Protocol Number: ADCT-402-201

Official Title: Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

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Statistical Analysis Plan

A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

PROTOCOL NO.: ADCT-402-201

SAP Version No./ Date: 1.0/ July 10, 2019

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Confidentiality Statement

SAP Approval – Sponsor Signatory

Study Title	A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)
Protocol Number	ADCT-402-201
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SAP accepted and approved by:

[redacted]

Signature

4 March 2020

Date

[redacted]

Signature

3/3/2020

Date

Table of Contents

1 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under ADC Therapeutics Protocol ADCT-402-201.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol Amendment 4 dated 09 Jul 2019 and CRF version 4.0 dated 08 Aug 2019.

2 Study Objectives

2.1 Primary Objectives

Evaluate the efficacy of single agent loncastuximab tesirine in patients with relapsed or refractory DLBCL.

2.2 Secondary Objectives

- Further evaluate the efficacy of loncastuximab tesirine
- Characterize the safety profile of loncastuximab tesirine
- Characterize the pharmacokinetic (PK) profile of loncastuximab tesirine
- Evaluate the immunogenicity of loncastuximab tesirine
- Evaluate the impact of loncastuximab tesirine treatment on health-related quality of life (HRQoL)

3 Study Design

This is a Phase 2, multi-center, open-label, single-arm study. The study will enroll approximately 140 patients.

A 2-stage design will be used, with an interim analysis for futility on the first 52 patients. If ≥10 patients respond (complete response [CR]+partial response [PR]), the study will proceed to complete full enrollment. Enrollment will continue during the interim analysis; however, further enrollment will be halted if futility is confirmed.

3.1 Sample Size Consideration

The primary hypothesis is that the overall response rate (ORR) based on central review for patients treated with loncastuximab tesirine is significantly greater than 20% (i.e., H_0: $p \leq 0.2$ vs. H_a: $p > 0.2$). This hypothesis will be tested at type I error of 0.05 (2-sided).

Using nQuery exact test for single proportion, a sample size of 140 patients has >99% power to achieve a 1-sided significance level of 0.025 (2-sided significance level of 0.05). This sample size will provide adequate precision for observed ORR in the expected range and a robust population for safety evaluation.

3.2 Randomization

This study is not randomized.

3.3 Modifications to the statistical section of the protocol

NA.

4 Statistical methods

All analyses use SAS® version 9.4 or higher. All available data will be used in the analyses, and important data will be included in data listings, sorted by patient, and by visit within patient. Missing data will not be imputed, except via censoring in survival analyses and as otherwise specified.

Unless otherwise noted, categorical data will be presented using counts and percentages, with the number of patients in the analysis population as the denominator for percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. Continuous data, unless otherwise noted, will be summarized using the number of observations (n), mean, standard deviation (std), median, minimum, and maximum. Minima and maxima will be rounded to the precision of the original value, and means, medians, and 95% confidence intervals (CIs) if presented will be rounded to 1 decimal place greater than the precision of the original value. The std will be rounded to 2 decimal places greater than the precision of the original value, up to a maximum of 3 decimal places.

4.1 Analysis Populations

4.1.1 All-Treated Population

All patients who receive at least 1 dose of loncastuximab tesirine. This population will be used in the primary analyses of efficacy and safety.

4.1.2 Per-Protocol Population

All patients in the all-treated population who met the inclusion/exclusion criteria, did not take a prohibited concomitant treatment, nor had other protocol deviation which have major impact on efficacy results.

4.1.3 Stem Cell Transplant (SCT) Population

All patients who have responded to loncastuximab tesirine and undergo stem cell transplant (either autologous or allogeneic) after permanent discontinuation of loncastuximab tesirine treatment without any intervening anticancer therapy.

4.1.4 Patient Reported Outcome (PRO) Population

All patients in the all-treated patients with baseline score (at least one instrument) and at least 1 postbaseline score (in at least one instrument).

4.2 Patient Disposition

The number and percentage of patients enrolled and treated in the study will be presented along with the number and percentage of patients in each analysis population. In addition, the number and percentage of patients who withdrew from study treatment and who discontinued the study for each reason will be tabulated.

Patient disposition data will be listed.

4.3 Protocol Deviations

The number and percentage of patients with any important clinical study report (CSR) reportable protocol deviation will be summarized overall and by type of deviation. The pre-defined important CSR reportable protocol deviations are listed below; in addition, any other protocol deviations deemed by ADCT medical to be important CSR reportable deviations will be included in the summary.

1. Patient entered the study even though they did not satisfy the entry criteria
2. Patient received a prohibited concomitant treatment during the study
3. Patient who met criteria for mandatory withdrawal of study drug during the study but did not have study drug withdrawn
4. Patient who received the wrong treatment or incorrect dose, specifically:
   - Actual dose of study drug was greater than 15% more or less than protocol defined planned dose level.
   - Patient started next cycle less than 18 days after Day 1 of the most recent treatment cycle.

Important protocol deviations will be listed.

4.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be tabulated for the all-treated population. Variables include the following:

- Sex (female, male)
- Race (white, black or African American, Asian, American Indian or Alaska native, native Hawaiian or other Pacific Islander, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Age (years)
- Age group (< 65, ≥ 65 - < 75, ≥ 75 years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Eastern Cooperative Oncology Group (ECOG) performance status

Demographic and baseline characteristics data will be listed.

4.5 Cancer History and Medications History

Cancer history will be presented for the all-treated population. Cancer history will include the following variables:

- Duration since diagnosis

- Diffuse large B-cell lymphoma subtype (NOS, Primary Mediastinal, and High-grade B-cell Lymphoma, with MYC and BCL2 and/or BCL6 rearrangements)
- DLBCL additional subtype (germinal center B-cell [GCB]/activated B-cell [ABC], double/triple hit, transformed, and other additional information)Stage of disease (Stage I, II, III, IV; constitutional symptoms A, B; Subtype E, X, S)
- Cytogenetic analysis (results available yes, t(11;14), t(11q), +12, del(11q), del(13q), del(17p), t(14;18), t(8;14), t(8;22), other)
- Immunophenotypic analysis (results available yes; IgVH status mutated, unmutated, not applicable; CD5, CD10, CD19, CD20, CD21, CD23, CD43, CD79b, BCL1, BCL2, BCL6, CYCLIN D1, ZAP70 negative, positive, not done)

Prior anticancer procedure or therapy will include the following variables:

- Number of lines of therapy/regimens per patient
- Response to the first line and/or most recent line of prior systematic therapy
- Any prior radiotherapy for the current malignancy (yes, no)
- Any prior surgery for the current malignancy (yes, no)
- Reason for stopping therapy (progression, toxicity, other)
- Best response (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], not evaluable [NE])
- Any prior stem cell transplant (yes, no)
- Type of transplant (allogenic, autologous, both, other)
- Conditioning therapy (yes, no)

Medical and cancer history data will be listed. Results of cytogenetic analysis and immunophenotypic analysis will be listed. Tumor tissue biopsy collection will not be listed, but will be contained in datasets.

Prior anticancer surgery, radiotherapy, systemic therapy, and stem cell transplant data will be listed.

4.6 Prior or Concomitant Medications (other than anticancer therapies)

All medications taken from the ICF signature date or within 14 days prior to Cycle 1 Day 1 (C1D1), whichever is earlier, and until at least 30 days after last dose of study drug are to be reported in the CRF pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

- Prior medications are those the patient used prior to the first dose. Prior medications can be discontinued before the first dose or can be ongoing during the treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to any loncastuximab tesirine from the first dose to the last dose + 30 days. A given medication can be classified both as a prior medication and as a concomitant

medication. Concomitant medications do not include medications started 30 days after the last dose.

Any technical details related to computation, dates, and imputation for missing dates are described in Section 7.

Prior medications will be listed together with concomitant medications.

4.7 Exposure to Treatment

4.7.1 Extent of Loncastuximab Tesirine Exposure

Loncastuximab tesirine exposure will be summarized for the all-treated population. Duration of treatment, total number of cycles dosed, total dose received (in µg and µg/kg), average dose per cycle (in µg and µg/kg), and relative dose intensity (actual dose taken / planned dose) will be tabulated. Patients will receive150 µg/kg every 3 weeks (Q3W) for 2 cycles, then 75 µg/kg Q3W for subsequent cycles as planned. When actual weight adjusted dose is needed, the last available weight before each infusion will be used. Patients with a BMI ≥35 kg/m^2 will have their dose calculated based on an adjusted body weight as follows:

Adjusted body weight in kg = 35 kg/m^2 * (height in meters)^2

Dose administered at each infusion (µg) is calculated by concentrated investigational product (IP) volume (in mL)* 5 mg/mL *1000. For incomplete infusion, adjust the calculated prepared dose by multiplying a factor of (1- volume of dosing solution not administered [in mL]/ 50 mL) for concentrated solution formulation, or (1- volume of dosing solution not administered [in mL]/ [50 + total volume of reconstituted solution] mL) for lyophilized formulation. The number of patients who received loncastuximab tesirine at each cycle will also be tabulated using frequency counts and percentages.

Dose delays and dose reductions may also be analyzed if relevant. A cycle is delayed if it starts more than 2 days post- scheduled date.

Relative dose intensity will be additionally presented categorized (<60%, >=60 - <80%, >=80 - <90%, >=90 - <110%, >=110%).

Exposure data and infusion details will be listed together.

4.7.2 Prophylactic Medications for Hypersensitivity

Prophylactic medications for hypersensitivity will be listed only.

4.7.3 Subsequent Anticancer Therapy or Procedure

Patients' subsequent anticancer therapies or procedures including systemic therapy, radiation, transplant, or other, along with the start date of new anticancer therapy or procedure will be collected and listed only.

4.8 Safety Analyses

The summary of safety results will be presented.

General common rules

All safety analyses will be performed on the all-treated population, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last non-missing value or measurement taken up to the first dose in the study.
- The analyses of the safety variables will be essentially descriptive and no systematic testing is planned.
- If relevant, selected safety analyses will be summarized by age, sex, racial subgroups, and any pertinent subgroups.
- The toxicity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be taken into account in the summary. For patients with multiple occurrences of the same event, the maximum grade is used. If a patient has both missing and non-missing severity grades for treatment-emergent adverse events (TEAEs) within the same preferred term (PT), the patient will be counted under the non-missing severity grade.

4.8.1 Adverse Events, Serious Adverse Events, and Deaths

4.8.1.1 Analyses of adverse events

The primary focus of adverse event reporting will be on TEAEs. An adverse event (AE) will be considered to be a TEAE if it begins or worsens on or after the first dose date and until 30 days after the last dose date, or start of a new anticancer therapy/procedure, whichever comes earlier.

An AE occurring before the first dose or more than 30 days after the last dose date or after the start of a new anticancer therapy/procedure will not be included in TEAE displays, but will be listed as non-TEAEs.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, TEAE, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is a non-TEAE (pre- or post-treatment). Some details on classification of AEs with missing or partial onset dates are provided in Section 7.

Analysis of all TEAE(s):

The following TEAE summaries will be generated for the all-treatment population.

- Overview of TEAEs, summarizing number of TEAE and number (%) of patients with any
  - TEAE
  - Related TEAE (including possibly related, probably related, or related)

  - Any TEAE ≥Grade 3
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment withdrawal
  - TEAE leading to loncastuximab tesirine delay or reduction or interruption (if applicable)
  - TEAE with at least one infusion related reaction
- All TEAEs ≥Grade 3 by PT, showing number (%) of patients with at least one TEAE, sorted by decreasing incidence of PTs
- All TEAEs by primary System Organ Class (SOC) and PT, showing number (%) of patients with at least one TEAE, sorted by SOC in alphabetic agreed order and decreasing incidence of PTs within SOC. This sorting order will be applied to all other tables, unless otherwise specified.
- All TEAEs by primary SOC, PT and Maximal CTCAE grade, showing number (%) of patients with at least one TEAE, sorted by SOC and PT in alphabetic order. This sorting order will be applied to all other tables, unless otherwise specified.
- All TEAEs ≥Grade 3 by primary SOC, PT and Maximal CTCAE grade
- All related TEAEs by primary SOC, PT and Maximal CTCAE grade (including possibly related, probably related, or related)
- All TEAEs leading to treatment withdrawal by primary SOC, PT and Maximal CTCAE grade
- All TEAEs leading to dose delay by primary SOC, PT and Maximal CTCAE grade
- All TEAEs leading to dose reduction by primary SOC, PT and Maximal CTCAE grade
- All TEAEs leading to infusion interruption by primary SOC, PT and Maximal CTCAE grade
- All TEAEs with fatal outcome by primary SOC, PT and Maximal CTCAE grade
- All Serious TEAEs by primary SOC, PT and Maximal CTCAE grade
- All infusion related reaction TEAEs by primary SOC, PT and Maximal CTCAE grade
- Summary of grouped TEAEs selected by Standardised MedDRA Query (SMQ), ADCT modified SMQ will also be provided by primary Grouped terms, PT and Maximal CTCAE grade. These group term include: effusion/edema, hepatic, fatigue, skin/nail, pain.

- Summary of TEAEs will also be provided by demographic factors including: sex, age group, race, disease subtype if appropriate.

All TEAEs, all serious adverse events (SAEs), all TEAEs leading to treatment withdrawal, all TEAEs leading to dose reduction, all TEAEs leading to dose delay, all TEAEs considered infusion related reactions, all TEAEs with fatal outcome and non-TEAEs will be listed.

4.8.1.2 Deaths

The following deaths summaries will be generated on the all-treated population.

- Number (%) of patients who died during the study and reasons for death
- Number (%) of patients who died within 30 days after the last dose of study drug (excluding those who died after taking any subsequent anticancer therapy/procedure) and reasons for death

4.8.1.3 AE for Transplant patients

The following analysis will be performed for patients who have responded to loncastuximab tesirine and undergo SCT (either autologous or allogeneic) after permanent discontinuation of loncastuximab tesirine treatment without any intervening anticancer therapy. The data will include the following information reported until 180 days post-transplant regardless of relationship to loncastuximab tesirine.

- Summary of AEs ≥Grade 3 suggestive of hepatic toxicity, veno-occlusive disease/sinusoidal obstruction syndrome, graft-versus-host disease, infectious complications, prolonged cytopenia(s), and pulmonary toxicity
- Serious TEAEs by primary SOC, PT and Maximal CTCAE grade
- Number (%) of patients who died after transplant and reasons for death

Similar analysis will be performed for patients who receive CAR-T therapy after permanent discontinuation of loncastuximab tesirine treatment. The data will include the following information reported until 90 days after receiving CAR-T therapy regardless of relationship to loncastuximab tesirine.

- Summary of AEs ≥Grade 3 of cytokine release syndrome, encephalopathy, edema or effusion, rash, hepatic toxicity
- Serious TEAEs by primary SOC, PT and Maximal CTCAE grade
- Number (%) of patients who died after CAR-T therapy and reasons for death

4.8.2 Laboratory Data

Laboratory data of hematology, biochemistry, and coagulation up to 30 days after the last dose of study drug or the end of treatment visit date, whichever is later, will be reported in SI units. Descriptive statistics (mean, standard deviation, median, and range) will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

All results will be summarized using shift from baseline. Shifts for clinical laboratory results that can be graded according to CTCAE version 4.0 will be summarized by CTCAE grade.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the nominal visit date for which it was recorded. Unscheduled data will be included in "worst case post-baseline" summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment.

Summary analyses will include data up to the start of subsequent anticancer therapy/procedure.

All laboratory data, including urinalysis, will be listed. Pregnancy test results will not be listed, but will be included in datasets.

4.8.3 Electrocardiogram

Descriptive statistics (mean, standard deviation, median and range) for ECG data will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

The following abnormal QTc (including QTcF and QTcB) will be reported by a frequency table:

At any post-baseline with absolute value

>450 - <=480 ms

>480 - <=500 ms

> 500 ms

Change from Baseline

>30 – <=60 ms

>60 ms

Summary analyses will include data up to the start of subsequent anticancer therapy/procedure.

All ECG data will be listed, both for quantitative data and for overall impression.

4.8.4 Vital Signs

Descriptive statistics (mean, standard deviation, median, and range) for vital signs data, including systolic and diastolic blood pressure, heart rate, respiration rate, and body temperature will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

Summary analyses will include data up to the start of subsequent anticancer therapy/procedure.

All vital signs data will be listed together with body weight.

4.8.5 ECOG Performance Status

Descriptive statistics (mean, standard deviation, median and range) will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

Summary analyses will include data up to the start of subsequent anticancer therapy/procedure.

ECOG performance score data will be listed.

4.8.6 Physical Examinations and Body Weight

Physical examination will be performed according to protocol. Clinically significant findings from the physical examinations will be recorded as medical history (prior to first administration of loncastuximab tesirine) or AEs (subsequent to first administration of loncastuximab tesirine).

Body weight will be listed together with vital signs.

4.9 Efficacy Analyses

Disease assessment will be performed according to protocol. The endpoints described in this section, if not mentioned specifically, use the independent reviewer's evaluation according to the 2014 Lugano Classification criteria before the start of subsequent anticancer therapy or procedure.

Lesion assessment data (target lesions, non-target lesions, and new lesions) and tumor response will be listed. A separate listing will contain derived data for duration of response (DOR), relapse-free survival (RFS), progression-free survival (PFS), and Overall survival (OS).

4.9.1 Overall Response Rate

Overall response rate is defined as the proportion of patients who achieve either CR or PR as best overall response (BOR) as determined by central review according to the 2014 Lugano Classification criteria before the start of subsequent anticancer therapy or procedure. For the primary ORR analysis in the all-treated population, patients with a CR or PR will be counted as successes and all other patients (including those with missing response information) will be counted as failures.

The order of overall response category is: CR, PR, SD, NE, PD (including disease recurrence/ relapse). The overall response category will be derived based on response assessment performed on or before the start of subsequent anticancer therapy/procedure. Patients without documented subsequent anticancer therapy and/or with missing start date of anticancer therapy will be considered as not having received subsequent anticancer therapy. A BOR of SD can only be made after the patient is on-study for a minimum of 35 days after the first dose of study drug. Any tumor assessment indicating SD before this time period will be considered as NE for BOR if no assessment after this time period is available.

The overall response rate and the corresponding 95% two-sided exact confidence interval will be presented. Subgroup analysis may be provided for disease subtype, disease stage, double/triple hit (yes/no), bulky disease (yes/no), GCB/ABC, transformed (yes/no), age group, sex, country, response to the first line and/or most recent line of prior systematic therapy (relapse: CR+PR vs. refractory: SD+PD vs. other: NE + missing), and other relevant variables.

Percent change from baseline in the sum of product of the perpendicular diameters (SPD) for target lesions will be presented for available data in the all-treated population . These data will also be displayed as a waterfall plot, with vertical bars representing the sorted values of best percent reduction for each patient.

A sensitivity analysis of ORR determined by the independent reviewer's evaluation will be conducted for the per-protocol population if relevant.

A sensitivity analysis of ORR will be conducted in which best overall response is determined by investigators.

4.9.2 Duration of Response

Duration of response will be defined for patients with CR or PR only as the interval between the date of initial documentation of a response and the date of the first documented evidence of progressive disease based on independent radiographic assessment or death, whichever occurs first. Clinical progression at EOT/EOS without radiographic assessment could be considered as an event in a sensitivity analysis. Patients who have the event after the start of subsequent anticancer therapy/procedure, or are progression-free and alive at the time of clinical cut-off, or have unknown status, will be censored at the last valid tumor assessment on or before the start of subsequent anticancer therapy/procedure or clinical cut-off time. When a subsequent anticancer therapy is used and progressive disease (based on radiographic or clinical progression at EOT/EOS) is observed within 6 days, they will be considered as the same visit (within the protocol specified +/-6 days visit window) and the patient will be counted as having an event (losing the response).

Patients with no post-baseline disease assessment will be censored on Day 1.

Duration of response will be estimated and displayed for the all-treated population using Kaplan-Meier methods (SAS® PROC LIFETEST). A Kaplan-Meier plot will be presented.

A sensitivity analysis of DOR will be conducted in which the DOR for patients undergo SCT will not be censored at SCT.

A sensitivity analysis of DOR per investigator assessments will also be conducted.

Subgroup analysis may be provided for disease subtype, disease stage, double/triple hit (yes/no), bulky disease (yes/no), GCB/ABC, transformed (yes/no), age group, response to the first line and/or most recent line of prior systematic therapy (relapse: CR+PR vs. refractory: SD+PD vs. other: NE + missing), best response to loncastuximab tesirine (CR/PR), and other relevant variables.

4.9.3 Time to Response:

Time to response (TTR) is defined among patients who achieve either CR or PR as BOR before the start of subsequent anticancer therapy or procedure as the time from the first dose to the initial documented response. For this subset of patients, TTR will be summarized using descriptive statistics.

4.9.4 Complete Response Rate

Complete Response Rate (CRR) will be defined as the proportion of patients with a best overall response of CR. The percentage of CRR with its 95% CI will be presented.

4.9.5 Relapse-free Survival

Relapse-free survival will be defined among CR patients as the time from the date of the first complete response until the date of the first disease relapse based on independent radiographic assessment (i.e., disease progression for CR patients) or death, whichever occurs first. The date of disease progression will be defined as the earliest date of disease progression based on central review. Clinical progression at EOT/EOS without radiographic assessment could be considered as an event in a sensitivity analysis. For patients who have the event after the start of subsequent anticancer therapy/procedure, or are progression-free and alive at the time of clinical cut-off, or have unknown status, censoring will be performed using the date of the last valid disease assessment on or before the start of subsequent anticancer therapy/procedure or clinical cut-off time. When a subsequent anticancer therapy is used and progressive disease (based on radiographic or clinical progression at EOT/EOS) is observed within 6 days, they will be considered as the same visit (within the protocol specified +/-6 days visit window) and the patient will be counted as having an event (losing the response).

Patients with no post-baseline disease assessment will be censored on Day 1.

RFS will be estimated and displayed for the all-treated population using Kaplan-Meier methods (SAS® PROC LIFETEST). A Kaplan-Meier plot will be presented.

A sensitivity analysis of RFS will be conducted in which RFS for patients undergo SCT will not be censored at SCT.

A sensitivity analysis of RPS per investigator assessments will also be conducted.

4.9.6 Progression-free Survival

Progression-free survival is defined as the interval between the date of the first dose and the date of the first disease progression based on independent radiographic assessment or death, whichever occurs first. Clinical progression at EOT/EOS without radiographic assessment could be considered as an event in a sensitivity analysis. Patients who have the event after the start of subsequent anticancer therapy/procedure, or who are progression-free and alive at the time of clinical cut-off, or have unknown status, will be censored at the time of their last valid disease assessment on or before the start of subsequent anticancer therapy/procedure or

clinical cut-off. When a subsequent anticancer therapy was used and progressive disease (based on radiographic or clinical progression at EOT/EOS) were observed within 6 days, they will be considered as the same visit (within the protocol specified +/-6 days window) and the patient will be counted as having an event.

Patients with no post-baseline disease assessment will be censored on Day 1.

PFS will be estimated and displayed for the all-treated population using Kaplan-Meier methods (SAS® PROC LIFETEST). A Kaplan-Meier plot will be presented.

A sensitivity analysis of PFS will be conducted in which the PFS for patients undergo SCT will not be censored at SCT.

A sensitivity analysis of PFS per investigator assessments will also be conducted.

4.9.7 Overall Survival

Overall survival is defined as the interval between the date of the first dose and the date of death from any cause. Patients who are known to be alive as of their last known status will be censored at their date of last contact. Patients who are lost to follow-up will be censored at the date the patient is last known to have been alive. The last confirmed alive date is the latest of the following: study visit date, telephone contact date, end of study last confirmed alive date, follow-up systemic (anticancer) therapy end date or start date (if ongoing or end date is missing), local or central radiologist scan date, or other date in the clinical database.

OS will be estimated and displayed for the all-treated population using Kaplan-Meier methods (SAS® PROC LIFETEST). A Kaplan-Meier plot will be presented.

4.9.8 Response for CAR-T patients

Response data collected after CAR-T therapy will be summarized separately.

4.10 Health-Related Quality of Life (HRQoL) Questionnaires

Scoring of QoL data and methods for handling of missing items or missing assessments will be based on each questionnaire's scoring manual.

4.10.1 European Quality of life (EuroQol)-5 Dimensions-5 Levels (EQ-5D-5L)

EQ-5D-5L is designed as an international, standardized, generic instrument for describing and evaluating QoL. The EQ-5D-5L consists of two parts:

- The descriptive system: QoL is classified according to five dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises five levels of perceived problems (e.g., none, slight, moderate, severe, extreme).
- The visual analog scale (VAS): patients are asked to indicate their health state today on a VAS with the endpoints labeled 'the best health you can imagine' (score 100) and 'the worst health you can imagine' (score 0). Patients are asked to mark an "X"

on the VAS to indicate their own health and then to report the score in a text box. If there is a discrepancy between where the patient has placed the X and the number he/she has written in the box, the number in the box is to be entered in the CRF together with a comment indicating the discrepancy.

Individual dimension responses will be summarized at each scheduled assessment with frequency counts and percentage of patients.

Descriptive statistics (mean, standard deviation, median and range) of actual values and changes from baseline will be presented at each scheduled assessment for the EQ-VAS.

A change of 7 points in VAS from the baseline is considered minimally important difference (MID) (Pickard et al., 2007). Patients will be classified as improved/deteriorated based on the established MID, i.e., if at least one of the post-baseline scores improves/deteriorates by the magnitude of the MID compared to baseline score. Proportion of patients with improvement/deterioration will be summaried.

Completion rate of EQ-5D-5L will be calculated as the number of patients who complete at least one question of EQ-5D-5L (e.g., either in descriptive system or VAS) divided by the number of patients treated at a visit. Summary of completion rate at each visit will be presented.

Summary analyses will include data up to the start of subsequent anticancer therapy/procedure.

A data listing for each individual dimension response, and the EQ-VAS will be presented for each patient at each visit.

4.10.2 Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)

FACT-Lym is a lymphoma-specific subscale for the Functional Assessment of Cancer Therapy (FACT) questionnaire. It consists of 15 specific items that are used together with the core 27-item questionnaire FACT-G. The patient is asked to respond to each item with a score of 0–4, where 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much.

The FACT-Lym questionnaire includes subscales for physical well-being (PWB, 7 items), social/ family well-being (SWB, 7 items), emotional well-being (EWB, 6 items), functional well-being (FWB, 7 items) and additional concerns (Lymphoma Subscale, LymS, 15 items). The FACT-Lym scoring guide identifies those negatively stated items that must be reversed before being added to obtain subscale totals. Negatively stated items are reversed by subtracting the response from “4”. After reversing proper items, all subscale items are summed to a total, which is the subscale score. For all FACT-Lym scales and symptom indices, the higher score is associated with the better quality of life. The scores in the following items need to be reversed:

- Physical well-being: all individual items

- Social/family well-being: none
- Emotional well-being: 5 individual items (except for the second item, "I am satisfied with how I am coping with my illness")
- Functional well-being: none
- Additional concerns: all individual items

The subscale scores will be a summation of each individual item score. If ≤ 50% of item scores are missing, the subscale score will be calculated by multiplying the sum of the item scores by the number of items in the subscale, then divided by the number of non-missing item scores. This imputes the missing scores by the mean of the non-missing scores within a subscale.

Prorated subscale score = [sum of item scores] x [N of items in subscale]/ [N of items answered]

The following composite scores will be derived from the above subscale total scores:

- FACT_Lym Trial Outcome Index (TOI, score range: 0-116) = PWB + FWB + LymS
- FACT_G Total Score (score range: 0-108) = PWB + SWB + EWB + FWB
- FACT_Lym Total Score (score range: 0-168) = PWB + SWB + EWB + FWB + LymS

The TOI, FACT-G, and FACT-Lym Total scores will be set to missing if 20% or more of the included items are missing (eg, only calculated if at least 22 of 27 FACT-G items are completed) or any of the component subscales are missing.

The mean and mean change from baseline to each subsequent assessment will be summarized for the subscale and composite scores. The best change from baseline during the study, defined as the highest positive value among all post-baseline visits minus the baseline value, will also be summarized.

A change of 3 points for LymS and FACT-G Total Score, 6 points for FACT-Lym TOI, and 7 points for FACT-Lym Total score are considered MID (Carter et al., 2008, Kimberly et al., 2003). Patients will be classified as improved/deteriorated based on the established MID for each measure. Proportion of patients with improvement/deterioration will be summaried.

Completion rate of FACT-Lym will be calculated as the number of patients with scores to calculate at least FACT-Lym TOI or FACT-G Total Score or FACT-Lym Total Score divided by the number of patients treated at a visit. Summary of completion rate at each visit will be presented.

Summary analyses will include data up to the start of subsequent anticancer therapy/procedure.

A data listing for each individual item, the subscale scores and the composite scores will be presented for each subject at each visit.

5 Interim Analyses

When the first 52 patients dosed have two tumor assessments (approximately 12 weeks after start of study drug), an interim analysis will be performed. The overall response rate and the corresponding 95% two-sided exact confidence interval will be reported. If <10 patients respond, the study enrollment will be halted.

Other analyses such DOR, PFS, CR rate, RFS, OS, and safety analyses may be performed if necessary.

6 Final Analysis

For primary and key secondary endpoints analyses, a database snapshot will be taken when all patients who achieve a response have a minimum of 6 months follow up after initial documented response. All efficacy, safety, and PK endpoints will be analyzed and reported in the clinical study report (CSR).

The exact binomial test will be used in the final analyses for the primary endpoint because of the practical consideration that accrual cannot be limited to exactly 140 patients and because patients included in the interim analysis as non-responding may be included in the final analysis as responding if they experience a late response.

Follow-up analyses will be performed when all the patients complete the study per protocol. The results will be reported in a CSR addendum.

7 Data handling conventions

7.1 General conventions

7.1.1 Missing data

Handling of missing/partial dates

In general, imputation of missing dates will be made for AE onset date, AE resolution date, date of death, medication start/end dates, start and end dates of prior and subsequent therapies, and date of initial diagnosis for reporting. No imputation should be done at the data level.

- If dates are completely missing, no imputation will be made.
- For any partial date with missing year, no imputation will be made.
- For missing initial diagnosis date and subsequent therapies, if only day is missing, then the 15th of the month will be used; if only year is present, then June 30th will be used. If such imputed date for initial diagnosis is on or after date of first dose, then date of first dose - 1 will be used. If such imputed date for subsequent therapies is before date of last dose, then date of last dose +1 will be used.
- If the imputed date is for an AE start date and is in the same year and month as but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as but after the last dose date + 30 days, then the last dose date + 30 days will be used.
- If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered as a prior and concomitant medication.
- If the imputed date is for a date of death and is before the last date that the patient is known to be alive, the latter date will be used.
- If the date part is missing for new anticancer therapy, the month and year will be used for comparison with disease assessment.

Handling of missing relationship to investigational product of TEAEs

If the assessment of the relationship to IP is missing, then the relationship to IP has to be assumed and the TEAE considered as such in the frequency tables of possibly related TEAEs, but no imputation should be done at the data level.

Handling of missing severity/grades of AEs

If the severity/grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity of the remaining occurrences will be considered. If the severity is missing for all the occurrences a “missing” category will be added in summary table.

No other imputation of values for missing data will be performed.

7.1.2 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline and worst values and/or grades. Re-windowing for unscheduled visits will not be performed

7.1.3 Duplicated visits

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per visit. Unless otherwise noted throughout the rest of this document, when a single value is needed, the following rule(s) will be used:

- If more than 1 assessment occurs during the same nominal visit, select the record closest to the nominal day for that visit.
- If there are 2 assessments that are equidistant from the nominal day, the data of the assessment after the scheduled study day will be used.
- The last measurement will be used if multiple measurements are taken on the same day.

8 Reference List

Carter GC, Liepa AM, Zimmerman AH, Morschhauser F. Validation of the functional assessment of cancer therapylymphoma (FACT-Lym) in patients with relapsed/refractory mantle cell lymphoma. *Blood* 2008; 112:828 (abstract 2376).

Kimberly Webster, David Cella and Kathleen Yost. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health and Quality of Life Outcomes* 2003; 1:79.

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ABC	Activated B-cell
AE	Adverse event
BMI	Body mass index
BOR	Best overall response
C1D1	Cycle 1 Day 1
CAR-T	Chimeric antigen receptor T-cell
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of study
EOT	End of treatment
GCB	germinal center B-cell
IP	Investigational product
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimally important difference
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per-protocol
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
Q3W	Every 3 weeks
QTc	Corrected QT interval
RFS	Relapse-free survival

SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem cell transplant
SD	Stable disease
SMQ	Standardised MedDRA Query
SOC	System organ class
SPD	Sum of product of the perpendicular diameters
std	Standard deviation
TEAE	Treatment-emergent adverse event
WHODRUG DD	World Health Organization Drug Dictionary

Appendix 2 List of Post-Text Tables, Figures, Listings, and Supportive SAS Output Appendices

This list of ouputs is for the purpose of programming instruction, the SAP is not required to be updated for changes in future list.

14.1 DISPOSITION DATA TABLES

14.1.1.1 Subject Disposition (All-Treated Population)

14.1.1.2 Subject Disposition (Per-Protocol Population)

14.1.1 Subject Analysis Sets (All Enrolled patients)

14.1.2 PROTOCOL DEVIATION DATA TABLE

14.1.2 Important Protocol Deviations (All-Treated Population)

14.1.3 DEMOGRAPHIC DATA TABLE

14.1.3.1.1 Demographic and Baseline Characteristics (All-Treated Population)

14.1.3.1.2 Demographic and Baseline Characteristics (Per-Protocol Population)

14.1.4 CANCER HISTORY DATA TABLE

14.1.4.1 Cancer History (All-Treated Population)

14.1.5 Prior Anticancer Procedure or Therapy DATA TABLE

14.1.5.1 Prior Systemic Anti-cancer Therapy, Surgery, Radiotherapy, and Stem Cell Transplant (All-Treated Population)

14.1.6 Medical History DATA TABLE

14.1.6 Medical History by System Organ Class and Preferred Term (All-Treated Population)

14.1.7 PRE-TREATMENT DISEASE CHARACTERISTICS DATA TABLE

14.1.7.1 Pre-treatment Disease Characteristics (All-Treated Population)

14.1.8 Cytogenetic Analysis DATA TABLE

14.1.8 Cytogenetic Analysis (All-Treated Population)

14.1.9 Immunophenotypic Analysis DATA TABLE

14.1.9 Immunophenotypic Analysis (All-Treated Population)

14.1.10 prior mdedications DATA TABLE

14.1.10 Prior Medications (All-Treated Population)

14.2 EFFICACY DATA TABLE

14.2.1.1.1 Overall Response Rate (All-Treated Population)

Note: Including the 95% CI for CR in the table

14.2.1.1.2 Overall Response Rate (Per-Protocol Population)

14.2.1.1.3 Overall Response Rate by Investigator (All-Treated Population)

14.2.1.1.4 Overall Response Rate by Investigator (Per-Protocol Population)

14.2.1.1.5 Overall Response Rate for CAR-T patients from Response Data Collected after CAR-T Therapy (All-Treated Population)

14.2.1.1.6 Overall Response Rate by Sex (All-Treated Population)

14.2.1.1.7 Overall Response Rate by Age Group (All-Treated Population)

14.3.3.4.3 Study Drug Related Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.4 Treatment-emergent Adverse Events Leading to Dose Delay by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.5 Study Drug Related Treatment-emergent Adverse Events Leading to Dose Delay by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.6 Treatment-emergent Adverse Events Leading to Dose Reduction by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.7 Study Drug Related Treatment-emergent Adverse Events Leading to Dose Reduction by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.8 Treatment-emergent Adverse Events Leading to Treatment Withdrawal by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.9 Study Drug Related Treatment-emergent Adverse Events Leading to Treatment Withdrawal by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.10 Treatment-emergent Adverse Events Leading to Infusion Interruption by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.11 Treatment-emergent Adverse Events with Fatal Outcome by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.12 Infusion Related Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.13 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Female Patients (All-Treated Population)

14.3.3.4.14 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Male Patients (All-Treated Population)

14.3.3.4.15 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Patients Age <65 years old (All-Treated Population)

14.3.3.4.16 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Patients Age between 65 - 74 years old (All-Treated Population)

14.3.3.4.17 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Patients Age ≥75 years old (All-Treated Population)

14.3.3.4.18 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Patients in USA (All-Treated Population)

14.3.3.4.19 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Patients in United Kingdom (All-Treated Population)

14.3.3.4.20 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Patients in Italy (All-Treated Population)

14.3.3.4.21 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Race = White (All-Treated Population)

14.3.3.4.22 Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for for Race other than White (All-Treated Population)

14.3.3.4.23 Treatment-emergent Adverse Events with Grade ≥3 by System Organ Class, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.24 Selected Treatment-emergent Adverse Events by Grouped AE, Preferred Term, and Maximum Severity (All-Treated Population)

14.3.3.4.25 Summary of Adverse Events ≥Grade 3 suggestive of Selected Conditions for Patients Undergo Stem Cell Transplant after Discontinuation of Study Drug (Stem Cell Transplant Population)

Note: conditions includes hepatic toxicity, veno-occlusive disease/sinusoidal obstruction syndrome, graft-versus-host disease, infectious complications, prolonged cytopenia(s), and pulmonary toxicity

14.3.3.4.26 Serious Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Patients Undergo Stem Cell Transplant after Discontinuation of Study Drug (Stem Cell Transplant Population)

14.3.3.4.27 Summary of Adverse Events ≥Grade 3 suggestive of Selected Conditions for Patients Receive CAR-T Therapy after Discontinuation of Study Drug (All-Treated Population)

Note: conditions includes cytokine release syndrome, encephalopathy, edema or effusion, rash, hepatic toxicity

14.3.3.4.28 Serious Adverse Events by System Organ Class, Preferred Term, and Maximum CTCAE Grade for Patients Receive CAR-T Therapy after Discontinuation of Study Drug (All-Treated Population)

14.3.3.5.1RG Non-serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term with a Frequency of ≥5% in Any Treatment Group (All-Treated Population)

14.3.3.5.2RG Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (All-Treated Population)

14.3.3.5.3RG Study Drug Related Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (All-Treated Population)

14.3.3.5.4RG Treatment-emergent Adverse Events with Fatal Outcome by System Organ Class and Preferred Term (All-Treated Population)

14.3.3.5.5RG Study Drug Related Treatment-emergent Adverse Events with Fatal Outcome by System Organ Class and Preferred Term (All-Treated Population)

14.3.3.5.6RG Non-serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (All-Treated Population)

14.3.3.5.7RG Number of Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (All-Treated Population)

14.3.3.5.8RG Number of Study Drug Related Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (All-Treated Population)

14.3.3.5.9RG Number of Non-Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (All-Treated Population)

14.3.4 LABORATORY DATA TABLES

14.3.4.1.1 Summary of Hematology Results by Visits (All-Treated Population)

14.3.4.2.1 Summary of Biochemistry Results by Visits (All-Treated Population)

14.3.4.3.1 Summary of Coagulation Results by Visits (All-Treated Population)

14.3.4.4.1 Shift Summary of Hematology Results by Maximum CTCAE Grade (All-Treated Population)

14.3.4.4.1a Hematology Shift CTCAE from Baseline Grade ≤2 to Post-baseline Grade ≥3 (All-Treated Population)

14.3.4.5.1 Shift Summary of Biochemistry Results by Maximum CTCAE Grade (All-Treated Population)

14.3.4.5.1a Biochemistry Shift CTCAE from Baseline Grade ≤2 to Post-baseline Grade ≥3 (All-Treated Population)

14.3.4.6.1 Shift Summary of Coagulation Results by Maximum CTCAE Grade (All-Treated Population)

14.3.4.7.1 Maximum Post-baseline Hematology CTCAE Grade (All-Treated Population)

14.3.4.8.1 Maximum Post-baseline Biochemistry CTCAE Grade (All-Treated Population)

14.3.4.9.1 Maximum Post-baseline Coagulation CTCAE Grade (All-Treated Population)

14.3.5 VITAL SIGN DATA TABLE

14.3.5.1 Summary of Vital Signs by Visit and Time Point (All-Treated Population)

14.3.6 ELECTROCARDIOGRAM DATA TABLES

14.3.6.1 Summary of ECG for Heart Rate and QTc by Visit and Time Point (All-Treated Population)

14.3.6.2 Summary of QTc Abnormality (All-Treated Population)

14.3.6.3 Shift Summary of QTc Interval (All-Treated Population)

14.3.7 DEATH DATA TABLE

14.3.7.1 Summary of Death (All-Treated Population)

14.3.7.2 Summary of Death after Transplant (Stem Cell Transplant Population)

14.3.7.3 Summary of Death after CAR-T Therapy (All-Treated Population)

14.3.8 ECOG DATA TABLE

14.3.8.1 Summary of ECOG Performance Score by Visits (All-Treated Population)

14.3.9 PRO DATA TABLE

14.3.9.1.1 Summary of EQ-5D-5L VAS Score by Visits (PRO Population)

14. 3.9.1.2 Frequency Distribution of the Individual Dimension Response from EQ-5D-5L Descriptive System by Visits (PRO Population)

14. 3.9.1.3 Summary of Patients Classified as Improvement/Deterioration Based on Minimally Clinically Important Difference for EQ-5D-5L VAS Score (PRO Population)

14. 3.9.1.4 Completion Rate for EQ-5D-5L Descriptive System and VAS Score by Visit (PRO Population)

14. 3.9.2.1 Summary of Subscale and Composite Scores from FACT-Lym by Visits (PRO Population)

14. 3.9.2.2 Best Change from Baseline in Subscale and Composite Scores from FACT-Lym (PRO Population)

14. 3.9.2.3 Summary of Patients Classified as Improvement/Deterioration Based on Minimally Clinically Important Difference for FACT-Lym Subscale and Composite Scores (PRO Population)

14. 3.9.2.4 Completion Rate for FACT-Lym Subscale and Composite Scores by Visit (PRO Population)

14 FIGURES

14.2 EFFICACY FIGURES

14.2.1.5.1 Waterfall Plot of Best Percent Change from Baseline in Tumor Size (All-Treated Population)

14.2.1.5.2 Waterfall Plot of Best Percent Change from Baseline in Tumor Size (Per-Protocol Population)

14. 2.1.6.1 Kaplan-Meier Plot of Progression-free Survival (All-Treated Population)

14. 2.1.6.2 Kaplan-Meier Plot of Progression-free Survival (Per-Protocol Population)

14. 2.1.6.3 Kaplan-Meier Plot of Progression-free Survival with Clinical Progression as an Event (All-Treated Population)

14. 2.1.6.4 Kaplan-Meier Plot of Progression-free Survival with Stem Cell Transplant not Censored (All-Treated Population)

14. 2.1.6.5 Kaplan-Meier Plot of Progression-free Survival by Primary Category of Disease Diagnosis (All-Treated Population)

14. 2.1.6.6 Kaplan-Meier Plot of Progression-free Survival by Double/Triple Hit (Yes/No) (All-Treated Population)

14. 2.1.6.7 Kaplan-Meier Plot of Progression-free Survival by First Line Prior Systemic Therapy Response Group (All-Treated Population)

14. 2.1.9.14 Kaplan-Meier Plot of Duration of Response by Bulky Disease (Yes/No) (All-Treated Population)

14. 2.1.9.15 Kaplan-Meier Plot of Duration of Response by Subtype of Germinal center B-cell/Activated B-cell (All-Treated Population)

14.2.1.10.1 Swimmer Plot (All-Treated Population)

14.2.1.10.2 Swimmer Plot (Per-Protocol Population)

14.2.1.11.1 Kaplan-Meier Plot of Time to First AE Leading to Dose Modification (All-Treated Population)

14.3 SAFETY FIGURES

14.3.4.1.1.1 Mean (SE) Plot of Basophils (10^9/L) by Dose Group (All-Treated Population)

14.3.4.1.1.2 Mean (SE) Plot of Eosinophils (10^9/L) by Dose Group (All-Treated Population)

14.3.4.1.1.3 Mean (SE) Plot of Hematocrit (fraction of 1) by Dose Group (All-Treated Population)

14.3.4.1.1.4 Mean (SE) Plot of Hemoglobin (g/L) by Dose Group (All-Treated Population)

14.3.4.1.1.5 Mean (SE) Plot of Lymphocytes (10^9/L) by Dose Group (All-Treated Population)

14.3.4.1.1.6 Mean (SE) Plot of Monocytes (10^9/L) by Dose Group (All-Treated Population)

14.3.4.1.1.7 Mean (SE) Plot of Neutrophils (10^9/L) by Dose Group (All-Treated Population)

14.3.4.1.1.8 Mean (SE) Plot of Platelets (10^9/L) by Dose Group (All-Treated Population)

14.3.4.1.1.9 Mean (SE) Plot of Leukocytes (10^9/L) by Dose Group (All-Treated Population)

14.3.4.1.1.10 Mean (SE) Plot of Basophils/Leukocytes (fraction of 1) by Dose Group (All-Treated Population)

14.3.4.1.1.11 Mean (SE) Plot of Eosinophils/Leukocytes (fraction of 1) by Dose Group (All-Treated Population)

14.3.4.1.1.12 Mean (SE) Plot of Lymphocytes/Leukocytes (fraction of 1) by Dose Group (All-Treated Population)

14.3.4.1.1.13 Mean (SE) Plot of Monocytes/Leukocytes (fraction of 1) by Dose Group (All-Treated Population)

14.3.4.1.1.14 Mean (SE) Plot of Neutrophils/Leukocytes (fraction of 1) by Dose Group (All-Treated Population)

14.3.4.2.1.1 Mean (SE) Plot of Albumin (g/L) by Dose Group (All-Treated Population)

14.3.4.2.1.2 Mean (SE) Plot of Alanine Aminotransferase (U/L) by Dose Group (All-Treated Population)

14.3.4.2.1.3 Mean (SE) Plot of Aspartate Aminotransferase (U/L) by Dose Group (All-Treated Population)

14.3.4.2.1.4 Mean (SE) Plot of Alkaline Phosphatase (U/L) by Dose Group (All-Treated Population)

14.3.4.2.1.5 Mean (SE) Plot of Bilirubin (umol/L) by Dose Group (All-Treated Population)

14.3.4.2.1.6 Mean (SE) Plot of Gamma Glutamyl Transferase (U/L) by Dose Group (All-Treated Population)

14.3.4.2.1.7 Mean (SE) Plot of Amylase (U/L) by Dose Group (All-Treated Population)

14.3.4.2.1.8 Mean (SE) Plot of Bicarbonate (mmol/L) by Dose Group (All-Treated Population)

14.3.4.2.1.9 Mean (SE) Plot of Blood Urea Nitrogen (mmol/L) by Dose Group (All-Treated Population)

14.3.4.2.1.10 Mean (SE) Plot of Calcium (mmol/L) by Dose Group (All-Treated Population)

14.3.4.2.1.11 Mean (SE) Plot of Cholesterol (mmol/L) by Dose Group (All-Treated Population)

14.3.4.2.1.12 Mean (SE) Plot of Creatine Kinase (U/L) by Dose Group (All-Treated Population)

14.3.4.2.1.13 Mean (SE) Plot of Chloride (mmol/L) by Dose Group (All-Treated Population)

14.3.4.2.1.14 Mean (SE) Plot of Creatinine (umol/L) by Dose Group (All-Treated Population)

14.3.4.2.1.15 Mean (SE) Plot of Creatinine Clearance (mL/min) by Dose Group (All-Treated Population)

14.3.4.2.1.16 Mean (SE) Plot of Glucose (mmol/L) by Dose Group (All-Treated Population)

14.3.4.2.1.17 Mean (SE) Plot of Potassium (mmol/L) by Dose Group (All-Treated Population)