**Protocol Number: ADCT-301-001**

**Official Title: A Phase 1 Adaptive Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-301 in Patients with Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma**

**NCT Number: NCT02432235**

**Document Date: 24-Mar-2020**

# Statistical Analysis Plan

## A Phase 1 Adaptive Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-301 in subjects with Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma

## PROTOCOL NO.: ADCT-301-001

**SAP Version No./ Date: 1.0/ Dec 20, 2019**

**SAP Version No./ Date: 2.0/ Mar 24, 2020**

**Statistician:** [redacted]

## Confidentiality Statement

# SAP Approval – Sponsor Signatory

| | |
|---|---|
| **Study Title** | A Phase 1 Adaptive Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-301 in subjects with Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma |
| **Protocol Number** | ADCT-301-001 |
| **Original SAP Version Date:** | 20 Dec 2019 |
| **SAP v2.0 Date** | 24 Mar 2020 |

[redacted]

[redacted]

# 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-301-001.

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 9 dated 04 January 2019 and CRF version PROD 10.0 dated 29 March 2018.

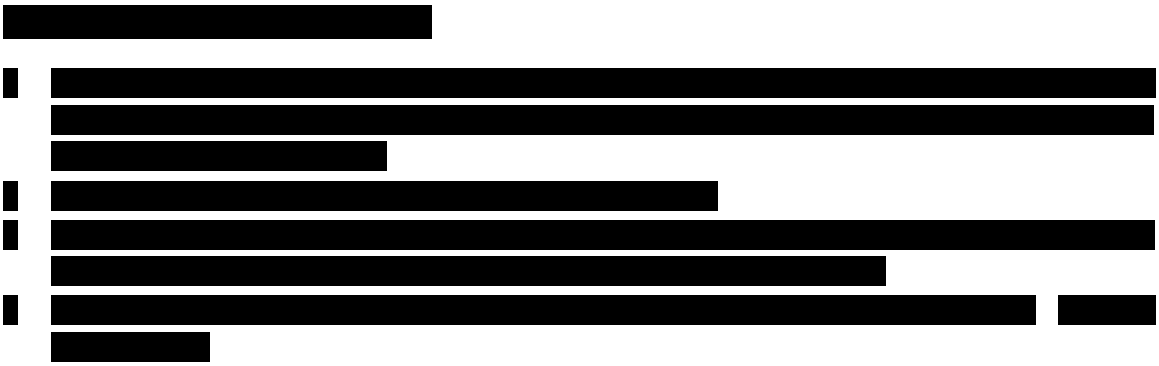
# 2 Study Objectives

## 2.1 Primary Objectives

- Evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) of ADCT-301 in subjects with relapsed/refractory lymphoma (Part 1).
- Determine the recommended dose of ADCT-301 for Part 2 (expansion).
- Evaluate the safety and tolerability of ADCT-301 in Part 2 at the dose level recommended in Part 1.

## 2.2 Secondary Objectives

- Evaluate the activity of ADCT-301 measured by overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).
- Characterize the pharmacokinetic (PK) profile of HuMax-TAC (total antibody; drug-to-antibody ratio [DAR] ≥0), pyrrolobenzodiazepine (PBD)-conjugated HuMax-TAC (DAR ≥1), and free warhead SG3199.
- Evaluate anti-drug antibodies (ADAs) in blood before, during, and after treatment with ADCT-301.



# 3 Study Design

This is a Phase 1, first in human (FIH), open-label, dose-escalation (Part 1) and expansion (Part 2) study of ADCT-301 in patients with relapsed and refractory lymphoma. The study will evaluate the safety and tolerability of ADCT-301 as monotherapy, as well as the preliminary activity, PK, PD, and formation of ADAs of ADCT-301 in patients. The patient population includes those with relapsed or refractory histologically confirmed non-Hodgkin lymphoma (NHL; including Stage ≥Ib cutaneous T-cell lymphoma [CTCL]) or Hodgkin lymphoma (HL).

In Part 1, patients will receive ADCT-301 administered as a 2-hour intravenous infusion on Day 1 of each 3-week cycle. The initial dose level for Part 1 will be 3 μg/kg. The highest possible dose will be 300 μg/kg. The MTD will be the highest safe dose that has at least a 60% probability that the dose-limiting toxicity (DLT) rate is less than 30%.

Dose escalation will be conducted according to a continual reassessment method (CRM). Dose levels from 3 to 300 μg/kg are possible, but the final dose level and number of doses will be dependent on the emergent toxicity profile and will be decided by a Dose Escalation Steering Committee (DESC). PK and PD evaluations may also inform decision making. See separate DESC Plan document.

The DLT period for dose escalation is changed from 2 cycles to 1 cycle in protocol amendment 4. However, the adaptive dose-escalation algorithm will incorporate cumulative DLTs occurring through Cycle 3. No intra-patient dose escalation will be allowed during the study. However, once the recommended Part 2 dose is determined, patients receiving lower dose levels of ADCT-301 may be offered continued treatment at the recommended dose.

During Part 1, the DESC may expand enrollment at doses below the current dose level being evaluated as part of the dose escalation process. Additional patients may only be added at a lower dose level provided there is at least 1 patient with documented stable disease. Not more than 10 patients in total can be treated at any dose level unless at least 3 of the 10 patients have documented partial response or better using the 2014 Lugano Classification criteria or other appropriate measures of response.

In Part 2 (expansion), patients will be assigned to receive the recommended dose(s) of ADCT-301, as determined by the DESC during Part 1 of the study. The patient population (e.g., disease subtypes) to be enrolled in Part 2 (expansion) may be refined based on results and observations from Part 1. Different recommended dose(s) for expansion may be defined and carried forward into part 2 for different lymphoma subtypes.

## 3.1 Sample Size Consideration

This is a Phase 1 study with a maximum total sample size of 140 patients. Part 1 will enroll approximately 80 patients and Part 2 will enroll approximately 60 patients.

## 3.2 Randomization

This study is not randomized.

## 3.3 Modifications to the statistical section of the protocol

The efficacy analysis set was defined in the protocol as all patients with valid baseline data who receive at least 2 doses of study drug or who have documented progression of disease at any time after the first dose of study drug. The efficacy analysis set is updated in the SAP to include all patients who have received at least one dose of ADCT-301 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 drug.

# 4 Statistical methods

All analyses use SAS® version 9.4 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 ADCT-301.

### 4.1.2 DLT-evaluable Analysis Set (Part 1)

The DLT-evaluable analysis set consists of patients who complete two cycle of ADCT-301 if enrolled prior to protocol amendment 4 and patients who complete one cycle of ADCT-301 if enrolled after protocol amendment 4. The patients with completed DLT information will be included even if they discontinue early before the end of cycle 2 or cycle 1 respectively.

### 4.1.3 Efficacy Analysis Set

The efficacy analysis set consists of patients who receive at least one dose of ADCT-301 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

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 set for each dose level. In addition, for the safety analysis set, the number and percentage of patients who withdrew 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. Patients who met criteria for mandatory withdrawal of study drug during the study but did not have study drug withdrawn. The criteria for mandatory withdrawal of study drug included:
   - Any patient who experiences a Grade 3 or higher hypersensitivity (Appendix 13.4 in the protocol) reaction, regardless of premedication, during any cycle of treatment.
   - Any patient who experiences a recurrent Grade 3 or 4 toxicity, excluding hematological toxicity.
   - Any patient who requires a dosing delay >21 consecutive days from the planned Day 1 dosing at any time during treatment (except in case of potential patient benefit, which must be approved by the Sponsor).
4. Patient who received the wrong treatment or incorrect dose. For example,
   - Actual dose of study drug was more than 15% greater than protocol defined planned dose level.
   - Patient started next cycle less than 18 days later 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 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 (<55, ≥55 - < 65, ≥ 65 - < 75, ≥ 75 years)
- Height (cm)
- Weight (kg)
- Body mass index ($kg/m^2$)
- 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 safety analysis set by dose level. Cancer history will include the following variables:

- Duration since diagnosis
- Disease diagnosis (non-Hodgkin lymphoma : T-cell lymphoma, B-lymphoma ; Hodgkin lymphoma)
- Disease diagnosis subtype (for non-Hodgkin lymphoma: diffuse large B-cell lymphoma, follicular lymphoma, mucosa-associated lymphatic tissue lymphoma/ extranodal marginal zone B-cell lymphoma, small cell lymphocytic lymphoma/chronic lymphocytic leukemia, mantle cell lymphoma, mediastinal [thymic] large B-cell lymphoma, lymphoplasmacytic lymphoma and Waldenstrom macroglobulinemia, nodal marginal zone B-cell lymphoma, splenic marginal zone lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, Burkitt lymphoma-Burkitt leukemia, lymphomatoid granulomatosis, peripheral T-cell lymphoma not otherwise specified, cutaneous T-cell lymphoma [Sézary], cutaneous T-cell lymphoma [mycosis fungoides], anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, lymphoblastic lymphoma [can sometimes be a B-cell subtype], NK-cell lymphoma, other; for Hodgkin lymphoma (classical Hodgkin lymphoma): nodular sclerosis classical Hodgkin lymphoma, lymphocyte-rich classical Hodgkin lymphoma, mixed cellularity classical Hodgkin lymphoma, lymphocyte-depleted classical Hodgkin lymphoma, other)
- Stage of disease (NHL and HL, non-CTCL; Stage I, II, III, IV; constitutional symptoms A, B; Subtype E, X, S)
- Stage of disease (CTCL, IA, IB, IIA, IIB, IIIA, IIIB, IVA1, IVA2, IVB)
- Cytogenetic analysis (results available yes, t [11;14], t [11q], +12, del [11q], del [13q], del [17p], t [14;18], t [8; 14], other)
- Immunophenotypic analysis (results available yes; IgVH status mutated, unmutated, not applicable; CD5, CD10, CD19, CD20, CD21, CD23, CD43, 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
- Any prior surgeries for the current malignancy (yes, no)
- Any prior radiotherapy for the current malignancy (yes, no)
- Any prior systemic therapy for the current malignancy (yes, no)
- Type of systemic therapy (Brentuximab Vedotin, Checkpoint inhibitor, other)
- 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)

Medical and cancer history data will be listed. Results of cytogenetic analysis and immunophenotypic analysis will be listed. CD25 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 therapy, and stem cell transplant data will be listed.

## 4.6 Prior or Concomitant Medications (other than anticancer therapies)

All medications taken within 14 days before dosing and until the end of the study 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.

## 4.7 Exposure to Treatment

### 4.7.1 Extent of ADCT-301 Exposure

ADCT-301 exposure will be summarized for the safety analysis set by dose level. Duration of treatment, total number of cycles dosed, total dose received (in µg and µg/kg), and average dose per cycle (in µg and µg/kg) will be tabulated. When actual weight adjusted dose is needed, the last available weight before each infusion will be used. Dose administered at each infusion (µg) is calculated by concentrated IP volume (in mL)* 6 mg/mL *1000 or serially diluted IP volume (in mL)/50* 6 mg/mL *1000; for partial infusion, multiply by (1- volume of dosing solution not administered [in mL]/ 50 mL).

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

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 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.
- 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 Dose-limiting Toxicities (Part 1)

DLT data will be tabulated for the DLT-evaluable analysis set by dose group and type of DLT for Part 1 of the study. The patients enrolled prior to and post protocol amendment 4 will be presented in separate tables.

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 84 days (12 weeks) 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 84 days (12 weeks) 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 withdrawal
  - TEAE leading to ADCT-301 delay or reduction or interruption
  - TEAE with at least one infusion related reaction
- All TEAEs by PT, showing number (%) of patients with at least one TEAE, sorted by decreasing incidence of PTs
- 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 Grouped PT term, and Maximal CTCAE grade. These group terms include: for effusion/edema, hepatic, fatigue, skin/nail, pain.
- Summary of common 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 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 deaths 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, biochemistry, coagulation, and urinalysis up to the end of study visit 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 for hematology, biochemistry, coagulation. 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 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 ADCT-301) or AEs (subsequent to first administration of ADCT-301).

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

## 4.9 Efficacy Analyses

Disease assessment will be performed according to protocol. The endpoints described in this section use the investigator's evaluation according to the Lugano Classification criteria or Global Response Score Grading Scales for CTCL patients and clinical progression from End of Treatment (EOT)/Study disposition page.

Tumor assessment data (target lesions, non-target lesions, and new lesions, overall response, SUV max, Deauville score, etc.) for non-CTCL patients, and modified Severity-Weighted Assessment Tool (mSWAT) scores for CTCL patients will be listed. A separate listing will contain derived data for DOR, PFS, and 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 as assessed by investigators according to the Lugano Classification criteria or Global Response Score Grading Scales for CTCL patients before the start of subsequent anticancer therapy or procedure.

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. If a patient only has one valid disease assessment which is SD, and the assessment is within 35 days after the first dose, the overall response for this patient will be considered as NE.

The overall response rate and the corresponding 95% two-sided exact confidence interval at each dose level will be presented. Subgroup analysis may be provided if relevant.

Percent change from baseline in the sum of product of diameters (SPD) for target lesions for non-CTCL patients and mSWAT total score for CICL patients will be presented for available data in the efficacy analysis set by dose level. These data will also be displayed as a waterfall plot, with vertical bars representing the sorted values of best percent reduction for each patient.

Tumor response and lesion measurement (or mSWAT) will be listed by assessment visit.

### 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 first documented evidence of progressive disease (based on radiographic or clinical progression at EOT/end of study [EOS]) or death. Patients who had 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.

Duration of response will be estimated and displayed by dose levels for the efficacy analysis set using Kaplan-Meier methods (SAS® PROC LIFETEST). A Kaplan-Meier plot will be presented.

Subgroup analyses may be provided for disease subtype, disease stage, double/triple hit (yes/no), bulky disease (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 ADCT-301 (CR/PR), and other relevant variables.

### 4.9.3 Time to Response:

Time to response (TTR) for the subset of patients who achieve a CR or PR will be summarized using descriptive statistics.

### 4.9.4 Progression-free Survival

Progression-free survival is defined as the interval between the date of first dose and the date of disease progression (based on radiographic or clinical progression at EOT/EOS) or death, whichever occurs first. 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 cutoff, 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.

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

PFS will be estimated and displayed by dose levels for the efficacy analysis set using Kaplan-Meier methods (SAS® PROC LIFETEST). Patients who do not have a PFS event during or after the study will be censored. A Kaplan-Meier plot will be presented.

### 4.9.5 Overall Survival

Overall survival is defined as the interval between the date of 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 by dose levels for the efficacy analysis set using Kaplan-Meier methods (SAS® PROC LIFETEST). A Kaplan-Meier plot will be presented.

## 5 Interim Analyses

No formal interim analysis is planned.

# 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, if only day is missing, then the 1st of the month will be used; if only year is present, then Jan 1st 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 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 + 84 days, then the last dose date + 84 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 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: | |
|---|---|
| **ADA** | Anti-drug antibody |
| **AE** | Adverse event |
| **AI** | Accumulation index |
| **AUC** | Area under the concentration-time curve |
| **CD** | Cluster of differentiation |
| **CI** | Confidence interval |
| **CL** | Clearance |
| **$C_{max}$** | Maximum concentration |
| **CR** | Complete response |
| **CRM** | Continual reassessment method |
| **CRF** | Case report form |
| **CSR** | Clinical study report |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **CTCL** | Cutaneous T-cell lymphoma |
| **DAR** | Drug-to-antibody ratio |
| **DESC** | Dose Escalation Steering Committee |
| **DLT** | Dose-limiting toxicity |
| **DOR** | Duration of response |
| **ECG** | Electrocardiogram |
| **ECOG** | Eastern Cooperative Oncology Group |
| **EOS** | End of study |
| **EOT** | End of treatment |
| **HL** | Hodgkin lymphoma |
| **IP** | Investigational product |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **mSWAT** | modified Severity-Weighted Assessment Tool |
| **MTD** | Maximum tolerated dose |
| **NE** | Not evaluable |
| **NHL** | Non-Hodgkin lymphoma |

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|---|---|
| **ORR** | Overall response rate |
| **OS** | Overall survival |
| **PBD** | Pyrrolobenzodiazepine |
| **PD** | Pharmacodynamics, progressive disease |
| **PFS** | Progression-free survival |
| **PK** | Pharmacokinetic |
| **PR** | Partial response |
| **PT** | Preferred term |
| **QTc** | Corrected QT interval (ms) |
| **SAE** | Serious adverse event |
| **SAP** | Statistical analysis plan |
| **SD** | Stable disease |
| **SMQ** | Standardised MedDRA Query |
| **SOC** | System organ class |
| **SPD** | Sum of product of diameters |
| **std** | Standard deviation |
| **TEAE** | Treatment-emergent adverse event |
| **TFLs** | Tables, figures, and listings |
| **TTR** | Time to response |
| $\lambda_z$ | Terminal elimination phase rate constant |
| $T_{max}$ | Time to maximum concentration |
| $t_{1/2}$ | Terminal half-life |
| $V_{ss}$ | Volume of distribution at steady-state |
| $V_z$ | Volume of distribution |
| **WBC** | White blood cells |
| **WHO-DD** | World Health Organization-Drug Dictionary |