Protocol B1931034

A PHASE 4, OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY OF INOTUZUMAB OZOGAMICIN IN CHINESE ADULT PATIENTS WITH RELAPSED OR REFRACTORY CD22-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Statistical Analysis Plan
(SAP)

Version: **2**

Date: **19 Aug 2024**

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B1931034 is based on the protocol dated 15 May 2023.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 02 Sep 2019	Original 2 Sep 2019	N/A	N/A
2 19 Aug 2024	2 15 May 2023		• Updates of analysis sets in Section 4 • Updates of start of new anti-cancer therapy in Section 5.2.5 • Sensitivity analysis of primary endpoint removed. • Subset analysis in Section 6.4 updated. • Updates on AESI in Section 6.6.1.1 • Updates in Section 6.6.4

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B1931034. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Any deviations from this analysis plan will be described in the Clinical Study Report (CSR).

The primary analysis will include all data up to a data cutoff date which is at least 9 months after last participant first dose. The final number of enrolled participants might deviate from the planned number. All summaries and analyses will include all data pertaining to assessments performed up to and including the data cutoff date.

2.1. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
Primary			
Efficacy	To evaluate the efficacy of inotuzumab ozogamicin based on a primary endpoint of complete remission [CR]/complete remission with incomplete hematologic recovery [CRi] per Investigator's assessment in Chinese adult patients with	CR/CRi per investigator's assessment.	The treatment effect of inotuzumab ozogamicin from the time of first dose until end of treatment for all participants who received at least one dose of inotuzumab ozogamicin regardless of tolerability and duration on treatment.

	relapsed/refractory B-cell ALL.		
Secondary			
Efficacy	• To futher evaluate the efficacy of inotuzumab ozogamicin.	• Duration of remission (DoR). • Minimal residual disease (MRD) negativity in participants achieving CR/CRi. • Progression-free survival (PFS). • Overall survival (OS). • Hematopoietic stem cell transplant (HSCT).	Not Applicable
Safety	• To evaluate the safety of inotuzumab ozogamicin.	• Adverse events as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to inotuzumab ozogamicin, including veno occlusive disease (VOD). • Laboratory abnormalities as characterized by type, frequency, severity (CTCAE v5.0 grade), timing.	Not Applicable
Pharmacokinetics	• To evaluate pharmacokinetic (PK) profile of inotuzumab ozogamicin.	• Inotuzumab ozogamicin C_{max} and $C_{trough.}$	Not Applicable
Immunogenicity	To evaluate the immunogenicity of inotuzumab ozogamicin.	Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb).	Not Applicable

2.1.1. Primary Estimand(s)

The primary estimand is the treatment effect of inotuzumab ozogamicin from the time of first dose until end of treatment regardless of tolerability, duration on treatment. The estimand includes the following 4 attributes:

- Population: Chinese adult participants with relapsed/refractory B-cell ALL, as defined by the inclusion and exclusion criteria in the protocol, and who meet the criteria for safety analysis set(Section 4).
- Variable: the incidence of a participant with a best overall response of CR or CRi from date of the first dose to the end of treatment per Investigator's assessment according to a modified Cheson Criteria (See Appendix 1).
- Intercurrent event(s): All data collected after subsequent anti-cancer therapies will be excluded.
- Population-level summary: Percentage of participants achieving CR/CRi among the safety analysis set.

2.1.2. Secondary Estimand(s)

The secondary estimand for Progression-free survival (PFS) is the treatment effect of inotuzumab ozogamicin regardless of tolerability, duration on therapy or whether treatment was administered under the scenario that subsequent anti-cancer induction therpay is not administered and an extended gap in tumor assessments prior to an event has not occurred. The estimand includes the following 4 attributes:

- Population: Chinese adult participants with relapsed/refractory B-cell ALL, as defined by the inclusion and exclusion criteria in the protocol, and who meet the criteria for safety analysis set.
- Variable: PFS is defined as the time from date of first dose to the date of disease progression, ie, objective progression, relapse from CR/CRi (Appendix 1) or death due to any cause, whichever occurs first.
- Intercurrent event(s): All data collected after an intercurrent event of subsequent induction therapy are censored. Events which occur after an unacceptable long interval will also be censored. Data will be collected regardless of discontinuation from treatment.
- Population-level summary: Kaplan-Meier estimation of the survival function.

The secondary estimand for overall survival (OS) is the treatment effect of inotuzumab ozogamicin regardless of tolerability, duration on treatment, or subsequent anti-cancer therapy. The estimand includes the following 4 attributes:

- Population: Chinese adult participants with relapsed/refractory B-cell ALL, as defined by the inclusion and exclusion criteria in the protocol, and who meet the criteria for safety analysis set.

- Variable: OS is defined as the time from first dose until death due to any cause.

- Intercurrent event(s): All data collected after an intercurrent event of subsequent anti-cancer therapy or discontinuation from treatment are not censored and utilized in the analysis.

- Population-level summary: Kaplan-Meier estimation of the survival function.

2.2. Study Design

This is an open-label, multi-center, single arm, phase 4 study of inotuzumab ozogamicin in Chinese adult participants with relapsed or refractory CD22-positive acute lymphoblastic leukemia (ALL), serving as a post approval commitment (PAC) study to confirm the efficacy, safety and pharmacokinetics (PK) of inotuzumab ozogamicin.

This study is designed to be a hypothesis test. A total of 44 participants will be enrolled to receive inotuzumab ozogamicin, which will provide at least 90% power to reject the null hypothesis (H0: CR/CRi rate ≤37%) when the true CR/CRi rate ≥61% under the 1-sided significance level 0.025. Assuming exactly 44 participants are enrolled, the null hypothesis will be rejected and it will be concluded that the study has demonstrated that the true CR/CRi rate exceeds 37% if 23 or more responders are observed. However, at the time of the analysis, the testing will depend on the actual number of participants enrolled.

Two cycles of treatment of inotuzumab ozogamicin are recommended for hematopoietic stem cell transplant (HSCT) if the participant achieves response within the time period and a suitable donor is available, otherwise one more cycle, ie, the third cycle, may be considered. For participants not proceeding to HSCT, the maximum length of treatment is 6 cycles.

All cases of veno occlusive disease (VOD, also known as sinusoidal obstruction syndrome, SOS) irrespective of causality or severity will be reported as serious adverse events (SAEs) for up to 2 years after the first dose of inotuzumab ozogamicin. An independent hepatic event adjudication committee will evaluate safety for potential VOD/SOS events. Survival will be followed up to 2 years from the first dose of inotuzumab ozogamicin.

The end of the study is defined as the date of completion of survival follow-up for the last participant, which corresponds to up to 2 years from the date of last participant first dose.

This study will also use a hepatic events adjudication board (HEAB). The HEAB will review safety data, eg, potential cases of VOD.

No formal interim analysis will be conducted for this study.

This study will not use a data monitoring committee (DMC).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint is incidence of CR/CRi from date of the first dose to the end of treatment per investigator's assessment. See Appendix 1 for definition of CR/CRi.

3.2. Secondary Endpoint(s)

3.2.1. Efficacy

PFS will be defined as the time from date of first dose to the date of disease progression (ie, objective progression, relapse from CR/CRi), or death due to any cause, whichever occurs first. Refer to Section 6.2.3 for details on censoring rules.

OS is defined as the time from date of first dose to the date of death due to any cause. Refer to Section 6.2.1 for details on censoring rules.

Duration of CR/CRi (DoR) based on investigator assessment is defined as the time from date of first response in responders (CR/CRi) to the date of disease progression (ie, objective progression, relapse from CR/CRi, death due to any cause, whichever occurs first (including post-study treatment follow-up disease assessments).

Minimal residual disease (MRD) negativity in participants achieving CR/CRi, ie, MRD negativity, is defined malignant B lymphocytes occurring at a frequency of $<10^{-4}$.

The percentage of patients who achieve MRD-negativity between the date of CR/CRi and end of treatment will be analyzed. The number and percentage of patients with MRD negativity in patients achieving CR/CRi will be summarized descriptively with corresponding two-sided 95% CI. This analysis is based on responders in the safety analysis set.

HSCT rate is defined as the percentage of participants who proceed to HSCT among participants who take at least one dose of inotuzumab ozogamicin.

3.2.2. Safety Endpoints

AEs including SAEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

All cases of VOD/SOS irrespective of causality or severity will be reported as SAEs for up to 2 years after the first dose of inotuzumab ozogamicin.

Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v5.0) and timing will be reported.

3.2.3. Pharmacokinetic Endpoints

Pharmacokinetic concentrations: observed maximum serum concentration (C_{max}) after single dose and multiple doses, and observed pre-dose serum concentration (C_{trough}) after multiple doses.

3.2.4. Immunogenicity Endpoints

Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb).

3.3. Exploratory Endpoint(s)

Not applicable.

3.4. Baseline Variables

Start and end dates of study treatment:

The date of first dose (start date) of study treatment is the earliest date of non-zero dosing of the study drug.

The date of last dose of study treatment is the latest date of non-zero dosing of the study drug.

Definition of baseline:

No windowing will be applied when defining baseline.

For efficacy analyses and baseline characteristics associated with tumor assessments, the last assessment prior to the first dose will serve as the baseline assessment.

For safety (including Eastern Cooperative Oncology Group (ECOG) performance status) and immunogenitiicy the last assessment performed on or prior to date of the first dose of study treatment will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing.

Participants who start treatment and discontinue from the treatment on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

Triplicate ECGs are collected; therefore the baseline for each ECG measurement is the average of the pre-dose triplicate measurements reported on during screen period or closest to the start date. Unscheduled assessments will not be included in the calculation of the average. If the last prior to Cycle1/Day 1 ECGs are triplicate ECGs (or only 2), they will be averaged. If the last prior to Cycle1/Day 1 ECG is a single, that will be used as baseline. Baseline heart rate (HR), derived from RR measured in seconds as 60/RR if RR is collected, and QT/QTc interval assessments will be derived from the visit where both HR and QT are not missing. QTcF (Fridericia's correction) and QTcB (Bazett's correction) will be derived based on RR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameters at each timepoint.

3.5. Safety Endpoints

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment is defined as the time from the first dose of study treatment through minimum (9 weeks after the last administration of the investigational product, start day of new anti-cancer therapy – 1 day). The start date of new anti-cancer therapy after the first dose of study treatment is derived as outlined in Section 5.2.5. Adverse events occurring on the same day as the first dose of study treatment will be considered to have occurred during the on-treatment period. All other assessments which occur on the same day as the first dose of study treatment will be considered baseline assessments (see Section 3.4 for the definition of baseline). If the exact time is collected, the last assessment before the time of first dose of study treatment will be considered as baseline assessments.

Safety data collected outside the on-treatment period as described above will be listed but not summarized.

3.5.1. Adverse Events

Adverse events (AEs) will be coded to preferred term (PT) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) and classified by severity using the National Cancer Institutes (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. For other AEs without specific NCI CTCAE v5.0 definitions, results will be identified according to NCI CTCAE v5.0 "other" categories.

An event will be considered treatment related if the investigator considers so.

An adverse event is considered treatment-emergent relative to a given treatment if the event start date is during the on-treatment period (including on the date of first dose). All cases of VOD/SOS irrespective of causality or severity will be reported as SAEs for up to 2 years after the first dose of inotuzumab ozogamicin.

Adverse Events of Special Interest (AESI)

AEs of special interest (AESI) are as follows:

- GRADE ≥3 HEPATOTOXICITY AND/OR SERIOUS HEPATOTOXICITY, INCLUDING VOD/SOS;
- MYELOSUPPRESSION/CYTOPENIA;
- INTERSTITIAL LUNG DISEASE;
- INFLAMMATORY GASTROINTESTINAL EVENT;
- PANCREATITIS;
- SECONDARY PRIMARY MALIGNANCY;

- REPRODUCTIVE AND DEVELOPMENT TOXICITY;
- NEPHROTOXICITY; and
- NEUROTOXICITY.

These events are defined in Appendix 2.

3.5.2. Laboratory Data

Hematology and chemistry result will be programmatically graded according to the NCI CTCAE version 5.0 for relevant parameters. Parameters which cannot be graded will be summarized relative to the normal range (ie, normal range high or normal range low). Additional details are provided in Section 6.6.3.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Only participants who signed informed consent will be included in the analysis sets below.

Population	Description
Safety	All enrolled participants who receive at least 1 dose of study intervention.
PK concentration	Subset of the safety analysis set and will include participants who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for inotuzumab ozogamicin.
Immunogenicity	Subset of the safety analysis set and will include participants who receive at least 1 dose of investigational product (inotuzumab ozogamicin) and have at least one ADA /NAb sample collected for immunogenicity.

Enrolled: “Enrolled” means a participant's, or their legally authorized representative’s, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size

The primary objective of this study is to evalute the treatment effect with inotuzumab ozogamicin, by demonstrating a greater CR/CRi rate than that observed with historical control. The statistical hypotheses for the primary endpoint CR/CRi per investigator's assessment are the same as those used in global pivotal Phase 3 Study B1931022, where based on review of the literature published historical data, the expected CR/CRi rate with historical control in the combined first and second salvage setting was approximately 37%. The observed results in the control arm in Study B1931022 didn't exceed 37% either. The study will test the null hypothesis H_0: CR/CRi rate per investigator's assessment ≤37% vs the alternative hypothesis H_a: CR/CRi rate >37%.

A single-stage design will be used to test the null hypothesis (H0) with 1-sided 0.025 significance level. A sample size of 44 pateints is planned to provide at least 90% power to reject the null hypothesis (H0: CR/CRi rate ≤37%) when the true CR/CRi rate ≥61% under the 1-sided significance level 0.025, based on single binomial proportion test under normal approximation with empirical estimate for variance.

A sufficient number of participants will be screened to ensure 44 participants enrolled and received at least one dose of inotuzumab ozogamicin.

5.1.2. Decision Rules

Assuming exactly 44 participants as planned in Section 5.1.1 are enrolled and take at least one dose of treatment, the null hypothesis will be rejected and it will be concluded that the study has demonstrated that the true CR/CRi rate exceeds 37% if 23 or more responders are observed. However, at the time of the analysis, the testing will depend on the actual number of participants enrolled.

5.2. General Methods

Except the hypothesis testing for CR/CRi, all anlayses will be descriptive.

5.2.1. Data Handling after the Cutoff Date

Data after the cutoff date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of Data Across Centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. A variable for 'center' will not be included in statistical models or for subgroup analyses since it is anticipated that there will be a high number of participating centers with a small number of participants randomized/treated at each center.

5.2.3. Definition of Study Day

The study day for assessments occurring on or after the first dose of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start date of inotuzumab ozogamicin + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event – start date of inotuzumab ozogamicin.

The study day will be displayed in all relevant data listings.

5.2.4. Definition of Cycle and Cycle Day

Cycle start and end dates are derived per participant and not per study treatment.

Study drug inotuzumab ozogamicin is administered once every week for 3 weeks (on Days 1, 8, and 15) for each cycle. Except for Cycle 1 where a 7-day treatment free interval is optional, all other cycles have such an interval following the 3 treatment administrations and hence the nominal cycle length is 21-28 days for cycle 1 and 28 days for other cycles. A participant can only go through 6 cycles at most.

- For Cycle X, the actual cycle start date for each participant is:
  - The earliest start date of dosing in the Cycle X day 1 visit CRF exposure page, if the participant received study treatment on that visit (ie, any study drug with dose>0 at that visit).
  - The first day of assessments in the Cycle X day 1 visit, if the participant did not receive study treatment on that visit (ie, all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.
- For all but the last cycle,
  - Actual cycle stop date is calculated as the start date of the next cycle minus one day.
  - Actual cycle duration is calculated from Day 1 of a cycle to the day prior to Day 1 of the next cycle, as follows:

    Actual Cycle Duration (weeks) = (cycle stop date – cycle start date + 1) / 7.
- For the last cycle, actual cycle duration is the planned cycle duration and actual cycle stop date is calculated as min(actual cycle start date + 28 – 1 day, new anti-cancer therapy date-1, death).

The cycle day will be calculated as:

Cycle day = Date of the assessment/event – cycle start date + 1.

5.2.5. Definition of Start of New Anti-cancer Therapy

Start date of new anti-cancer therapy is used to determine the end of the on-treatment period (see Section 3.5).

The start date of new anti-cancer therapy is the earliest date after first dose of inotuzumab ozogamicin amongst the following:

- Start date recorded in the 'Follow-up Cancer Therapy' eCRF pages.
- Start date of radiation therapy recorded in 'Follow-up Radiation Therapy' eCRF pages.
- Start date of surgery recorded in 'Follow-up cancer surgery' eCRF pages.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied

Start date of new induction therapy is used for censoring in efficacy analyses, and it is defined as

- Start date of "INDUCTION" subcategory recorded in the 'Follow-up Cancer Therapy' eCRF pages.

5.2.6. Date of Last Contact

The date of last contact will be derived for participants not known to have died at the data cutoff date using the latest complete date (ie, imputed dates will not be used in the derivation) among the following:

- All assessment dates (eg, blood draws (laboratory, Pharmacokinetics (PK)), vital signs, physical exam, performance status, ECG, tumor assessments);
- Start and stop dates of concomitant therapies including non-drug treatments or procedures;
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation including systemic therapy, radiation, and surgeries;
- AE start and end dates;

- Last date of contact collected on the 'Survival Follow-up' CRF (do not use date of survival follow-up assessment unless status is 'SUBJECT REMIANS IN FOLLOW-UP);
- Study treatment start and end dates;
- Date of discontinuation on disposition CRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Only dates associated with actual examinations of the participant will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed or dates data were entered into the CRF will not be used. Assessment dates after the data cutoff date will not be applied to derive the last contact date.

5.2.7. ALL Disease Assessment Date

The date of ALL disease assessment at each nominal timepoint as provided by the investigator on the ALL response assement CRF will be utilized for the respective analyses.

5.2.8. Adequate Baseline ALL Disease Assessment

Subject had an adequate baseline tumor assessment if the subject had the following two procedures at screening: bone marrow biopsy or aspirate with blasts ≥5%; hematology test with presence of peripheral blast cells (% or absolute).

5.2.9. Adequate Post-baseline ALL Disease Assessment

An adequate post baseline assessment is defined as an assessment for hematologic disease status and extramedually disease response (if applicable) has been provided by the investigator. Timepoints where the response is indeterminate or no assessment was performed will not be used for determining the censoring date.

5.2.10. Nominal and Unscheduled Visits

For all algorithms and analyses, visit labels as specified on the CRF will be used as the nominal timepoint (ie, assessment will not be slotted).

Unless otherwise specified, unscheduled assessments will not be displayed in summary tables by nominal visit/timepoint. Unscheduled assessments will be used when deriving baseline and worst case on-treatment for safety analyses (except where noted for baseline ECGs). Additionally, unscheduled assessments will be used for efficacy analyses (eg, defining date of progression/censoring, best overall response, date of last contact).

5.2.11. Standard Deviations and Reporting Conventions

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer/first decimal using the common mid-point between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

The following conversion factors will be used to convert days into weeks, months or years:
1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - year of given informed consent - year of birth.
- Body Mass Index (BMI, kg/m^2) = weight (kg) / [height (m)]^2.
- Body Surface Area (BSA, m^2) = $0.007184 \times \text{Weight(kg)}^{0.425} \times \text{Height(cm)}^{0.725}$, (Du Bois Formula).

5.2.12. Analyses for Continuous and Qualitative Variables

Continuous variables will be summarized using descriptive statistics, ie, number of non-missing values, mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of participants still present in the study at that visit, unless otherwise specified.

5.2.13. Analyses for Time-to-Event Endpoints

Kaplan-Meier estimates (product-limit estimates) will be presented for treatment arm together with a summary of associated statistics including the median time with two-sided 95% CIs. Probabilities of an event at particular timepoints will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at particular timepoints will be derived using the log(-log) method.

5.3. Methods to Manage Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Any imputations will occur at the analysis dataset level. Additionally, in all data listings imputed values will be presented and flagged as imputed.

Missing statistics, eg, when they cannot be calculated, should be presented as 'ND' for not done, 'NR' for not reached or 'NA' for not applicable. For example, if N=1, the measure of variability cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1. Missing Pharmacokinetic Data

Concentrations below the limit of quantification

For all calculations, all concentrations assayed as below the limit of quantification (BLQ) will be set to zero. The BLQ values will be excluded from calculations of geometric means and their confidence intervals. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures. In listings BLQ values will be reported as below limit of quantification ("<LLOQ"), where LLOQ will be replaced with the corresponding value from the analytical assay used.

Deviations, Missing Concentrations and Anomalous Values

In summary tables, concentrations will be set to missing if one of the following cases is true:

- A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
- A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular timepoint if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

In summary tables of concentration-time profiles or PK parameters, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are not collected, not calculated, or below LLOQ. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual participant has a known biased estimate of a PK parameter (due for example to a deviation for the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Missing ECG Data

For QTc analyses, no values will be imputed for missing data. If one or two of the triplicate measurements for an ECG parameter are missed, the average of the remaining two measurements or the single measurement can be used in the analyses. If all triplicate measurements are missing at a timepoint for an ECG parameter, no values will be imputed for this timepoint. If the triplicate needs to be repeated because of an artifact, then the repeated triplicate will be reported on an unscheduled CRF page. Based on a review of the

data these unscheduled assessments may be used in place of the assessments at the nominal time. Data review and consultation with the study team is required to flag these cases.

5.3.3. Handling of Incomplete or Missing Dates

5.3.3.1. Adverse Events

AE Onset Date:

The following imputation rules apply if the event is unique for a participant or it is the first of a series of similar events; otherwise, the AE Onset Date will not be imputed:

- If the first active day of study intervention is less than AE stop date, then the onset date will be set to first active day of study intervention;
- Otherwise if the first active day of study intervention is after AE stop date, then set the onset date to the earliest of non-missing AE stop date or informed consent date.

AE Stop Date:

Ongoing events will have the AE Stop Date set to the latest of the subject withdrawal/completion date, death date, last active day of study intervention, or AE Onset date.

Imputation will only occur if event is unique for the participant, or it is the last of a series of similar events; otherwise the Stop Date will not be imputed. Adverse Events are deemed similar if they have the same verbatim term.

Resolved events will have the AE Stop Date set to the AE Onset date.

5.3.3.2. Exposure

No imputation will be done for first dose date. Date of last dose of study treatment, if unknown or partially unknown, will be imputed as follows:

- If the last date of study treatment is completely missing and there is no Disposition page with Phase= “Treatment”and no death date, the participant should be considered to be ongoing and use the data cutoff date for the analysis as the last dosing date; or
- If the last date of study treatment is completely or partially missing and there is EITHER an EOT CRF page OR a death date available (on or prior to the data cutoff date), then impute this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date),

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date), or

= min (EOT date, death date), for all other cases.

5.3.3.3. Date of Death

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact.
- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death;
  - Missing day and month: January 1st of the year of death.

5.3.3.4. Date of Start of New Anti-cancer Therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is:
  - Completely missing then it will be ignored in the imputations below.
  - Partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy.
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy.
- For participants who have not discontinued study treatment at the analysis cutoff date, last dose of study treatment is set to the analysis cutoff date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is derived as follows:
  - <u>Start date of new anti-cancer therapy is completely missing</u>

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - <u>Only year (YYYY) for start of anti-cancer therapy is available</u>

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy];

THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy];

ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy];

THEN imputed start date = 01JANYYYY.

- Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy].

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY.

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy].

THEN

imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy].

THEN

imputed start date = 01 MMM YYYY.

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy].

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY.

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy].

THEN

imputed start date = 01 MMM YYYY.

5.3.3.5. Other Dates

Imputation methods for other partial dates as follows:

- If the day of the month is missing for a start date used in a calculation, the first day of the month will be used to replace the missing date.
- If both the day and month are missing, the first day of the year is used.
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.
- If the date is completely missing, no imputation will be performed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. CR/CRi

6.1.1.1. Main Analysis

The primary endpoint is the incidence of a participant with a best overall response of CR or CRi from date of the first dose to the end of treatment per investigator's assessment according to a modified Cheson Criteria.

Estimand strategy: The analysis applies while on treatment strategy (Section 2.1.1).

Analysis set: Safety analysis set (Section 4).

Intercurrent events and missing data: All data collected after an intercurrent event of subsequent anti-cancer therapy is excluded.

Analysis methodology: Test the null hypothesis H0: CR/CRi rate ≤37% using the observed sample rate, actual sample size based on single binomial proportion test under normal approximation with empirical estimate of variance, ie, Wald test.

Estimate the CR/CRi rate per investigator's assessment and obtain the corresponding two-sided 95% CI using Wald method and Clopper–Pearson method separately for all participants in the safety analysis set from the time of first dose until the end of treatment. In addition, the frequency (number and percentage) of participants with CR, CRi, and CR/CRi will be tabulated.

Participants with death prior to first post-baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will be considered as non-responders. Data collected after the end of treatment will be excluded from the analysis.

6.2. Secondary Endpoint(s)

6.2.1. Overall Survival

Estimand strategy: treatment policy.

Analysis set: Safety analysis set.

Analysis methodology: using Kaplan-Meier method, plot the estimation of the survival function and estimate its associated statistics on OS (including the quartiles of OS with two-sided 95% CI, the OS rates at clinical meaningful timepoints with two-sided 95% CI). The CI for the quartiles will be calculated according to Brookmeyer and Crowley method, and the CIs for the survival probability estimates at the timepoints will be derived using the log(-log) method.

Intercurrent events: the analysis is conduced without regard to discontinuation from treatment or start of new anti-cancer therapy.

Participants without confirmation of death will be censored on date of last contact.

Frequency (number and percentage) of participants with an event (death) and censoring reasons will be presented. Censoring reasons are as follows: alive, withdrawal of consent and lost to follow-up.

6.2.2. Progression-Free Survival

6.2.2.1. Main Analysis

Progression-Free Survival (PFS) is defined as the time from date of first dose to the date of the first documentation of disease progression (ie, objective progression, relapse from CR/CRi) as assessed by the investigator, or death due to any cause, whichever occurs first.

Estimand strategy: Hypothetical strategy. The analysis will consider intercurrent events of start of subsequent new induction therapy and an extended gap in tumor assessment prior to an assessement of disease progression or death.

Analysis set: Safety analysis set.

Intercurrent events and missing data: Partial dates will be imputed as described in Section 5.3. No other imputations for missing data will be performed. PFS data will be censored as follows:

- For participants who start a new induction therapy (as defined in Section 5.2.5) prior to an event, censoring will be at the last adequate tumor assessment prior to the start of new induction therapy. Note: if date of progression occurs on the same date as the start of new induction therapy, the progression will be counted as an event.

- For participants who do not have an adequate baseline tumor assessment or any post-baseline tumor assessments, censoring will occur on the date of first dose unless death occurred on or before 12 weeks after first dose in which case the death will be considered an event.

- For participants having adequate baseline tumor assessment and without defined PFS events, censoring will occur on the date of last valid disease assessment (date of first dose if no post-baseline assessment).

- For participants with defined PFS events occurring after an unacceptable long interval (>28 weeks if there was post-baseline disease assessment, or >12 weeks if there was no post-baseline assessment) since the previous disease assessment, censoring will occur at the date of the previous assessment (or date of first dose if there is no post-baseline assessment).

Analysis methodology: The Kaplan-Meier method will be used to plot the estimated survival function and estimate its associated statistics on PFS (including the median PFS with two-sided 95% CI, the PFS rates at clinical meaningful timepoints with two-sided 95% CI) for safety analysis setwithout regard to discontinuation from treatment.

Frequency (number and percentage) of participants with each event type (disease progression or death) and censoring reasons will be presented along with the overall event and censor rates.

Reasons for censoring should be summarized according to the categories in Table 2. If a participant meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 2. Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment.	No adequate baseline assessment
2	Start of new induction therapy before event.	Start of new induction therapy
3	Event more than 28 weeks if there was post-baseline disease assessment, or more than 12 weeks if there was no post-baseline assessment after previous tumor assessment.	Event after missing assessments[a]
4	No event and [withdrawal of consent date ≥ start date OR End of study (EOS) = WITHDRAWAL BY SUBJECT.	Withdrawal by participant
5	No event and lost to follow-up in any disposition page.	Lost to follow-up
6	No event and EOS present and no adequate post-baseline tumor assessment.	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met.	Ongoing without an event

[a] more than 28 weeks if there was post-baseline disease assessment, or more than 12 weeks if there was no post-baseline assessment after previous tumor assessment.

The PFS time or censoring time and the reasons for censoring will also be presented in a data listing.

6.2.2.2. Sensitivity Analysis

Sensitivity analysis for PFS is conducted in the same fashion as in Section 6.2.2.1 except that the PFS event is now expanding to include treatment discontinuation due to global deterioration of health status and starting new induction therapy/post-therapy HSCT without achieving CR/CRi.

Specifically, PFS in this section is defined as the time from date of first dose to the date of disease progression (ie, objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), death due to any cause, or starting new induction therapy/post-therapy HSCT without achieving CR/CRi, whichever occurs first (including post-study treatment follow-up disease assessments).

As a consequence, for participants who do not achieve CR/CRi, starting of new induction therapy is no longer an intercurrent event for estimand purpose, and the start of new induction therapy in hierarchy #2 of Table 2 should be ignored for censoring reasoning among that group of participants.

All other censoring rules, analysis methodology and summaries (including censoring reason) from Section 6.2.2.1 still apply in this section.

6.2.3. Duration of Remission

Duration of remission (DoR) is defined as the time from date of first response in responders (CR/CRi) to the date of disease progression (ie, objective progression, relapse from CR/CRi), death due to any cause, whichever occurs first (including post-study treatment follow-up.

The censoring rules for DoR are as described for PFS in Section 6.2.2.1, but the censoring occurs on the date of first dose for PFS analysis will occur on the date of first remission of responders for DOR analysis.

The Kaplan-Meier method will be used to plot the estimated survival function and estimate its associated statistics on DoR (including the median DoR with two-sided 95% CI) for responders to investigational product without regard to discontinuation from treatment.

This analysis is based on responders in the safety analysis set.

The CI for the median DoR will be calculated according to Brookmeyer and Crowley method.

Duration of Complete Remission (DoCR) and Duration of Complete Remission with Incomplete Hematologic Response (DoCRi) will also be analyzed separately in the safety analysis setfollowing the same methods described above. DoCR is defined as the time from the date of CR in participants who achieved a CR to the date of disease progression (ie, objective progression, relapse from CR/CRi) as assessed by the investigator, or death due to any cause, whichever occurs first. DoCRi is defined as the time from the date when a CRi is first achieved to the date of disease progression (ie, objective progression, relapse from CR/CRi) as assessed by the investigator, or death due to any cause, whichever occurs first. The censorship of DoCR and DoCRi follows the same as DoR.

Note that DoCRi is the same as DoR for CRi participants.

6.2.4. MRD Negativity

Minimal residual disease (MRD) negativity is defined as in Section 3.2.1. Number and percentage of participants with MRD negativity among participants who achieve CR/CRi will be reported. The count and percentage will be summarized descriptively as well as the corresponding two-sided 95% CI using Clopper-Peasron exact method.

The analysis is based on responders in the safety analysis set.

6.2.5. HSCT

HSCT prior and post inotuzumab ozogamicin will be summarized by descriptive analyses (ie, the count, percent of participants proceeding to HSCT and the associated 2-sided 95% CI using Clopper-Peasron exact method. This analysis is based on safety analysis set.

If there are considerate number of participants who undergo HSCT post Inotuzumab ozogamicin, post transplant mortality, post transplant relpase and non-relpase mortality may be analyzed accordingly.

6.2.6. Pharmacokinetic/Pharmacodynamics

Pharmacokinetic concentrationanalyses will be based on the PK concentration analysis set.

Descriptive summary statistics will be provided for serum concentration at scheduled visits. Serum concentration value below the limit of quantitation will be treated as zero in the descriptive statistics calculation. N, mean, standard deviation, percent coefficient of variation (%CV), median, range, geometric mean and gometric %CV will be presented by cycle, day and nominal time in tabular form.

PK and PD data from this study may be analyzed using compartmental modeling approaches and may also be pooled with data from other studies to investigate any association between inotuzumab ozogamicin exposure and biomarkers or significant safety and/or efficacy endpoints. The results of these modeling analyses, if performed, will be reported separately from the clinical study report.

6.3. Other Endpoint(s)

6.3.1. Incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb)

The percentage of participants with positive ADA and NAb will be summarized using immunogenicity population. The magnitude (titer), time of onset, duration of ADA and NAb will also be described if data permits.

6.4. Subset Analyses

Estimate the CR/CRi rate per investigator's assessment for participants who receive at least one dose of investigational product from the time of first dose until the end of treatment for each of the participants stratum characterized by baseline CD22 ≥90%, 90% >CD22 ≥70% , and CD22 <70%

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Analyses of baseline data will be based on the safety analysis set.

6.5.1.1. Demographic Characteristics

The following demographic and baseline characteristics will be summarized by number and percentage:

- Gender (male, female).
- Age (18-<45; 45- <65; ≥65).
- Eastern Cooperative Oncology Group (ECOG) Performance status.

will be summarized by category (number and percent).

Age (continuous), height (cm), weight (kg), Body Mass Index (BMI) (kg/m^2), Body Surface Area (BSA) (m^2) will be summarized with descriptive statistics (mean, median, standard deviation, Q1, Q3, minimum, and maximum).

6.5.1.2. Medical History

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's System Organ Class (SOC) and PT from the 'Medical History' eCRF page. Each participant will be counted only once within each PT or SOC. Summaries will be ordered by primary SOC and PT in descending order of frequency by the experimental treatment arm. Separate summaries will be provided for past and present conditions.

6.5.1.3. Disease Characteristics

The following baseline disease characteristics will be summarized by number and percentage:

- Primary diagnosis (if all participants have the same diagnosis this may be omitted).
    - Time since initial diagnosis (months), defined as (date of first dose – date of initial diagnosis)/30.4375, will be summarized by descriptive statistics (mean, median, standard deviation, minimum, and maximum).
- Cytogenetics (Abnormal, Normal, Unknown) and cytogenetics abnormality details

6.5.1.4. Prior Anti-cancer Therapy

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one type of prior anti-cancer treatment;
- Participants with at least one prior anti-cancer drug therapy;
- Participants with at least one prior anti-cancer radiotherapy;
- Participants with at least one prior anti-cancer surgery
- Participants with at least one prior HSCT
    - Participants in salvage 1 and 2;Salvage 1: Morphological relapse after initial treatment or resistant disease (no CR/CRi) after initial treatment;

- Salvage 2: Morphological relapse after salvage 1 therapy or resistant disease after salvage 1.

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants:

- Number of prior anti-cancer therapy regimens: missing/1/2/3/≥4;
- Intent of Therapy:induction, consolidation, maintenance, conditioning or intensification.

The prior anti-cancer drugs will be coded in the WHO Drug coding dictionary and will be summarized based on the number and percentage of participants by preferred term. A participant will be counted only once within a given preferred term, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency. In case of equal frequency, alphabetical order will be used.

Specific details on surgeries and radiotherapy will be listed.

6.5.2. Study Conduct and Participant Disposition

6.5.2.1. Disposition

The percentages below will be calculated based on the number of enrolled participants .

- Number of participants who discontinued from the study prior to first dose overall and by the main reason for discontinuation.
- Number and percentage of participants in each of the analysis sets defined in Section 4.
- Number and percentage of participants with study drug ongoing, discontinued or not given.
- Number and percentage of participants who discontinued study drug overall and by the main reason for discontinuation of study drug.
- Number and percentage of participants who entered follow-up.
- Number and percentage of participants who discontinued follow-up overall and by the main reason for discontinuation.

6.5.2.2. Protocol Deviations

Protocol deviations will be compiled prior to database closure and will be summarized by category (n(%)) for the safety analysis set for treatment arm. Categories will be assigned by the study Clinician.

6.5.3. Study Treatment Exposure

Exposure will be summarized for the safety analysis set.

6.5.3.1. Exposure to Inotuzumab Ozogamicin

The summary of treatment exposure for inotuzumab ozogamicin will include the following information (by dose level for safety population):

- Treatment duration (weeks).
- Treatment cycles.
- Cumulative dose (mg/m^2).
- Dose intensity (DI, mg/m^2 /cycle).
- Relative dose intensity (RDI, %).

The duration of inotuzumab ozogamicin (in weeks) is defined as:

Treatment duration (weeks) = (last dose date – first dose date + 1)/7.

The cumulative dose (mg/m^2), the dose intensity (DI) and the relative dose intensity (RDI) of inotuzumab ozogamicin in each cycle and overall will be calculated for each participant.

The cumulative dose (mg/m^2) of inotuzumab ozogamicin in a cycle or overall will be the sum of the actual dose levels that the participant received (ie, total dose administered [mg/m^2]).

The dose intensity (DI, mg/m^2/cycle) of inotuzumab ozogamicin during the study will be defined as follows:

- Overall DI (mg/m^2/cycle) = [overall cumulative dose (mg/m^2)]/[number of cycles].

The RDI of inotuzumab ozogamicin will be defined as the ratio of the DI and planned dose intensity and expressed in percentage as follows:

- By cycle RDI (%) = 100× [cumulative dose in the cycle]/[planned cumulative dose per cycle];
- Overall RDI (%) = 100 × [overall cumulative dose]/[overall planned cumulative dose].
- Overall planned cumulative dose is the sum of planned doses across all cycles that the participant planned before reveiving the actual doses.

6.5.3.2. Dose Reductions and Delays

A dose reduction is defined as a non-zero dose that is less than the planned dose.

The number and percentage of participants with at least one dose reduction as well as a breakdown of dose reductions (1/2/3/≥4) will be summarized for safety population.

A dose delay is defined for non-continual dosing regimens, in this case inotuzumab ozogamicin, and will be derived based on study drug administration date and will be grouped into the following categories based on the deviation of the actual to the planned treatment administration day (relative to the previous treatment administration date):

- No delay (including 1-2 day delays).
- 3-6 days delay.
- 7 or more days delay.

For example, for inotuzumab ozogamicin, administered on a 1-week schedule, if one participant receives inotuzumab ozogamicin on Day 1, then the next inotuzumab ozogamicin administration date will be on Day 8; however, if the participant receives inotuzumab ozogamicin at Day 9 or 10, this is not considered as a delay.

The number and percentage of participants with delayed study drug administration and maximum length of delay, ie, the worst case of delay if participants have multiple dose delays will be summarized, as applicable.

Reasons for delays will be summarized. Participants can contribute to more than one reason if multiple dose delays occurred for different reasons, but will only be counted once per reason. Percentages will be calculated based on the total number of participants in safety analysis set.

6.5.4. Concomitant Medications and Nondrug Treatments

The following analyses will be based on the safety analysis set for treatment arm.

Concomitant medications are medications, other than study medications, which started prior to first dose date of study treatment and continued on on-treatment period as well as those started during the on-treatment period. **Prior medications** are medications, other than study medications and pre-medications for study drug, which are started before the first dose of study treatment.

Summary of prior medications, summary of concomitant medications and summary of pre-medications will include the number and percentage of participants by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under

each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

A listing of prior medications and a listing of concomitant medications will be created with the relevant information collected on the 'General Concomitant Medications' eCRF page. A listing of pre-medications will be created with the relevant information collected on the 'Pre-Medication Treatment' eCRF page.

All concurrent procedures, which were undertaken any time during the on-treatment period, will be listed according to the eCRF page 'General Non-drug Treatments'.

A listing of concurrent procedures will be created with the relevant information collected on the 'General Non-drug Treatments' eCRF page.

6.5.5. Subsequent Anti-cancer Therapies

The following analyses will be based on the safety analysis set.

Anti-cancer treatment will be provided in a data listing with data retrieved from related eCRF pages.

Number and percentage of participants with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy' and 'Follow-up Surgery' eCRF pages.

6.6. Safety Summaries and Analyses

Summaries of AEs and other safety parameters will be based on the safety analysis set.

6.6.1. Adverse Events

All analyses will be based on treatment emergent events unless otherwise specified. Treatment emergent is defined in Section 3.5.1. AEs not considered treatment emergent will be flagged in data listings.

A high level summary of TEAEs (all causality), TEAEs (treatment related) and Cycle 1 TEAEs (treatment related) will include the number and percentage of participants with:

- Any TEAE;
- Serious TEAE;
- TEAEwith CTCAE Grade 3-4;
- Grade 5 TEAE;

- TEAEs leading to dose reductions of inotuzumab ozogamicin;
- TEAEs leading to dose delay of inotuzumab ozogamicin;
- TEAEs leading to permanent discontinuationof inotuzumab ozogamicin.

Additionally, the number of events reported for each of the categories above will be provided. Each unique adverse event at the PT level for a participant is included in the count.

Seriousness, toxicity grade, action taken (interruption, reduction, and withdraw) are as reported by the investigator on the adverse event CRF.

Summaries of TEAE by SOC and PT in decreasing frequency will be provided for:

- TEAEs (All Causality);
- TEAEs by Maximum Toxicity Grade (All Causality);
- TEAEs (Treatment related);
- TEAEs by maximum toxicity grade (Treatment related);
- Serious TEAEs (All causality);
- Post-HSCT SAE (All causality);
- Serious TEAEs (Treatment related); and
- Post-HSCT SAE (Treatment related).

An event will be considered treatment related if the investigator considers so.

The following summaries will be provided by PT only (ie, summaries will not include SOC) in decreasing frequency:

- TEAEs (All causality);
- TEAEs (All causality) experienced by ≥10% of participants;
- TEAEs (All causality) by maximum toxicity grade;
- Grade 3-5 TEAEs (All causality and Treatment related);
- TEAEs leading to dose delays of inotuzumab ozogamicin (all causality);
- TEAEs leading to dose reductions of inotuzumab ozogamicin (all causality);

- TEAEs leading to permanent discontinuation of inotuzumab ozogamicin (all causality);
- Serious TEAEs (all causality); and
- Post-HSCT SAEs (all causality).

Each participant will be counted only once within each SOC and PT.

As described in Section 5.3, in case a participant has events with missing and/or non missing toxicity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed in the event that only one event has been reported for a participant and the grade is missing.

6.6.1.1. Adverse Events of Special Interest

All cases of VOD/SOS irrespective of causality or severity will be reported as SAEs for up to 2 years after the first dose of inotuzumab ozogamicin.

If data permits, number and percentage in patients with VOD/SOS and in patients with VOD/SOS following post-study HSCT will be summarized. The VOD/SOS patients above are also summaried considering different risk factors, including prior study HSCT (yes/no), prior history of hepatic disease (yes/no), baseline ALT/AST/Total serum bilirubin abnormal by CTCAE (Grade 0,1).

Summary of AESI by PT will also be provided.

6.6.2. Deaths

The frequency (number and percentage) of participants in the safety analysis set who died ,who died within 28 days after last dose of study treatment, who died after 28 days after last dose of study treatment as well as the primary reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' CRFs.

The frequency (number and percentage) of participants in the safety analysis set who died within 30 days of first dose of study treatment will also be provided.

Date and cause of death will be provided in individual participant data listing together with selected dosing information (study treatment received, date of first/last administration).

6.6.3. Laboratory Data

Laboratory results will be converted to International System of Units (Système International d'unités, SI) units which will be used for applying toxicity grades and for all summaries. The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade (CTCAE version 5.0) observed for each

laboratory assay. A shift summary of baseline grade by maximum postbaseline grade will be presented.

As described in Section 3.4, baseline will defined as the last assessment performed on or prior to date of the first dose of study treatment. If there are multiple assessments that meet the baseline definition on the same day without the ability to determine which was truly last, then the worst grade will be assigned as the baseline grade. Several of the CTCAE terms (including Hypo/Hypercalcemia, Chronic Kidney Disease, and Activated Partial Thromboplastin) can be derived using several laboratory tests (analytes).

Results collected as strict inequalities (eg, >10, <10) will be converted to numeric values subtracting a factor of <0.001>. Expressions of the form" ≥" or "≤" will be converted to the end point. These numeric values will be evaluated for clinically significant abnormalities, but will not be included in calculations of summary statistics.

Additionally, laboratory results will be programmatically classified according to NCI-CTCAE version 5.0 grade. Non-numerical qualifiers will not be taken into consideration in the derivation of grade (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). In summary statistics the number and percentage of participants corresponding to grades that only include non-quantitative criteria will be displayed as a blank or NA (not assessed) rather than 0. If there is any overlap between grade criteria (eg, CTCAE grading criteria for Creatinine Increased – a value can fall into one range based on comparison to ULN and another range based on comparison to baseline), the highest (worst) grade would be assigned to that record. Grade 5 is defined in the CTCAE criteria guidance as an event with an outcome of death. Since laboratory data does not collect an outcome, Grade 5 is not used when programmatically grading laboratory data.

Grade 0 or Outside Toxicity Reference (OTR) is not defined specifically by in the CTCAE guidance. However, programmatically this is used as a category to represent those participants who did not meet any of the Grades 1 to 4 criteria. If the laboratory value is evaluable for CTCAE criteria grading (numeric value is present, valid units and ranges are present as required to allow conversion to standard units and grading), and does not qualify for any of the Grade 1-4 criteria for a given lab test, then the value is assigned as Grade 0 or OTR.

Several of the CTCAE terms (including Hypo/Hypercalcemia, Chronic Kidney Disease, and Activated Partial Thromboplastin) can be derived using several laboratory tests (analytes).

Abnormalities will be described using the worst grade by scheduled timepoint and overall. Worst grade by scheduled timepoint will be determined using local laboratory results. Worst case overall will be determined using local laboratory results from scheduled and unscheduled visits. Several laboratory tests have bi-directional grading criteria defined so that both low (hypo) and high (hyper) values can be graded separately. Each criterion will be summarized separately. In the cases where a value is graded as a Grade 1, 2, 3, or 4 for one

of the directions, that value will also be assigned as a Grade 0 for the opposite direction for that test. For example, a value meeting the criteria for Grade 3 Hypercalcemia will be classified as a Grade 0 Hypocalcemia. For CTCAE terms that can be derived using one of several laboratory tests, the maximum post-baseline grade for a given participant and CTCAE term will be the maximum across all possible laboratory tests.

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the following categories by scheduled timepoint as well as overall: below normal limit, within normal limits, and above normal limits. In the unlikely event that for a given participant, clinically significant abnormalities are noted in both directions (eg, > Upper Limit of Normal (ULN) and < Lower Limit of Normal (LLN)), then both abnormalities are counted.

The following summary tables will be created:

- Shift summary of laboratory parameters during the on-treatment period by maximum CTCAE grade;
- Shift summary of laboratory parameters from ⩽ Grade 2 at baseline to ⩾ Grade 3 postbaseline;
- Shift summary of laboratory test results with no CTCAE criteria by worst on treatment assessment.

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over the ULN will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized by treatment arm:

- ALT ≥3×ULN, ALT ≥5xULN, ALT ≥10×ULN, ALT ≥20×ULN.
- AST ≥3×ULN, AST ≥5xULN, AST ≥10×ULN, AST ≥20×ULN.
- (ALT or AST) ≥3×ULN, (ALT or AST) ≥5×ULN, (ALT or AST) ≥10×ULN, (ALT or AST) ≥20×ULN.
- TBILI ≥2×ULN.
- Concurrent ALT ≥3×ULN and TBILI ≥2×ULN.
- Concurrent AST ≥3×ULN and TBILI ≥2×ULN.
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN.

- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and ALP >2×ULN.
- Concurrent (ALT or AST) ≥3×ULN and TBILI ≥2×ULN and ALP ≤2×ULN or missing.

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment arms, by graphically displaying the following:

- Peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin=2×ULN.
- Peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin=2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with a post-baseline TBILI ≥2×ULN, ALT ≥3×ULN or AST ≥3×ULN will be provided.

6.6.4. Vital Signs

Vital sign parameters will be listed. All other vital signs collected during the course of the study will be considered source data only and will not be required to be reported on the CRF. Vital signs associated with AEs may be collected in the CRF.

6.6.5. Electrocardiograms

Triplicate ECGs were required at each assessment. A mean score is calculated for any replicate measurements having the same nominal visit. The mean measurement is reported.

ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate.

Fridericia's correction (QTcF) will be programmatically derived using the following formula:

$$QTcF(msec) = QT(msec) / \sqrt[3]{RR(sec)}$$

and Bazett's correction (QTcB) will be programmatically derived using the following formula:

$$QTcB(msec) = \frac{QT(msec)}{\sqrt{RR}(sec)},$$

where RR represents the RR interval of the ECG, in seconds.

The correlation between RR and QTcF will be explored graphically. If these are correlated and there are a sufficient number of participants (eg, >30) with baseline ECGs, a study specific correction (QTcS) will be performed as follows:

- b will be estimated from ln(QT)=a+b*ln(RR);
- and QTcS will be derived as QTcS=QT(msec)/(RR(sec))^1/b.

Data will be summarized using QTcB and QTcF. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcS.

QT, heart rate, QTcB and QTcF will be summarized using simple descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (ie, unscheduled assessments will be excluded). The total number of participants for change from baseline will include all participants in the treatment arm who have both a baseline and a value at the nominal visit. Baseline will be selected as defined in Section 3.4.

The mean absolute QTc, QTcB, QTcF, RR, PR, and QRS will be presented with two-sided 95% confidence intervals and the baseline adjusted mean QTc, QTcB, QTcF, RR, PR, and QRS will be presented with two-sided 90% confidence intervals.

Additionally QTcB and QTcF (and QTcS if applicable) will be summarized by maximum on-treatment values using the following categories:

- ≤450 msec;
- >450 msec but ≤480 msec;
- >480 msec but ≤500 msec; and
- >500 msec.

Unscheduled assessments will be utilized in addition to planned assessments.

Shift tables will be provided for baseline value versus worst on-treatment value.

Additionally maximum increases from baseline (including scheduled and unscheduled assessments) will be summarized based on the following categories:

- Change >60 msec;
- Change >30 msec but ≤60 msec; and
- Change ≤30 msec.

If more than one ECG is measured at a nominal time post-dose (eg, triplicate ECGs within 2-4 minutes), the mean will be used to represent a single observation per participant and time post-dose. If any of the three individual ECGs results in a QTc ≥500 msec and the mean is not ≥500 msec, then that participant's data will be described in the safety section in the study report in order to place the ≥500 msec value in appropriate clinical context. On the other hand, such individual ≥500 msec value within a triplicate will not be included in the categorical analysis unless the average from that triplicate is also ≥500 msec. Data listings will contain the means from a triplicate as well as the parameters from each of the three ECGs. Note that using the mean value may result in a participant having a measurement that is not represented by an actual ECG.

6.6.6. Physical Examination

Physical examination, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE.

7. INTERIM ANALYSES

Not applicable.

8. APPENDCES

8.1. Appendix 1. Outcome Definitions

The below outcome definitions will be used for reporting of disease assessments:

- Complete response (CR) is defined as a disappearance of leukemia as indicated by <5% marrow blasts and the absence of peripheral blood leukemic blasts, with recovery of hematopoiesis defined by absolute neutrophil count (ANC) ≥1000/µl and platelets ≥100,000/µl. C1 extramedullary disease status is required.

  Extramedullary disease status:

  - C1: Complete disappearance of all measurable and non-measurable extramedullary disease with the exception of lesions for which the following must be true: For participants with at least one measurable lesion, all nodal masses >1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤1.5 cm in GTD and all nodal masses ≥1 cm and ≤1.5 cm in GTD at baseline must have regressed to <1 cm GTD or they must have reduced by 75% in sum of products of greatest diameters (SPD). No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable. All disease must be assessed using the same technique as at baseline.

  - C2: Participant does not qualify for C1 status.

- Complete response with incomplete count recovery (CRi) is defined as CR except with absolute neutrophil count (ANC) <1000/µl and/or platelets <100,000/µl.

- Partial response (PR) is defined as an improved or no worsening of ALL as indicated by no peripheral blood blasts, neutrophils ≥1000/µl, platelets ≥100,000/µl, and either or both of the following:

  - At least a 50% decrease in the marrow blast percentage, compared to the pretreatment value, and marrow blast percentage ≥5% and ≤25%.

  - C2 extramedullary disease status.

- Treatment failures are defined as participants who fail to achieve CR, CRi or PR will be classified according to the type of failure:

  - Resistant disease: Participant survives ≥7 days following completion of initial treatment course and has persistent leukemia in the most recent peripheral blood smear or bone marrow and/or persistent disease involvement at any extramedullary site after completion of therapy.

  - Death during aplasia: Participant survives ≥7 days following completion of initial treatment course then dies while cytopenic, with the last post-induction bone marrow without leukemic blasts.

- Indeterminate:
  - Participant survives <7 days after completion of initial treatment course.
  - Participant survives ≥7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post-induction bone marrow examination or extramedullary disease examination.
- Relapse from CR or CRi:
  - Appearance of leukemic blasts in the peripheral blood.
  - Appearance of extramedullary disease.
  - ≥5% blasts in the bone marrow not attributable to another cause (eg, recovery of normal cells following chemotherapy-induced aplasia). If there are no circulating blasts and no extramedullary disease and the bone marrow blast percentage is ≥5% but <20%, then a repeat bone marrow performed at least 7 days after the first marrow examination and documenting bone marrow blast percentage is 5% is necessary to establish relapse.
- Progressive disease (PD) is defined as a doubling of peripheral blasts with an absolute increase of >5 x 10^9/L and/or appearance of or progression of extramedullary disease.

The following criteria will be used for evaluation of extramedullary disease:

- Measurable extramedullary disease: Lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), or other conventional technique and a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters ≥2 cm. Note: although CT scans remain the standard for evaluation of nodal disease, radiographic scans are not required for participants with easily palpable/superficial nodes.
- Non-measurable extramedullary disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques or disease documented by indirect evidence only (eg, lab values).

Modified from: Cheson et. al., Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003 Dec 15;21(24):4642-9.

8.2. Appendix 2. Definitions of Adverse Events of Special Interest

IMPORTANT IDENTIFIED RISKS

- Grade ≥3 hepatotoxicity and/or serious hepatotoxicity, including VOD/SOS.

  GRADE ≥3 HEPATOTOXICITY AND/OR SERIOUS HEPATOTOXICITY, INCLUDING VOD/SOS AEs will be defined as:

  - Grade ≥3 AEs and/or SAEs retrieved by applying the following MedDRA SMQs: Cholestasis and jaundice of hepatic origin (SMQs narrow); Hepatic failure, fibrosis, cirrhosis, and other liver damage related conditions (SMQs narrow); Hepatitis, noninfections (SMQs narrow); Liver related investigations signs and symptoms (SMQs narrow and broad);

  - Grade ≥3 AEs and/or SAEs encoded to the following MedDRA PTs: Hepatic vein occlusion, Hepatic vein thrombosis, Portal vein thrombosis, Budd-Chiari Syndrome, Chronic graft-versus-host disease in liver, and Acute graft-versus-host disease in liver;

  - All AEs encoded to the following MedDRA PTs: Venoocclusive liver disease and Venoocclusive disease.

- Myelosuppression/cytopenia.

  MYELOSUPPRESSION/CYTOPENIA AEs will be defined as:

  - Any reported PTs retrieved by applying the following MedDRA SMQs: Haematopoietic thrombocytopenia (SMQ narrow and broad), Haematopoietic leukopenia (SMQ narrow), Haematopoietic erythropenia (SMQ narrow and broad), and Haematopoietic cytopenias affecting more than one type of blood cell (SMQ narrow).

  INFECTION AEs (not considered a separate risk, but considered to be complications of myelosuppression/cytopenia) will be defined as:

  - Any reported PTs retrieved by applying the MedDRA SOC: Infections and Infestations.

  HAEMORRHAGE AEs (not considered a separate risk, but considered to be complications of myelosuppression/cytopenia) will be defined as:

  - Any reported PTs retrieved by applying the MedDRA SMQ: Haemorrhage terms (excluding laboratory terms) (SMQ narrow).

IMPORTANT POTENTIAL RISKS

- Interstitial lung disease (ILD).

  INTERSTITIAL LUNG DISEASE AEs will be defined as:

  - Any reported PTs retrieved by applying the MedDRA SMQ: Interstitial lung disease (SMQ narrow);
  - All AEs encoded to the following MedDRA PT: Graft versus host disease in lung.

- Inflammatory gastrointestinal events.

  INFLAMMATORY GASTROINTESTINAL EVENT AEs will be defined as:

  - Any reported PTs retrieved by applying the MedDRA Version SMQ Gastrointestinal nonspecific inflammation (SMQ narrow);
  - All AEs retrieved by applying the MedDRA higher level term (HLT) Colitis (excluding infective) (all paths) and Stomatitis and ulceration (all paths);
  - All AEs encoded to the following MedDRA PTs: Oral pain, Oropharyngeal pain, and Mucosal inflammation.

- Pancreatitis

  PANCREATITIS AEs will be defined as:

  - Any reported PTs retrieved by applying the MedDRA Version SMQ: Acute pancreatitis (SMQ narrow);
  - All AEs encoded to the following MedDRA PTs: Amylase abnormal, Amylase creatinine clearance ratio abnormal, Amylase increased, Lipase abnormal, Lipase increased, Lipase urine increased, Pancreatic enzyme abnormality, Pancreatic enzymes abnormal, and Pancreatic enzymes increased.

- Second primary malignancy.

  SECONDARY PRIMARY MALIGNANCY AEs will be defined as:

  - Any reported PTs retrieved by applying the MedDRA SOC: Neoplasms benign, malignant and unspecified (including cysts and polyps).

- Reproductive and developmental toxicity (post exposure during pregnancy and while breast feeding).

  REPRODUCTIVE AND DEVELOPMENT TOXICITY AEs will be defined as:

  - Any reported PTs retrieved by applying the following MedDRA SMQs: Termination of pregnancy and risk of abortion (SMQ narrow), Fertility disorders (SMQ narrow and broad), Foetal disorders (SMQ narrow and broad), Neonatal disorders (SMQ narrow and broad), Congenital, familial, and genetic disorders (SMQ narrow);

  - All AEs encoded to the following MedDRA PTs: Pregnancy of partner, Exposure via father, Foetal exposure during pregnancy, and Maternal exposure during pregnancy.

- Nephrotoxicity.

  NEPHROTOXICITY AEs will be defined as:

  - Any reported PTs retrieved by applying the following MedDRA SMQ: Acute renal failure (SMQ narrow and broad).

- Neurotoxicity.

  NEUROTOXICITY AEs will be defined as:

  - Any reported PTs retrieved by applying the following MedDRA SMQs: Demyelination (SMQ narrow and broad) and Peripheral neuropathy (SMQ narrow and broad) and by searching for the following specific PTs under the higher level term: Cranial nerve disorders NEC (all paths).