Janssen Research & Development *

Statistical Analysis Plan

An Open Label, Phase 2 Study to Assess the Clinical Efficacy and Safety of Daratumumab in Patients With Relapsed or Refractory Natural Killer/ T-Cell Lymphoma (NKTCL), Nasal Type

Protocol 54767414NKT2001

JNJ 54767414 (Daratumumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

AMENDMENT HISTORY

ABBREVIATIONS

AE	adverse event
TEAE	Treatment-emergent adverse event
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	electronic case report form
ORR	Overall response rate
CR	Complete response
PR	Partial response
PFS	Progression free survival
OS	Overall survival
DoR	Duration of response
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analysis.

1.1. Trial Objectives

Primary Objectives

The primary objective of the study is to evaluate the efficacy of daratumumab in subjects with NKTCL by ORR including complete response (CR) and partial response (PR) based on a blinded independent central review (BICR) per Revised Criteria for Response Assessment of Hodgkin and non-Hodgkin Lymphoma: LUGANO classification.

Secondary Objectives

- To evaluate the efficacy of daratumumab in NKTCL by CR rate, progression free survival (PFS), duration of response (DoR), time to response based on a BICR, and OS
- To evaluate safety and tolerability
- To evaluate PK and immunogenicity

1.2. Trial Design

This is an open-label, single arm, multicenter, phase 2 study to evaluate the efficacy and safety of daratumumab monotherapy in subjects with relapsed and refractory extranodal NKTCL, nasal type. Each cycle will consist of 28 days.

The study is designed as Simon's 2-stage with an interim analysis conducted after approximately 15 subjects who have received at least one dose of study drug and had at least one post-baseline disease evaluation. The purpose of the interim analysis is to evaluate efficacy and safety data in stage 1 and facilitate the early preparation for the next step of development. The totality of efficacy (ORR), safety, and biomarker data will be analyzed at the interim. Enrollment may be put on hold pending the decision of interim analysis unless the decision is clear based on available data before IA. The study may be terminated if the futility criteria are met and supported by totality of data. In addition, at interim, the association between daratumumab activity and CD38 expression level will be explored. A population enrichment strategy may be applied after the interim analysis if such a strategy is supported by emerging data. If the study proceeds to the second stage, the total sample size will be 32 with 2 stages combined. Following that, additional patients (ie, up to 35 patients) may be enrolled in an expansion phase to confirm the clinical response rate of daratumumab, if supported by emerging data.

1.3. Statistical Hypotheses for Trial Objectives

It is hypothesized that treatment with daratumumab results in an ORR of >30% versus a null hypothesis of at most 15% in relapsed or refractory NKTCL, nasal type subjects who failed (relapsed or refractory after achieving complete or partial remission) at least one line of chemotherapy.

1.4. Sample Size Justification

The study is designed to evaluate the effect of daratumumab on ORR utilizing Simon's 2-stage design. The null hypothesis is that ORR is at most 15%, and the alternative hypothesis is that ORR is at least 30%. With a 1-sided alpha of 10%, and a power of 78%, a total of 32 subjects are to be enrolled into the study. The stage 1 analysis is to be performed when approximately 15 subjects are enrolled in the study and have sufficient data for response evaluation. The futility criterion of ORR is defined as when at most 1 out of 15 subjects have achieved CR/ PR after stage 1 according to Simon's 2-stage design. Future enrollment into stage 2 may be terminated if it is determined during the first stage that the treatment group is considered as ineffective or not well tolerated. If study proceeds to second stage with a total of 32 subjects with 2 stages combined, the null hypothesis is to be rejected if 8 or more responders are observed.

To achieve 1-sided alpha of 2.5% and a power of 80%, additional patients (ie, up to 35 patients) may be enrolled in an expansion phase to confirm the clinical response rate of daratumumab if supported by emerging data.

1.5. Randomization and Blinding

Not applicable.

2. GENERAL ANALYSIS DEFINITIONS

Unless specifically stated, the summary will be analyzed and presented by total subjects combined.

The analyses for continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, and range). Categorical variables will be presented with frequency, percentage, or 95% CI if appropriate. Time to event variables will be summarized by descriptive Kaplan-Meier statistics, or 95% CI if appropriate.

2.1. Visit Windows

Any analysis that uses time-to-event data will be based on the exact determination of time from first dose of Dara to the date of the event. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus 1 day will be used.

For analyses of data by cycle, if data are collected by date (ie, AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study treatment administration data. The start date of a particular cycle is defined as the date of the first Dara, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or the minimum of last study treatment date plus 30 days or subsequent anticancer therapy minus 1 day, if the end of treatment visit date is not available.

In general, if data (e.g., laboratory and vital sign, etc.) are collected by cycle, the nominal cycle will be used to summarize data.

2.2. Pooling Algorithm for Analysis Centers

All data will be pooled together regardless of analysis centers.

2.3. Study Treatment and Study Drug

In this study, Study treatment/Study drug refers daratumumab.

2.4. Study Treatment Dosing Date

Study treatment dosing date is the date on which a subject actually received study treatment (partial or complete) and will be recorded in the study treatment administration dataset. The first study treatment date is defined as the earliest date of non-zero dose of daratumumab. The last study treatment date is defined as the latest date of non-zero dose of the daratumumab.

2.5. Treatment Cycle

A subject is considered as treated in a cycle if he/she receives any non-zero dose of daratumumab in that cycle.

2.6. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the date of first study agent administration (including time if available). If the first study treatment date is missing, the corresponding visit date should be used.

2.7. Imputation of Partial Dates

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purpose, missing or partial dates in adverse event (AE onset date; AE end date), concomitant therapies (start date; end date), prior therapy (start date; end date), initial disease diagnosis date and start date of subsequent anticancer therapy will be imputed.

2.7.1. Missing/Partial Adverse Event Onset Date

If the onset date of an adverse event is missing partially, the following imputation rules will be used.

- When month and year are present and the day is missing,
  - If the onset month and year are the same as the month and year of first study treatment, the day of first study treatment or the day-component of the AE end date (possibly imputed) is imputed, whichever is earlier
  - If the onset month and year are not the same as the month and year of first study treatment, then the first day of the month is imputed
- When only a year is present or no components of the onset date are present,
  - If the onset year is the same as the year of first study treatment. If AE end date is available and is prior to first study treatment, the day and month of AE end date are imputed. Otherwise, the day and month of first study treatment are imputed
  - If the onset year is different from the year of first study treatment, the 1st of January is imputed
- If the onset date is completely missing, the date of first study treatment is imputed as the onset date.

No imputation will be done for partial or missing AE onset time.

If AE onset date needs imputation, but the AE onset time is available, the AE onset time will be dropped in the imputed AE onset date/time variable.

2.7.2. Missing/Partial Adverse Event End Date

If the end date of an adverse event is missing partially, the following imputation rules will be used.

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.
- If the imputed date is later than the date of death (if available), the date of death will be used as the imputed date instead.

No imputation will be done for partial or missing AE end time.

If AE end date needs imputation, but the AE end time is available, the AE end time will be dropped in the imputed AE end date/time variable.

2.7.3. Partial Concomitant Medication Start/End Date

In case of partially missing concomitant medication start/end dates, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed.

- If only the day is missing, the 15th day of the month will be used
- If both the day and month are missing, the 30th of June will be used

If the medication was taken prior to study start, and the imputed start date is after first treatment date, further adjust the imputed start date as the day prior to first dosing date; if the medication was taken after study start, and the imputed start date is prior to first dosing date, further adjust the imputed start date as first dosing date.

After applying above adjusting method, if it results in medication start date that is after medication end date, the medication start date needs re-adjustment as follows:
If medication start date was imputed then adjust as follows:

- Impute the same month and year as mediation end date if the non-imputed date parts are the same
- Impute the first day of the month as medication start day

If medication end date was imputed then re-adjust medication end date to be the same as the medication start date if the corresponding non-imputed date parts match the medication start date.

Also adjust the imputed medication end date so that it is on or after first dosing date.

2.7.4. Partial Initial Disease Diagnosis Date

For partially missing initial diagnosis dates, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed.

- If only the day is missing:
  - If month and year of start of 1st line of prior therapy are the same year and month of diagnosis, and day of start of 1st line of prior therapy is available, impute day with day of start of 1st line of prior therapy;
  - Otherwise, impute day with 15.

- If both the day and month are missing:
  - If year of diagnosis is the same as year of start of 1st line of prior therapy, and month information is available for start of the 1st line of prior therapy;
    - Impute month with month of start of 1st line of prior therapy;
    - If day of start of 1st line of prior therapy is available, impute diagnosis day with day of start of 1st line of prior therapy; otherwise, impute diagnosis day with 15.
  - Otherwise, impute with June 30.

2.7.5. Partial Subsequent Anticancer Therapy Start Date

If year or month of subsequent anticancer therapy start date is missing or no components of the start date are present, no imputation will be performed.

If only the day-component is missing, the following steps apply:

- If the month and year of the start date are the same as the month and year of last dosing date, the day of last dosing date or the day-component of the stop date of subsequent anticancer therapy is imputed, whichever is earlier.

- If the start month and year are not the same as the month and year of last dosing date, the first day of the month is imputed.

If after the above imputation are applied, the imputed start date is after the non-imputed end date then re-adjust the start to be the same as the end date.

No imputation will be applied for missing or partial subsequent anticancer therapy end date.

2.8. Analysis Sets

2.8.1. Efficacy Analysis Set(s)

The all treated analysis set will consist of all subjects who receive at least 1 dose of daratumumab. This analysis set will be used for efficacy analysis unless otherwise stated.

The response evaluable analysis set will consist of all subjects who satisfy all of the following:

– Received at least 1 dose of study drug;

– Had a baseline and at least 1 post-treatment disease evaluation.

Response evaluable analysis set will be used for the efficacy analyses at interim analysis.

2.8.2. Safety Analysis Set

The all treated population will be used for safety analysis unless otherwise stated.

2.8.3. Pharmacokinetics Analysis Set

The PK analysis population will consist of all subjects who received at least 1 dose of daratumumab and have at least 1 sample collected during treatment to determine the concentration. This analysis wet will be used for PK analysis.

2.8.4. Pharmacodynamics Analysis Set

The PD analysis population will consist of all subjects who received at least 1 dose of daratumumab and have at least 1 sample collected to determine PD biomarker response. This analysis set will be used for PD analysis.

2.9. Definition of Subgroups

No specific subgroup analysis will be performed.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

The study is designed with an interim analysis performed at the end of stage 1 when approximately 15 subjects have received at least one dose of study drug and had at least one post-baseline disease evaluation. Enrollment may be put on hold pending the decision of interim analysis unless the decision is clear based on available data before the interim analysis. The purpose of the interim analysis is to evaluate efficacy and safety data in stage 1 and facilitate the early preparation for the next step of development. The totality of efficacy (ORR), safety, and biomarker data will be analyzed at interim. The futility criterion of ORR is defined as at most 1 out of 15 subjects have achieved CR/PR after stage 1. This futility boundary is considered non-binding. Study may be terminated if the futility criteria are met or supported by the totality of data including biomarker and safety data.

In addition, at interim, the association between daratumumab activity and CD38 expression level will be explored. If a strong association between daratumumab activity and CD38 expression level is confirmed by emerging data or a low response rate is observed from stage 1 data due to low CD38 expression levels, then an enrichment strategy may be applied for stage 2 to mitigate the risk of low responses possibly attributed to low CD38 expression. The final analysis may be adjusted accordingly (e.g., primary analysis would be based on enriched population) if an enrichment strategy is applied in stage 2.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Unless specified otherwise, all demographic and baseline characteristics variables will be summarized for the all treated analysis set.

The distribution of subject enrollment will be presented according to region and country. Subjects who did not meet study inclusion/exclusion criteria will be listed by subject ID, and specific criteria not met.

Subject demographic and baseline characteristic variables: age (< 65 years, 65 to < 75 years, and ≥75 years), sex, ethnicity, race, weight (kg), height (cm), and ECOG performance status will be summarized. A listing of subject demographic and baseline characteristics will be provided as well.

Baseline disease diagnosis including CD38 expression, ß2-microglobulin, and months since initial diagnosis will be summarized. A listing of disease diagnosis will be provided as well.

Medical history collected at baseline or screening visit will be summarized by system-organ class and preferred term.

4.2. Disposition Information

An overview of subject disposition will be provided. The overview includes a summary of total number of subjects who are treated. For all treated subjects (defined as subjects who have received at least 1 administration of daratumumab), the number and percentage of subjects who discontinued study treatment including reason for discontinuation as indicated by the investigators will be summarized. The similar summaries will be presented for all treated subjects who discontinued from study participation.

A listing of subjects who discontinued study treatment or study participation including reasons for discontinuation will be provided.

4.3. Treatment Compliance

Compliance will be analyzed as part of exposure. Please refer to 4.4

4.4. Extent of Exposure

Extent of exposure to study treatment will be summarized and presented based on all treated population.

The number and percentage of subjects treated within each cycle will be summarized. The maximum number of treatment cycles received for each subject will be summarized by frequency and descriptive statistics.

Duration of study treatment, defined as the number of days from the date of the first administration of study treatment to the date of the last administration of study treatment, will be summarized. The number of daratumumab infusions will be summarized for all treated subjects.

Daratumumab dose intensity, which is defined as the sum of total dose administered (mg/kg) in all cycles divided by the number of treatment cycles, will be summarized. Additionally, the daratumumab dose intensity will be summarized for cycles with high-intensity (Cycles 1-2) or low-intensity (Cycles 3-6 and Cycles 7+).

The relative dose intensity (%) defined as the ratio of total actually received dose and total planned dose will be calculated and summarized using descriptive statistics.

The number of subjects with cycle delays or dose modifications (dose delays or dose skipping) including reasons (AE or other) for cycle delays or dose modifications, will be reported.

A listing of subjects with daratumumab infusions will be provided.

4.5. Protocol Deviations

A listing of subjects with major protocol deviations including subject ID, type of deviation, and reasons for deviation will be provided.

4.6. Prior Medications

A summary of prior therapies (systemic therapy, radiotherapy, or cancer-related surgery/ procedure) will be provided. Specifically, the number of prior lines of therapy will be calculated and summarized by the following categories: 1, 2, or ≥ 3 through frequency and descriptive statistics. Additionally, the prior systemic therapy will be summarized by therapeutic class, pharmacologic class and drug name.

4.7. Concomitant Medications

Concomitant medications collected in the CRF page during the study will be summarized by therapeutic class, pharmacologic class, and drug name. A similar summary will be provided for pre-infusion medication and post-infusion medication, respectively. A listing will be provided for pre-infusion medication and post-infusion medication, respectively.

4.8. Subsequent Anticancer Therapy

The total number of subjects who received subsequent anticancer therapy will be reported. A summary of subsequent anticancer therapy will be presented by therapeutic class, pharmacologic class and drug name.

5. EFFICACY

5.1. Analysis Specifications

The analysis of efficacy will be based on BICR for all treated population. Sensitivity analysis will be performed based on investigators' assessment.

5.1.1. Level of Significance

Not applicable.

5.1.2. Data Handling Rules

No data imputation will be performed for missing efficacy endpoint values.

5.2. Primary Efficacy Endpoint(s)

Study will evaluate evidence of clinical responses with primary efficacy endpoint of objective response rate.

5.2.1. Definition

Objective response rate (ORR) is defined as the proportion of subjects who achieve CR or PR per Revised Criteria for Response Assessment of Hodgkin and non-Hodgkin lymphoma: LUGANO classification based on BICR.

5.2.2. Analysis Methods

An estimate of the ORR will be presented along with a two-sided 95% exact confidence interval. The number and percentage of subjects in the following response categories will be presented: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE), overall response (CR+PR) and Clinical benefit rate (CR+PR+SD).

5.3. Secondary Endpoints

Secondary endpoints include complete response (CR) rate, progression-free survival (PFS), duration of objective response (DOR), time to response, and overall survival (OS).

5.3.1. Definition

Complete response (CR) rate is defined as the proportion of subjects who achieve CR based on BICR and will be analyzed similarly as the primary endpoint ORR.

Progression-free survival (PFS) is defined as the duration from the date of the first daratumumab dose to the date of progression/relapse based on BICR or death, whichever comes first. For those subjects who are still alive without progression/relapse, PFS will be censored at the last adequate tumor assessment. Subjects who are progression-free and alive or have unknown status will be censored at last tumor assessment. Subjects with no post baseline disease assessment will be censored on Day 1. Subjects who started a subsequent anti-cancer therapy in the absence of progression will be censored at the last disease assessment before the start of subsequent therapy. Subjects whose diseases have not progressed and who are still alive at the end of the study or clinical cutoff will be censored at the last adequate disease assessment.

Duration of response (DoR) will be duration from the date of the initial documentation of a response to the date of first documented evidence of progressive disease based on BICR (PD; or relapse for subjects who experience CR) or death and calculated only for responders. For those subjects who are still without progression/relapse, DoR will be censored at the last adequate tumor assessment.

Time to response (TTR) is defined as the duration from the date of the first dose of daratumumab to the earliest date that a response (CR/PR based on BICR) is first documented. Descriptive analysis will be performed for responders including median, mean, standard deviation, and range.

Overall survival (OS) is defined as the duration from the date of the first daratumumab dose to the date of death. Subjects who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up. For those subjects who are still alive at the time of analysis, OS will be censored at the last date known to be alive.

5.3.2. Analysis Methods

Descriptive analysis will be performed for secondary endpoints. The Kaplan-Meier method will be used to estimate the distribution of PFS, OS and DoR. The number of events, subjects censored, the estimate of medians, and 95% confidence interval for medians will be presented. Plots of PFS, OS and DoR using Kaplan-Meier method will be presented. For CR rate, point estimate as well as

exact 95% CI will be provided. For TTR, mean, standard deviation, and range will be provided for responders.

6. SAFETY

Unless specifically stated, the observations that occurred during treatment period (i.e., within 30 days from the last study drug dosing) will be used for safety analyses. All observations will be presented in listings.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Toxicities will be graded for severity according to CTCAE, Version 4.03. All reported adverse events with onset during the treatment period (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline, and within 30 days from the last dose) will be included in the analysis and reported using descriptive statistics and frequency tabulations.

The incidence of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term, by toxicity grade, and by relationship to study treatment administration.

Specifically, the following will be summarized or listed:

- All adverse events
- Grade 3 or higher adverse events
- Serious adverse events
- Adverse events leading to discontinuation of treatment
- Treatment-emergent infusion related reactions
- Adverse events leading to treatment cycle delays or dose modifications
- Adverse events leading to death

6.2. Deaths

6.2.1. All Deaths

A summary of all deaths and cause of death will be summarized for all treated population. The primary cause of death collected on CRF page will be reported. Similar summaries will be presented for subjects who died within 30 days of last study treatment.

A listing of death information will be provided.

6.3. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre-

versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

NCI-CTCAE version 4.03 will be used to derive toxicity grades for clinical laboratory tests when applicable. Shift tables from baseline to worst value on study (from treatment start to 30 days after last dose or the End of Treatment visit date, whichever is later) will also be provided. The worst toxicity grade during the study will be tabulated.

6.4. Electrocardiogram

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

6.5. Vital Signs

Descriptive statistics of temperature, pulse, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

7. PHARMACOKINETICS/PHARMACODYNAMICS/IMMUNOGENICITY

7.1. Pharmacokinetics Analyses

Pharmacokinetic (PK): PK analyses will be performed on the PK-evaluable population, defined as subjects who have received at least 1 dose of daratumumab and at least 1 post-infusion sample.

All serum concentrations below the lowest quantifiable concentration in a sample or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration in a sample will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the clinical study report.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point and PK parameters of daratumumab (C_{max}, t_{max}, AUC) following the 1st infusion. In addition, above PK parameters following the first infusion, if available, may be summarized by response status. Mean serum daratumumab concentration time profiles will be plotted after the first dose of study drug. Composite serum concentration time profiles and Cycle 3 Day 1 pre-dose serum concentrations stratified by response status may also be plotted. Further exploratory analyses of PK data may be performed.

7.2. Pharmacokinetics/ Pharmacodynamics Analyses

If sufficient data are available, then the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy and safety may be analyzed graphically.

7.3. Immunogenicity Analyses

The incidence of antibodies to daratumumab (immunogenicity) will be summarized for all subjects who received at least 1 administration of daratumumab and have at least 1 during-treatment-sample collected to assess the generation of antibodies to daratumumab. A listing of subjects whose sample(s) are positive will also be presented. Daratumumab concentrations will be summarized at all immunogenicity time points. The maximum titers of antibodies to daratumumab will be summarized for subjects who are positive for antibodies to daratumumab. The impact of antibodies to daratumumab on drug exposure and efficacy/safety may be analyzed if there are positive samples.

8. BIOMARKER ANALYSES

Biomarker analyses will be focused on CD38 expression and EBV-DNA at baseline, over time performance of total natural killer cells and EBV-DNA. The relationship of biomarkers with efficacy outcome, e.g. disease response, may also be explored. The corresponding summaries and figures will be provided.

If data are available, disease-related or mechanism-based biomarkers will be also explored. Details and results of the analysis will be presented in a separate report.

9. HEALTH ECONOMICS

Not applicable.