Protocol Number: ADCT-502-101

Official Title: A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-502 in Patients With Advanced Solid Tumors With HER2 Expression

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16.1.9 Documentation of Statistical Methods

ADCT-502-101 Statistical Analysis Plan FINAL version 1.0 July 5, 2018

Statistical Analysis Plan

A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-502 in Patients with Advanced Solid Tumors with HER2 Expression

PROTOCOL NO.: ADCT-502-101

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[redacted]

Confidentiality Statement

SAP Approval – Sponsor Signatory

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SAP accepted and approved by:

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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-502-101.

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

2 Study Objectives

2.1 Primary Objectives

- Evaluate safety, tolerability, and determine the MTD and/or RDE of single agent ADCT-502 in patients with advanced solid tumors with known HER2 status (IHC ≥1+ or HER2 amplified/mutated) (Part 1).

- Further evaluate safety and tolerability at the dose level determined in Part 1 in patients with advanced solid tumors including breast cancer, lung, gastroesophageal, and bladder cancer or a basket of other solid tumors known to express HER2 (HER2-high or HER2-low status confirmed prospectively for study entry) (Part 2).

2.2 Secondary Objectives

- Evaluate the preliminary antitumor activity of ADCT-502.
- Characterize the PK profile of ADCT-502.
- Determine the immunogenicity of ADCT-502.

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

Due to early termination of this trial, the dose-expansion portion (Part 2) of the study has not been performed. Therefore, only dose-escalation (Part 1) data has been analyzed and selected or modified analysis from the statistical section of the protocol will be performed. Please see details in each section.

4 Statistical methods

All analyses use SAS® version 9.4 or higher. Summary tables will be organized by each dose level for Part 1; if some dose levels have only a few subjects, then dose levels can 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 for Part 1, subject, and by visit within subject. Missing data will not be imputed, except via censoring in survival analyses and otherwise specified.

Unless otherwise noted, categorical data are presented using counts and percentages, with the number of subjects in the analysis set by treatment group as the denominator for percentages. Percentages are 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, are summarized using the number of observations (n), mean, standard deviation (std), median, minimum, and maximum. Minima and maxima are rounded to the precision of the original value, and means, medians, and confidence intervals (CIs) if presented are rounded to 1 decimal place greater than the precision of the original value. The std is 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 subjects who receive ADCT-502.

4.2 Subject Disposition

For the Safety analysis set, the number and percentage of subjects who discontinued study treatment and discontinued the study for each reason will be tabulated for each dose level.

Subject disposition data will be listed.

4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be tabulated for the Safety analysis set.
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)

- ECOG PS

Demographic and baseline characteristics data will be listed.

4.4 Pre-treatment disease characteristics and medical history

Cancer history will be listed for the Safety analysis set. Cancer history will include the following variables:

- Primary tumor type (Breast, Gastric, Esophageal/GEJ, etc.)
- Histology/ Genetics (where applicable)
- Date of initial diagnosis
- Initial staging (0, IA, IB, etc.)
- Date of most recent occurrence
- Stage at most recent occurrence

HER2 testing results and medical history data will be listed.

4.5 Prior anticancer therapy

The number and percent of patients who had prior anticancer surgery and radiotherapy will be summarized.

The number of lines of systemic therapies will be summarized. Number of lines is counted from the unique number of regimen number reported on the CRF.

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

4.6 Prior or Concomitant Medications (other than anticancer therapies)

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

Patient listing of all prior and concomitant medications will be provided. Pre-medication for dosing (for example, prophylaxis for hypersensitivity) will listed separately.

4.7 Exposure to Treatment

4.7.1 Extent of ADCT-502 Exposure

ADCT-502 exposure will be summarized for the Safety analysis set by dose level. The following items will be tabulated:

- Duration of treatment (in weeks) = (date of last dose – date of first dose +1)/7
- Number of infusions
- Number of patients treated by cycle
- Cumulative dose (in µg/kg) = sum of (dose administered at each infusion [µg] /last available weight[kg]),
  where dose administered at each infusion[µg]=Actual Volume [of IP, in mL]* 5 mg/mL *1000; if partial infusion, dose administered at each infusion[µg]= (1- volume of dosing

solution not administered [in mL]/ 50 mL) * (Actual Volume [of IP, in mL]* 5 mg/mL *1000)

Exposure data and infusion details will be listed together.

4.7.2 Subsequent Anticancer Therapy or Procedure

Subjects' subsequent anticancer therapy or procedure including systemic therapy, radiation, or other, along with the start date of subsequent anticancer therapy or procedure will be collected and listed.

4.8 Safety Analyses

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 of the study drug
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.
- If relevant, selected safety analyses may be summarized by age, sex, racial subgroups and any pertinent subgroups.
- The toxicity grade will be taken into account in the summary. For subjects with multiple occurrences of the same event, the maximum grade is used. If a subject has both missing and non-missing severity grades for TEAEs within the same PT, the missing severity of the TEAE will be treated as the lower severity grade (ie, the subject will be counted under the non-missing severity grade). If there is non-missing severity grade, the subject will be counted under the non-missing severity grade.

4.8.1 Dose-limiting Toxicities

DLT data will be listed.

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 the treatment-emergent adverse events (TEAEs). A TEAE is defined as an adverse event that occurs or worsens in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study.

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. For example, if only the day of the AE onset is missing, the year and month will be compared

with the first dose and 30 days after the last dose of study drug. And if the month and day of the AE onset are missing, the year will be compared with the first dose and 30 days after the last dose of study drug. The algorithm for imputing TEAE will be conservative and will classify an AE as a treatment emergent unless there is definitive information to determine it is non-TEAEs (pre- or post-treatment).

Analysis of all TEAE(s):
The following TEAE summaries will be generated for the safety analysis set.

- Overview of TEAEs, summarizing number of TEAE and number (%) of subjects with any
  - TEAE
  - Related TEAE (including possibly related, probably related, or related)
  - Any ≥ grade 3 TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
  - TEAE leading to ADCT-502 delay or reduction or interruption
  - TEAE with at least one infusion related reaction
- All TEAEs by PT, showing number (%) of subjects with at least one TEAE, sorted by decreasing incidence of PTs
- All TEAEs by SOC and PT, showing number (%) of subjects 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 AE tables, unless otherwise specified
- All TEAEs by SOC, PT and Maximum CTCAE grade
- All ≥ grade 3 TEAEs by SOC, PT and Maximum CTCAE grade
- All related TEAEs by SOC, PT and Maximum CTCAE grade (including possibly related, probably related, or related)
- All Serious TEAEs by SOC and PT by SOC, PT and Maximum CTCAE grade

All AEs (including non-TEAEs), all TEAEs leading to treatment withdrawal, all TEAEs leading to dose reduction, all TEAEs leading to dose delay, infusion related reaction and all TEAEs with fatal outcome will be listed.

4.8.2.2 Deaths

Reasons for deaths will be summarized separately for 1) all deaths, 2) death on therapy or within 30 days after last dose of study drug.

4.8.3 Laboratory Data

Laboratory data of hematology, chemistry, and coagulation will be reported in SI units.

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.

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

4.8.4 Electrocardiogram

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

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

4.8.5 Vital Signs

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

4.8.6 ECOG Performance Status

All ECOG data will be listed.

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) will be listed.

4.10 Pharmacokinetic Analyses and Pharmacodynamic Analyses

Pharmacokinetic and biomarker data will be listed in the CSR Appendices.

5 Interim Analyses

Due to the early termination of the trial, interim analyses were not performed.

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 date of death, 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 a date of death and is before the last date that the subject is known to be alive, the latter date will be used.

Handling of missing relationship to investigational product of AEs
If the assessment of the relationship to investigational product is missing, then the relationship to investigational product has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, 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 on 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 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 visit
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.