Protocol Number: ADCT-402-104

Official Title: A Phase 1 Open-Label Study to Evaluate the Safety and Antitumor Activity of Loncastuximab Tesirine and Durvalumab in Patients with Advanced Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, or Follicular Lymphoma

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Statistical Analysis Plan

A Phase 1 Open-Label Study to Evaluate the Safety and Antitumor Activity of Loncastuximab Tesirine and Durvalumab in Patients with Advanced Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, or Follicular Lymphoma

PROTOCOL NO.: ADCT-402-104

SAP Version No./ Date: Final 1.0/ Nov. 02, 2020

Statistician: [redacted]

Confidentiality Statement

SAP Approval – Sponsor Signatory

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13 November 2020
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Nov 13, 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-402-104.

This SAP should be read in conjunction with the study protocol and case report form (CRF).

2 Study Objectives

2.1 Primary Objectives

- To characterize the safety and tolerability of loncastuximab tesirine in combination with durvalumab, and to identify the recommended dose and schedule for future studies.

2.2 Secondary Objectives

- To evaluate the antitumor effect of the combination of loncastuximab tesirine with durvalumab.
- To characterize the pharmacokinetic (PK) profile of loncastuximab tesirine when given in combination with durvalumab.
- To evaluate the immunogenicity of loncastuximab tesirine when given in combination with durvalumab.

[redacted]

3 Study Design

Refer to the corresponding section in the protocol.

3.1 Sample Size Consideration

Refer to the corresponding section in the protocol.

3.2 Randomization

This study is not randomized.

3.3 Modifications to the statistical section of the protocol

The trial was terminated early. Therefore, only dose escalation (Part 1) data for enrolled patients will be analyzed and a selected or modified analysis from the statistical section of the protocol will be performed.

4 Statistical methods

All analyses use [redacted] or higher. Summary tables will be organized by each dose level; if some dose levels have few patients, then dose levels could be combined into dose ranges. All available data will be used in the analyses, and important data will be included in data listings, sorted by dose level, 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 set by treatment group 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.

No hypothesis testing will be performed in this study.

4.1 Analysis Sets

4.1.1 Safety Analysis Set

The safety analysis set consists of all patients who receive any study drug.

4.1.2 DLT-evaluable Analysis Set (Part 1)

The DLT-evaluable analysis set consists of all patients in Part 1 who received study drugs and excludes patients who discontinue from the study during the DLT evaluation period without experiencing a DLT. The patients with completed DLT information will be included even if they discontinue early before the end of DLT evaluation period. The DLT evaluation period will be the 21 days after the first durvalumab dose.

4.1.3 Efficacy Analysis Set

The efficacy analysis set consists of patients who receive at least one dose of study drug with a valid baseline and at least one valid post-baseline disease assessment or patients who have documented progression of disease or death at any time after the first dose of study.

4.2 Patient Disposition

For the enrolled patients, the number and percentage of enrolled and treated patients who were on treatment as well as reason for screen failure will be tabulated. For the safety analysis set, the number and percentage of patients who discontinued from study treatment and who discontinued the study for each reason will be tabulated for each dose level.

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 received the wrong treatment or incorrect dose. For example,
   - Actual dose of study drug was more than 15% off the protocol defined planned dose level.
   - Lonca dosing interval is less than 18 days.

Important protocol deviations will be listed.

4.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be tabulated for the safety analysis set by dose level. 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 (kg/m^2)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Country (Spain, USA)

Demographic and baseline characteristics data will be listed.

4.5 Cancer History and Medications History

Cancer history will be presented for the safety analysis set by dose level. Cancer history will include the following variables:

- Duration since diagnosis
- Non-Hodgkin lymphoma (NHL) subtype (diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma)
- Disease staging (Stage I, II, III, IV; Subtype E, X, S; Extra-nodal involvement at study entry and number of sites of involvement)
- Cytogenetic analysis (cytogenetic abnormalities: t (2;3), t (2;18), t (3;14), t (3;22), t (8;14), t (8;22], t (11q), t (11;14), del (11q), +12, del (13q), t (14;18), del (17p), t (18;22), BCL2 rearrangement, BCL6 rearrangement, MYC rearrangement, other)

- Immunophenotypic analysis (IgVH status: mutated, unmutated, not applicable; Results of negative, positive or not done for expression BCL2, BCL6, CD3, CD5, CD10, CD19, CD20, CD21, CD23, CD43, CD45, CYCLIN D1, IRF4/MUM1, Ki-67, MYC, and ZAP70)

Prior anticancer procedure or therapy will include the following variables:

- Number of lines of therapy/ regimens per patient
- Any prior surgeries for the current malignancy (yes, no)
- Any prior radiotherapy for the current malignancy (yes, no)
- Reason for stopping prior systemic treatment (progression, toxicity, Completed Treatment, other)
- Best response while on regimen for prior systemic treatment (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)

Bone marrow evaluation (bone marrow aspirate and/or bone marrow biopsy) at screening may be listed if applicable. Medical and cancer history data will be listed. Results of cytogenetic analysis and immunophenotypic analysis will be listed. CD19 expression level data will be listed if available. Tumor tissue biopsy collection will not be listed, but will be contained in datasets.

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

4.6 Prior or Concomitant Medications (other than anticancer therapies)

All medications taken from ICF signature date or from 14 days before dosing and continuing until 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) and presented by dose level for the safety analysis set.

- Prior medications are those the patient used prior to first investigational product (IP) intake. Prior medications can be discontinued before first dosing or can be ongoing during the treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to any IP(s), from first dose (or start of the observation period) 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 6.

Prior medications will be listed together with concomitant medications. Premedication for dosing will be listed separately.

4.7 Exposure to Treatment

4.7.1 Extent of ADCT-402 Exposure

ADCT-402 exposure will be summarized for the safety analysis set by dose level. The following items will be tabulated.

- Duration of treatment (in days) = last dose date – first dose date +1
- Total number of cycles dose administered
- Total dose administered (in µg and µg/kg)
- Average dose per cycle (in µg and µg/kg)

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 IP volume (in mL)* 5 mg/mL *1000 or serially diluted IP volume (in mL)/50* 5 mg/mL *1000; for partial infusion, multiply by (1- volume of dosing solution not administered [in mL]/ 50 mL).

4.7.2 Extent of Durvalumab Exposure

Durvalumab exposure will be summarized for the safety analysis set by dose level. The following items will be tabulated.

- Duration of treatment (in days) = last dose date – first dose date +1
- Total number of cycles dose administered
- Total dose administered (in mg)
- Average dose per cycle (in mg)

For partial infusion, dose administered at each infusion (mg) is calculated as 1500 mg*(1- volume of dosing solution not administered [in mL]/ total volume of dosing solution prepared [in mL]).

Dose delays and dose reductions could also be analyzed if relevant. A cycle is delayed if it starts more than 3 days post-scheduled date. Durvalumab will be given at full dose when resumed after being held for toxicity, i.e., there will be no dose reduction.

Exposure data and infusion details will be listed together.

4.7.3 Prophylactic Medications for Hypersensitivity

Prophylactic medications for hypersensitivity will be listed only.

4.7.4 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 listed only.

4.8 Safety Analyses

The summary of safety results will be presented by treatment group.

General common rules

All safety analyses will be performed on the safety analysis set, 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.
- 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 Dose-limiting Toxicities (Part 1)

DLT data will be listed for Part 1 of the study.

4.8.2 Adverse Events, Serious Adverse Events, and Deaths

4.8.2.1 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 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 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 a treatment-emergent unless there is definitive information to determine it is a non-TEAE (pre- or post-treatment).

Details on classification of AEs with missing or partial onset dates are provided in Section 6.

Analysis of all TEAE(s):

The following TEAE summaries will be generated for the safety analysis set in each dose level.

- 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 discontinuation
  - TEAE leading to ADCT-402 delay or reduction or interruption
  - TEAE with at least one infusion related reaction

    For related TEAE and TEAE leading to dose modification (treatment discontinuation, dose delay/reduction/interruption), summary will be broken up for each study drug respectively.
- All TEAEs by PT and all TEAEs with CTCAE 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 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 with CTCAE 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 Serious TEAEs by primary SOC, PT and Maximal CTCAE grade

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

4.8.2.2 Deaths

The following death summaries will be generated on the safety analysis set.

- Number (%) of patients who died during the study and reasons for death

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

All deaths will be listed.

4.8.3 Laboratory Data

Laboratory data of hematology, chemistry, and coagulation 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.

4.8.4 Electrocardiogram

Electrocardiogram (ECG) parameters (e.g., corrected QT interval [QTc] in ms) will not be converted or derived, but will be reported as provided by investigational sites.

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.

The following abnormal QTc (including QTcF, QTcB and QTc with unspecified method) will be reported:

At any post-baseline with absolute value

>450 - <=480 ms

>480 - <=500 ms

> 500 ms

Change from Baseline

>30 – <=60 ms

>60 ms

For patients with unspecified QTc method at either baseline or post-baseline, consistent correction method is assumed within a patient when calculating the change from baseline.

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.

4.8.5 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 and ECOG performance score.

4.8.6 ECOG Performance Status

ECOG results will be summarized using shift from baseline. ECOG performance score data will be listed together with vital signs and body weight.

4.8.7 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 study drug) or AEs (subsequent to first administration of study drug).

Body weight will be listed together with vital signs and ECOG performance score.

4.9 Efficacy Analyses

Due to the early termination of the trial, efficacy data will be listed only. Lesion assessment data (target lesions, non-target lesions, and new lesions) and overall disease assessment will be listed.

5 Interim Analyses

NA.

6 Data handling conventions

6.1 General conventions

6.1.1 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.

Handling of missing relationship to investigational product of TEAEs

If the assessment of the relationship to investigational product is missing, then the relationship to investigational product 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.

6.1.2 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

6.1.3 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.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of study
EOT	End of treatment
IP	Investigational product
MedDRA	Medical Dictionary for Regulatory Activities
NE	Not evaluable
NHL	Non-Hodgkin lymphoma
PD	Pharmacodynamics, progressive disease
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
QTc	Corrected QT interval (ms)
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
std	Standard deviation
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures, and listings
WHO-DD	World Health Organization-Drug Dictionary