applicable) after the end date (or date/time) of the previous record and any features of the AE (i.e.: toxicity grades/seriousness/action taken) are different between these two records, these 2 records should be linked together and considered as 1 event.

The incidence of TEAEs will be summarized overall, by MedDRA SOC and preferred term, by maximum toxicity grade, and by relationship to any study treatment administration. No toxicity grade or AE relationship will be imputed when missing. Specifically, the following AE summaries will be presented by cohort:

- TEAEs
- TEAEs by maximum toxicity grade
- TEAEs by relationship to any study treatment
- Toxicity grade 3 or 4 TEAEs
- TEAEs related to any study treatment
- Serious AEs (SAEs)
- TEAEs leading to cycle delays or dose modifications
- TEAEs leading to discontinuation of daratumumab
- TEAEs leading to discontinuation of all study treatments

8.1.1. Overview of TEAEs

An overview of TEAEs reported through the study will be provided for each cohort. The overview will include summaries of subjects with TEAEs, TEAEs of max toxicity grade of 1 to 5, TEAEs with toxicity grade 3 or 4, TEAEs related to daratumumab, TEAEs related to any backbone therapy, SAEs, TEAEs with fatal outcome, TEAEs leading to discontinuation of daratumumab, and TEAEs leading to discontinuation of all study treatments.

8.1.2. All TEAEs

- Incidence of TEAEs by MedDRA SOC and preferred term
- Incidence of TEAEs by MedDRA SOC, preferred term and maximum toxicity grade
- Incidence of TEAEs by MedDRA SOC, preferred term, and relationship to any study treatment
- Incidence of most Common (at least 10%) TEAEs by MedDRA SOC, preferred term

- A similar summary of incidence of TEAEs by MedDRA SOC and preferred term will be presented by treatment cycle.

8.1.3. Toxicity Grade 3 or 4 TEAEs

- Incidence of toxicity grade 3 or 4 TEAEs, by MedDRA SOC and preferred term
- List of subjects with toxicity grade 3 or 4 TEAEs

- A similar summary of incidence of toxicity grade 3 or 4 will be presented by treatment cycle.

8.1.4. Any Study Treatment-Related TEAEs

- Incidence of TEAEs considered by the investigator to be related to any study treatment, by MedDRA SOC, preferred term, and relationship
- Incidence of TEAEs with toxicity grade 3 or 4 considered by the investigator to be related to any study treatment, by MedDRA SOC, preferred term, and relationship

8.1.5. Serious Adverse Events

- Incidence of treatment-emergent SAEs, by MedDRA SOC and preferred term
- Incidence of treatment-emergent SAEs considered by the investigator to be related to any study treatment, by MedDRA SOC, preferred term and relationship to treatment
- List of subjects with SAEs

- A similar summary of incidence of SAEs will be presented by treatment cycle.

8.1.6. TEAEs Leading to Cycle Delays or Dose Modifications

The incidence of TEAEs leading to treatment cycle delays or dose modifications will be summarized by MedDRA SOC, preferred term and maximum toxicity grade. This table will include TEAEs leading to cycle delays or at least 1 of study treatments dose modifications (dose delays, dose interruption, dose skipping, or dose reduction). The AEs leading to cycle delay are based on the cycle delay due to AE in the cycle delay CRF page. The AEs leading to dose modifications are based on action taken of dose skip or dose delay for any study treatment due to an AE in the study drug administration CRF pages.

8.1.7. TEAEs Leading to Discontinuation of Daratumumab

A summary of number of subjects who discontinued daratumumab because of 1 or more TEAEs by MedDRA system-organ class, preferred term and maximum toxicity grade will be provided. The AEs leading to discontinuation of daratumumab are based on AEs recorded in the AE CRF page with an action taken of drug withdrawal for daratumumab.

A list of subjects with TEAEs leading to discontinuation of any study treatment will be provided.

8.1.8. TEAEs Leading to Discontinuation of All Study Treatment

A summary of number of subjects who discontinued all study treatment because of 1 or more TEAEs by MedDRA SOC, preferred term and maximum toxicity grade will be provided. This table includes AEs leading to discontinuation of all study treatment for those subjects indicated as having discontinued all study treatment due to an AE in the treatment disposition CRF page.

8.2. Deaths

8.2.1. All Deaths

A summary of all deaths and cause of death will be tabulated overall and by cohort. Specifically, the number of subjects who died within 30 days of last dose of study treatment will be summarized for the all treated analysis set. The primary cause of death collected on CRF page will be reported. If the primary cause of death reported is a TEAE, the number of subjects who have a treatment related AE and unrelated AE will be further reported.

Listings of subjects who died during the will be provided.

8.2.2. Death Due to TEAEs

The number of subjects who died due to TEAEs will be summarized by preferred term and relationship to any study treatment for each cohort. The TEAEs included in this table are AEs with outcome death or toxicity grade of 5 recorded in the AE CRF page.

A listing of subjects who died due to TEAEs will be provided.

8.3. Adverse Events of Clinical Interest

8.3.1. Infusion-related Reactions

The incidence of infusion-related reactions (IRRs), as recorded on eCRF, will be presented by SOC, preferred term and maximum toxicity grade. In addition, the total number of subjects with IRRs in more than 1 infusion will be presented. The timing of IRR will also be evaluated through a summary of IRR by event onset time. Listings will be provided for IRRs:

- List of subjects with any IRRs;
- List of subjects with any toxicity grade 3 or higher IRRs;
- List of subjects with any IRRs resulting in discontinuation of Daratumumab.

8.3.2. Infections and Infestations

Infections and infestations refer to the adverse events with SOC of infections and infestations. The grade 3 or 4 treatment-emergent infections and infestations will be summarized by preferred term and relationship to treatment. Treatment-emergent infections and infestations may also be summarized by preferred term and treatment cycles.

8.3.3. Haemorrhage Events

Haemorrhage events refer to the adverse events defined by Standardized MedDRA Queries (SMQ) with the first subcategory SMQ of haemorrhage terms (exclude laboratory terms). Incidences will be summarized by MedDRA SOC, preferred term and maximum toxicity grade.

8.3.4. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) events refer to the adverse events defined by narrow SMQ of tumor lysis syndrome (e.g., haemorrhagic tumor necrosis, tumor lysis syndrome, or tumor necrosis). A listing of subjects who reported any treatment-emergent TLSs during the study will be provided.

8.3.5. New Malignancies

A listing of subject who reported second primary malignancies during the AE reporting period will be provided. The listing will include general information of the corresponding AEs.

8.4. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for subjects included in the all treated analysis set. Descriptive statistics will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit for each cohort. Line plot of mean lab result with standard error for selected laboratory parameters over time will be displayed by cohort. The laboratory parameter included in the analysis will be focus on:

- Hematology panel: hemoglobin, platelet count, WBC count, absolute lymphocyte count, ANC, and peripheral blast count
- Chemistry panel: sodium, potassium, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (direct bilirubin if total bilirubin is abnormal), amylase, alkaline phosphatase, lactic acid dehydrogenase, uric acid, calcium, phosphate, albumin, total protein, lipase
- CSF: RBC count, WBC count, Lymphoblasts count, Lymphoblasts/Leukocytes

Shift tables from baseline to worst toxicity grade for hematology and chemistry analytes during the treatment will be provided for parameters with predefined NCI-CTCAE version 4.03 or later toxicity grades. These tables will summarize the number of subjects with each baseline CTCAE grade and changes to the worst post-baseline CTCAE grade.

8.5. Vital Signs Measurements

Descriptive statistics of observe values and change from baseline of heart rate (beats/min), oxygen saturation (%), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) values will be summarized at each scheduled visit by cohort based on the all treated analysis set.

8.6. Physical Examination Findings

A by-subject listing will also be presented for physical examination findings.

8.7. Karnofsky and Lansky Performance Status

Descriptive statistics of baseline Karnofsky/Lansky performance status and change from baseline values will be summarized at each scheduled visit by cohort based on the all treated analysis set.

8.8. Electrocardiogram

A listing of subjects with clinically significant abnormal results will be provided.

REFERENCES

1. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Acute Lymphoblastic Leukemia. Version 2.2016.
2. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999;17:1244-125