Statistical Analysis Plan I5B-JE-JGDK Version 1

A Phase 1 Study of Olaratumab in Japanese Patients with Advanced Soft Tissue Sarcoma or Advanced Solid Tumors

NCT02377752

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1. Statistical Analysis Plan: I5B-JE-JGDK: A Phase 1 Study of Olaratumab in Japanese Patients with Advanced Soft Tissue Sarcoma or Advanced Solid Tumors

Olaratumab (LY3012207)

This Phase 1 study is a multicenter, nonrandomized, open–label study to evaluate intravenous olaratumab in combination with doxorubicin in Japanese patients with advanced soft tissue sarcoma or advanced solid tumors (Part A), and intravenous olaratumab alone in Japanese patients with advanced solid tumors (Part B).

Eli Lilly Japan K.K.
Kobe, Hyogo Japan

Protocol I5B-JE-JGDK
Phase 1

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 04-Mar-2015 GMT

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3. Revision History

SAP Version 1 was approved prior to the first patient visit. This version of SAP was based on the protocol approved on December 9, 2014.

4. Study Objectives

4.1. Primary Objective

The study is divided into two parts:

The primary objective of Part A is to evaluate the safety and tolerability of olaratumab in combination with doxorubicin in Japanese patients with advanced solid tumors, especially soft tissue sarcoma (STS).

The primary objective of Part B is to evaluate the pharmacokinetics (PK) profile of olaratumab in Japanese patients with advanced solid tumors.

4.2. Secondary Objectives

The secondary objectives of Part A are:

- To evaluate the PK of olaratumab and doxorubicin
- To evaluate the immunogenicity of olaratumab
- To document any antitumor activity of olaratumab in combination with doxorubicin

The secondary objectives of Part B are:

- To evaluate the safety and tolerability of olaratumab
- To evaluate the immunogenicity of olaratumab
- To document any antitumor activity of olaratumab

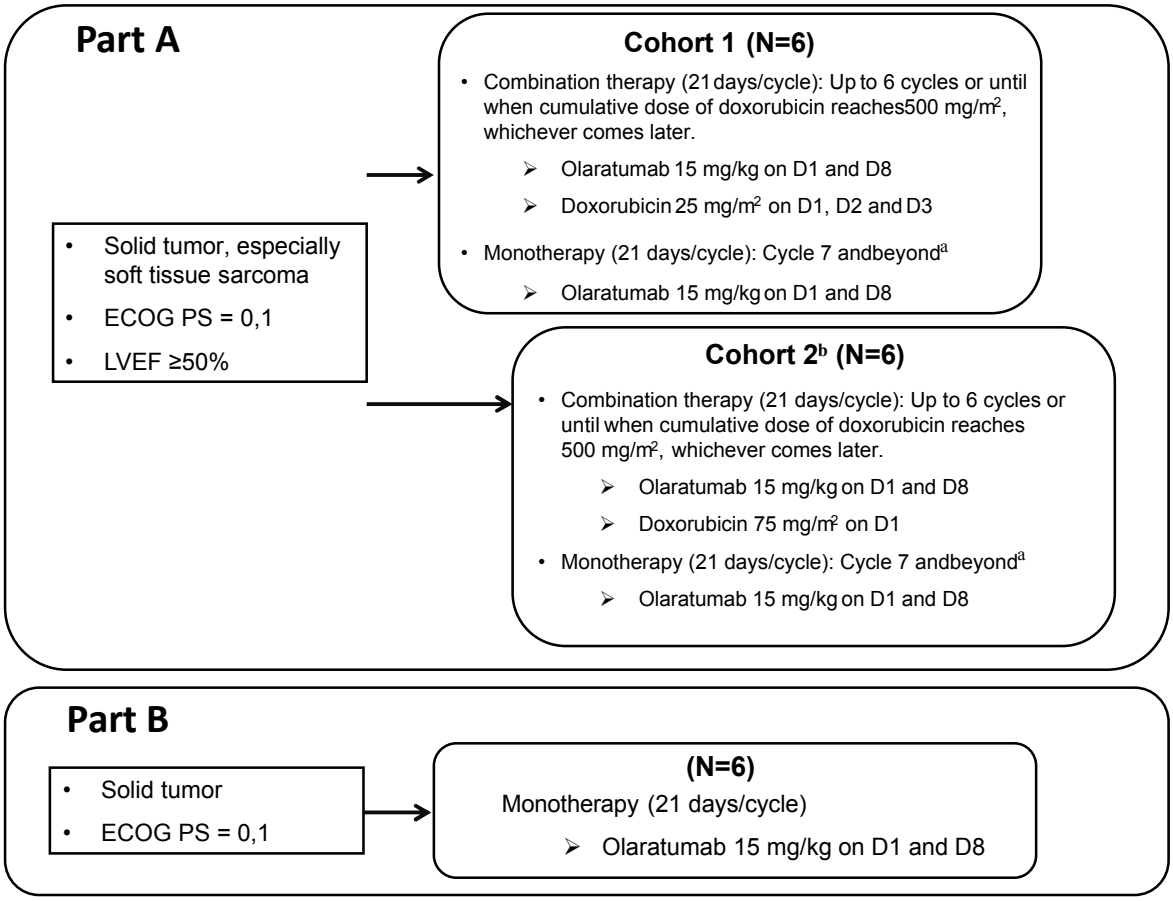
4.3. Exploratory Objectives

The exploratory objective of Part A and Part B is to evaluate potentially relevant biomarkers related to the mechanism of olaratumab, the PDGF signaling pathway, and the pathobiology of cancer.

5. Study Design

5.1. Summary of Study Design

This is a multicenter, nonrandomized, open-label, Phase 1 study. The study is divided into 2 parts, Part A and Part B. Part A and Part B will be conducted in parallel. The DLT evaluation of Cohort 1 and Cohort 2 in Part A will be performed independently. The study design is summarized in Figure JGDK.5.1.



Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance score; D= day; N = number of patients; LVEF = left ventricular ejection fraction

a For patients whose cumulative dose of doxorubicin does not reach 500 mg/m2 during the first 6 cycles due to dose reductions or omissions, doxorubicin can be administrated up to 500 mg/m2 on Cycle 7 and beyond, at the discretion of the investigator.

b Refer to Section 7.2.1.4 in the protocol for the timing to open Cohort 2.

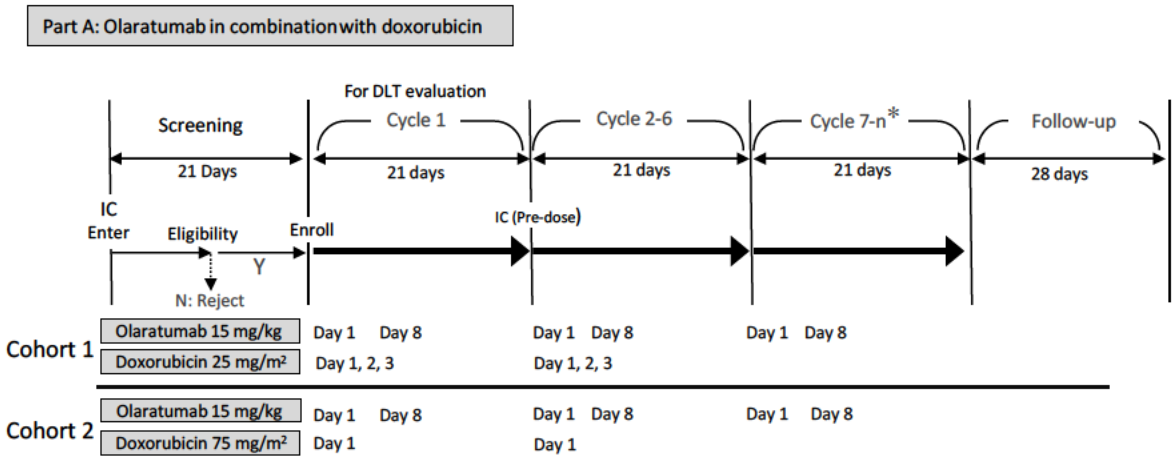
Figure JGDK.5.1. Illustration of study design for Protocol I5B-JE-JGDK.

Part A is designed to evaluate the safety and tolerability of olaratumab in combination with doxorubicin in Japanese patients with advanced solid tumors, especially advanced STS.

Part A consists of 2 cohorts (Figure JGDK.5.1). At least 6 patients will be assigned to Cohort 1. Similarly, at least 6 patients will be assigned to Cohort 2:

- Cohort 1: 15 mg/kg of olaratumab on Day 1 and Day 8, and 25 mg/m^2 of doxorubicin on Day 1, Day 2, and Day 3 up to 6 cycles or until when cumulative dose of doxorubicin reaches 500 mg/m2, whichever comes later, every 21 day-cycle.
- Cohort 2: 15 mg/kg of olaratumab on Day 1 and Day 8, and 75 mg/m2 of doxorubicin on Day 1 up to 6 cycles or a cumulative dose of doxorubicin reaches 500 mg/m2, whichever comes later, every 21 day-cycle.

An overview of the study design for Part A is shown in Figure JGDK.5.2.

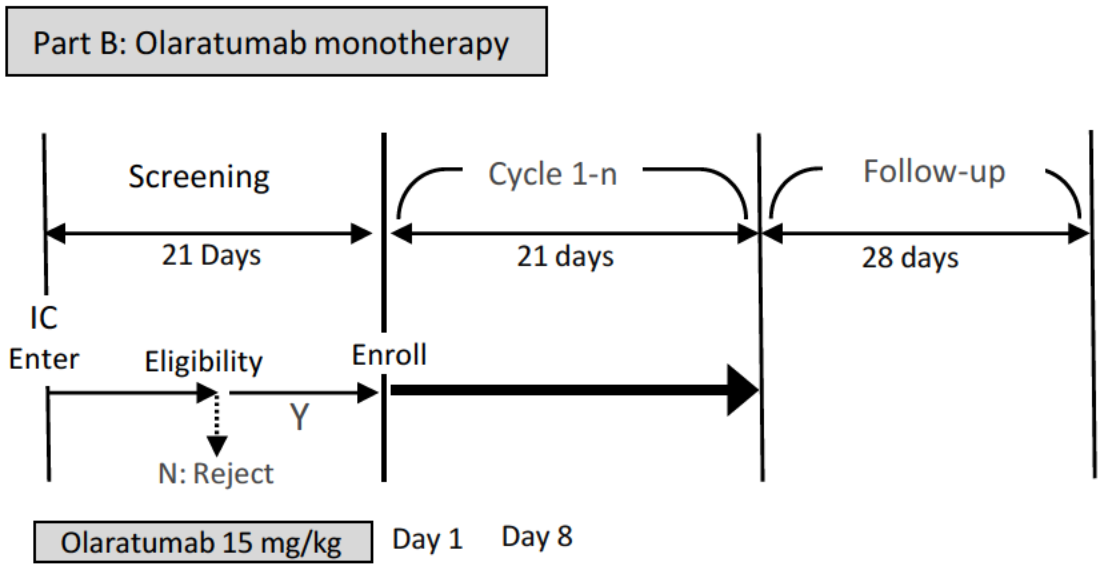


Abbreviations: DLT = dose-limiting toxicity; IC = informed consent; n = number; N = no; Y = yes.

Figure JGDK.5.2. Illustration of study schedule in Part A.

Part B is designed to evaluate the PK profile of olaratumab monotherapy in Japanese patients with advanced solid tumors. This part consists of 1 dose regimen (Figure JGDK.5.1). At least 6 patients will be assigned to receive olaratumab monotherapy treatment: 15 mg/kg of olaratumab on Day 1 and Day 8 every 21 day-cycle.

An overview of the study design for Part B is shown in Figure JGDK.5.3.



Abbreviations: IC = informed consent; n = number; N= no; Y = yes.

Figure JGDK.5.3. Illustration of study schedule in Part B.

5.2. Determination of Sample Size

The study design requires 6 patients at each cohort in Part A for assessing the DLTs observed. This sample size was not based on a statistical power calculation.

In Part B, 6 patients are needed to evaluate PK and safety profile of olaratumab monotherapy. This sample size was estimated empirically based on other Phase 1 oncology studies. The estimation precision of PK parameters in this study is expected to be similar to that in previous studies (Study JGDC and Study JGDF), although there are no inter-subject variability data on a new assay.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive olaratumab in combination with doxorubicin (Cohort 1 or Cohort 2 in Part A) or olaratumab monotherapy (Part B), at the investigator's discretion. Before each patient's enrollment into the study, an eligibility check must be conducted at the investigational site to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor or designee will confirm the dose and identification number assignment for each patient. Initiation of Cohort 2 refers to Section 7.2.1.4 in the protocol.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly Japan K.K. Pharmacokinetic analyses will be planned separately from this SAP.

6.1.1. Analysis Populations

The Analysis populations are defined as follows:

- Enrolled Population: Anyone who signed the informed consent and who was confirmed to be eligible and have been assigned to a treatment will be included in this population.
- FAS Population: All enrolled patients who received any amount of study drugs (either olaratumab or doxorubicin) will be included in the FAS Population. The FAS Population is based on the intent-to-treat principle and will be used for the analysis of baseline characteristics, efficacy data, safety data, and biomarkers.
- DLT Population: All enrolled patients who will complete Cycle 1 (initial 21-day treatment period), or who will discontinue due to DLT during Cycle 1, will be included in the DLT Population. Patients who will discontinue during Cycle 1 due to other reasons than DLT will be excluded from the DLT Population. The DLT Population will be used for summarizing a proportion of patients with DLT.

6.1.2. Data Analyses

All summary tables, figures and data listings will be produced by using the statistical packages SAS version 9.2 (or a more recent version).

Data will be summarized by part and cohort.

Baseline is defined as the last non-missing observation prior to the time of the first infusion of the study drug, unless otherwise stated. Observations on the same day of the first infusion of the study drug for which the time (hours and/or minutes) is missing and, according to the study schedule, to be collected prior to treatment, will also be considered baseline.

Descriptive statistics will include counts and percentages for categorical variables, and number of observations, mean, standard deviation, median, minimum and maximum for continuous variables unless otherwise stated.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

The following data handling conventions will be applied in the analyses.

Study Day: Study day indicates the number of days the patient has been receiving study treatment. It is calculated as (assessment date)-(date of the first infusion of the study drug)+1 days if the assessment is done on or after the first infusion day of the study drug. If the assessment is done prior to the first infusion day of the study drug, study day will be calculated as (assessment date)-(date of the first infusion of the study drug). Date of the first infusion of the study drug is defined as study day 1.

6.2. Adjustments for Covariates

Adjustments for covariates will not be performed in any analysis of this study.

6.3. Handling of Dropouts or Missing Data

The birth date will be imputed by assigning month and day with July 1st to calculate age.

The following rules will be used for the imputation of incomplete initial pathological diagnosis date for the purpose of deriving duration of disease:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, July 1st will be used to replace the missing information.

Patient data listings will show partial dates without applying the above imputation rules.

In other measurement for efficacy and safety variables, the imputation for missing values will not be performed.

6.4. Multiple Comparisons/Multiplicity

No adjustments for multiplicity will be made in this study.

6.5. Use of an "Efficacy Subset" of Patients

No particular efficacy subsets will bedefined in this study.

6.6. Patient Disposition

Frequency distributions of patients in the Enrolled population, the FAS population or the DLT population (Part A only), will be summarized by part and cohort.

Summary of the screen failure and reason will be provided.

For the Enrolled population, frequency distributions of patients with a specific value for disposition (i.e. completion or discontinuation) will be summarized by part and cohort. Also, frequency distributions of patients who discontinued will also be summarized by part, cohort and reason for discontinuation.

Listing of patient disposition and of primary reason for discontinuation will be provided for the Enrolled population.

6.7. Patient Characteristics

For the FAS population, demographic and baseline disease characteristics will be summarized by part and cohort.

Demographic characteristics are as follows:

age (years), age categories (<65 years vs. ≥65 years), gender, race, height (cm), weight (kg), body surface area (m^2) and Body Mass Index (kg/m^2),

where body surface area is calculated using DuBois method; $0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$ and Body Mass Index = weight / $(\text{height} / 100)^2$.

Baseline disease characteristics are as follows:

Alcohol use, Tobacco use, Eastern Cooperative Oncology Group (ECOG) performance status, initial pathological diagnosis (or cancer type), disease stage at diagnosis, TNM at diagnosis, sites of Metastatic Disease, and duration of disease (months from the first confirmation of cancer to the first infusion)

In addition, prior anticancer treatments or surgery (radiotherapy, surgical procedure and systemic therapy), historical conditions and pre-existing conditions will be summarized by part and cohort.

Listings of demographic and baseline disease characteristics, of historical conditions and of pre-existing conditions also will be provided for the FAS population.

6.8. Treatment Compliance

Details are described in Section 6.11.1.

6.9. Concomitant Therapy

Concomitant therapies will be categorized using World Health Organization Drug dictionary.

Granulocyte colony stimulating factors (G-CSF) and other concomitant therapies will be summarized by part and cohort for the FAS population, respectively. Listings of G-CSF, other concomitant therapies and transfusion will be provided.

6.10. Efficacy Analyses

6.10.1. Primary Outcomes and Methodology

The objective response rate (ORR) and the disease control rate (DCR) will be primarily evaluated.

The ORR will be calculated as the number of patients who achieve a best overall response (BOR) of complete response (CR) or partial response (PR) using the investigator response assessments, divided by the total number of patients.

The DCR will be similarly calculated as the number of patients who achieve a BOR of CR, PR or stable disease (SD) using the investigator response assessments, divided by the total number of patients.

Patients who do not have a tumor response assessment for any reason are considered as not evaluable (NE) and are included in the denominator when calculating these response rates.

It should be noted that the BOR is determined from the sequence of cycle responses (i.e. responses obtained from the start of the study treatment until the study discontinuation). CR or PR will be claimed only if the criteria for each are met at a subsequent time point (at least 4

weeks). In the case of SD, measurements must have met the SD criteria at least once, at least 6 weeks after the first infusion of the study drug.

For the FAS population, the ORR, DCR and BOR will be summarized by part and cohort with 95% CI using the Wilson formula (Altman et al. 2000; Wilson 1927).

6.10.2. Other Secondary Efficacy Analyses

6.10.2.1. Tumor assessment including tumor size evaluation

For the FAS population, the waterfall plot of the best percentage change in tumor size will be provided. Also, line plot of percent change from baseline in tumor size may also be provided. Percent change from baseline in tumor size is calculated as follows and the smaller means better:

- Percent change from baseline = $(SUM_{Postbaseline} - SUM_{Baseline}) \times 100 / SUM_{Baseline}$,
- SUM = Longest diameter for extranodal lesions + short axis diameter for nodal lesions ,

where SUM is calculated only when all target/measurable lesions observed at baseline are measured.

Listings will be prepared presenting relevant information on response (response on target lesions including the percentage changes, response on non-target lesions, new lesions and overall response for each tumor assessment) for the FAS population.

6.10.2.2. Other efficacy outcomes

The overall survival (OS), the progression-free survival (PFS) and the duration of response (DOR) will be evaluated using the Kaplan-Meier method as described bellow.

For the FAS population, a listing of efficacy outcomes (i.e. BOR, OS, PFS and DOR) will be provided.

6.10.2.2.1. Overall Survival

The OS is defined as the time from the date of the first infusion of the study drug to the date of death from any cause. If a patient is not known to have died on or before the date of data cut-off, the OS will be censored on the last date (on or before the cut-off date) the patient was known to be alive.

For the FAS population, the number of events and the OS will be summarized by part and cohort.

6.10.2.2.2. Progression-free Survival

The PFS is defined as the time from the date of the first infusion of the study drug to the date of objectively determined PD or death from any cause, whichever is first. Censoring rules are described in Table JGDK.6.1.

Table JGDK.6.1. Censoring rules

Situation	Date of Progression or Censoring	Outcome

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Date of the first infusion of the study drug	Censored
Progression documented between scheduled visits	Earliest of the following dates: • Date of radiological assessment showing new lesion (if progression is based on new lesion) • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason	Date of last radiological assessment of measured lesions	Censored
New anticancer treatment started	Date of last radiological assessment of measured lesions	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions	Censored

For the FAS population, the number of events and the PFS will be summarized by part and cohort.

6.10.2.2.3. Duration of Response

The DOR is derived from data of patients who achieved response (CR or PR) and is defined as the time from the date of response achievement (the first observation of response before confirmation) to the date of objectively determined PD.

For the responders in the FAS population, the number of events and the DOR will be summarized by part and cohort.

6.11. Safety Analyses

6.11.1. Extent of Exposure

The exposure data of the study drug (i.e. number of cycles, number of infusions, duration of treatment, cumulative dose, dose intensity and relative dose intensity) will be listed for the FAS population.

These data are defined as follows:

- Number of cycles = Maximum cycle given per patient
- Number of infusions for olaratumab = Total number of infusions
- Duration of treatment for olaratumab (weeks) = (Date of Day 1 of last cycle + 21 – Date of Cycle 1 Day 1) / 7
- Cumulative dose for olaratumab (mg/kg) = Sum of (total doses administered [mg] / baseline weight [kg] or available weight [kg] prior to each infusion in case of more than 10% change from baseline)
- Dose intensity for olaratumab (mg/kg/week) = (Cumulative dose for olaratumab) / (Duration of treatment for olaratumab)
- Relative dose intensity for olaratumab (%) = (Dose intensity) / (Planned weekly dose intensity) × 100,

  where planned weekly dose intensity (mg/kg/week) = 15 mg/kg × 2 intravenous administrations / 3 weeks = 10 mg/kg/week.

[Part A only]

- Number of infusions for doxorubicin = Total number of infusions
- Duration of treatment for doxorubicin (weeks) = (Date of Day 1 of last cycle + 21 – Date of Cycle 1 Day 1) / 7
- Cumulative dose for doxorubicin (mg/m^2) = Sum of (total doses administered [mg] / baseline body surface area [m^2] or available body surface area [m^2] prior to each infusion in case of more than 10% change from baseline)
- Dose intensity for doxorubicin (mg/m^2/week)
- Relative dose intensity for doxorubicin (%), where planned weekly dose intensity is 25 mg/m^2/week.

A listing of study drug exposures will be provided. Also, details of treatment delays, treatment omissions, treatment reductions, and treatment interruptions will be listed.

6.11.2. Dose-limiting toxicity

In Part A, frequency distributions of patients who experienced any DLTs during Cycle 1 will be summarized by cohort using the DLT population. A listing of DLTs will be produced.

6.11.3. Adverse Events

The available latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be utilized for categorizing to System Organ Class (SOC) and Preferred Term (PT). National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be referred for identifying grade and/or relevant event term.

Treatment-emergent adverse events (TEAEs) are defined as events that first occurred or worsened in severity after/on the first infusion of the study drug.

Adverse events will be summarized by CTCAE term and MedDRA term.

The summary by MedDRA term would be primary for the study report. For the FAS population, the following summaries will be provided by part and cohort:

- An overview of AEs
- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT
- Summary of TEAEs by SOC, PT and Maximum Grade

These analyses will be repeated for AEs related to study drug. Also, a listing of AEs will be prepared.

Using CTCAE term, TEAEs by CTCAE SOC, CTCAE Term and Maximum Grade will be summarized.

6.11.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

All deaths that occur after the first infusion of the study drug together with primary cause of death will be listed based on the FAS population.

The following items for AEs leading to death will be provided:

- Summary of AEs leading to death by PT
- Summary of AEs leading to death related to study drug by PT
- Listing of AEs leading to death

For the FAS population, the following items for treatment emergent SAEs will be generated:

- Summary of SAEs by PT
- Summary of SAEs related to study drug by PT

- Listing of SAEs

As other significant AEs, the following items will be provided:

- Summary of AEs leading to olaratumab discontinuation by PT
- Summary of AEs leading to doxorubicin discontinuation by PT in Part A
- Summary of AEs leading to olaratumab delay/omission/reduction/interruption by PT
- Summary of AEs leading to doxorubicin delay/omission/reduction/interruption by PT in Part A

The above four items will be repeated for AEs related to study drug. Also, a listing of AEs leading to study drug discontinuation (olaratumab or doxorubicin in Part A and olaratumab in Part B) will be prepared.

6.11.5. Clinical Laboratory Evaluation

Laboratory results will be graded according to NCI-CTCAE Version 4.03, when applicable. Grading will be purely based on the numeric results and no investigator's assessment will be considered. Laboratory values will be converted to standard units. The laboratory results not corresponding to terms in NCI-CTCAE Version 4.03 will not be graded.

For the FAS population, shift tables of graded laboratory parameters from baseline to the worst value on the study will be generated by part and cohort.

For the FAS population, the laboratory results will be presented in a listing with a flag for values outside of the laboratory normal range. Laboratory reference ranges will be listed. Also, a line plot of the laboratory results will also be provided.

6.11.6. Vital Signs and Other Physical Findings

Listings of vital signs, physical examinations, and Eastern Cooperative Oncology Group performance status will be provided for the FAS population.

6.11.7. Electrocardiograms and Echocardiography

Three replicate electrocardiograms (ECGs) will be obtained at each time point. All parameters will be fully read at the first measurement and only RR interval, QT interval and heart rate will be read at the second and third measurements. The average of them will be used for analysis, if applicable. If missing values exist, the average will be derived without the missing values.

QT analyses will be performed with Bazett and Fridericia correction (QTcB and QTcF), respectively. QTcB and QTcF based on each read are calculated as follows:

- $QTcB = QT / RR^{1/2}$
- $QTcF = QT / RR^{1/3}$

6.11.7.1. PK matched ECG Data

The change will be calculated using the time-matched baseline for Cycle 1. Frequency distributions of patients who fulfill the following criteria will be summarized by part and cohort for the FAS population.

- QTc values: >450, >480, and >500 msec
- The change from baseline in QTc: >30 and >60 msec

Line plot of QTc values and their time-matched changes from baseline will be provided based on the FAS population.

Also, the time-matched changes will be plotted against the blood concentration of olaratumab by part and cohort for the FAS population. A linear regression model will be used to investigate the relationship between the QTc changes and the concentration of olaratumab and the fitted model and the 90% confidential interval will also be shown in the plot. It should be noted that, in Cohort 2 of Part A, ECG data at the sampling time of '0.5 h ± 5 min Postinfusion of doxorubicin' in both Cycle 1 and Cycle 3 will be excluded to avoid the effect of doxorubicin. Especially when olaratumab and doxorubicin will be administered on Day 8 in Cycle 3, additional sampling times ('1 h ± 10 min Postinfusion of olaratumab', '48 ± 6 h Postinfusion of olaratumab', '72 ± 6 h Postinfusion of olaratumab' and '168 ± 8 h Postinfusion of olaratumab') will be excluded.

ECG data including QTc values and their time-matched changes from baseline will be listed. A listing of blood concentration of olaratumab will be provided.

6.11.7.2. Echocardiography

Normal/Abnormal results of echocardiography will be listed.

6.12. Biomarker Analyses

For the FAS population, descriptive statistics for biomarkers obtained from blood samples will be provided by part and cohort. Also, listings of all biomarkers will be prepared.

6.13. Subgroup Analyses

Subgroup analyses are not preplanned, but some subgroup analyses may be conducted, if needed.

6.14. Protocol Deviations

Important protocol deviations will be described in a separate document and the information will be provided by the Clinical Trial Manager to the Statistician in an Excel file. The Statistician will convert the Excel file to a SAS dataset, and store both of them in SAS Drug Development (SDD) for the use of analysis.

A listing of protocol deviations will be provided with the Enrolled population.

6.15. Interim Analyses and Data Monitoring

Interim access to safety data will be performed during the study for safety review.

In this study, preplanned interim analysis will be conducted after completing Cycle 1 and the DLT evaluation in Cohort 2 of Part A. Interim safety analyses will be conducted for the decision of joining future global phase 3 studies. Deatils of the safety analyses will refer to Section 6.11.

Additional interim analyses may be conducted, if needed.

6.16. Annual Report Analyses

The datasets including the following tables and listings will be generated for the Development Safety Update Report (DSUR) reports based on the resource document 'Statistical Guidance and Mock Tables for the Development Safety Update Report (DSUR) and Periodic Safety Update Report (PSUR) / Periodic Benefit Risk Evaluation Report (PBRER)':

- Summary of patients demographics by age and gender
- Summary of patients demographics by racial groups
- Summary of cumulative patient exposure information
- Listing of patients who died
- Listing of patients who discontinued study rugs or study due to AEs

Investigator's Brochure (IB) related analyses may be conducted at the same time as the DSUR analyses if applicable.

6.17. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by part and cohort, by MedDRA term.

- An adverse event is considered 'Serious' whether or not it is a TEAE.
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term, part and cohort, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in every part and cohort may not be included if a 5% threshold is chosen (5% is the minimum threshold).

- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. References

Altman DG, Bryant TN, Gardner MJ, Machin, D. (Eds) Statistics with Confidence: confidence intervals and statistical guidelines, 2nd ed. London: British Medical Journal; 2000.

Wilson EB. Probable inference, the law of succession, and statistical inference. *J Am Stat Assoc*.1927;22:209-212.

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