Janssen Research & Development *

Statistical Analysis Plan For Interim Analysis

An Open Label, Phase 2 Study to Evaluate Efficacy and Safety of Daratumumab in Relapsed or Refractory Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma

Protocol 54767414LYM2001; Phase 2

JNJ-54767414 (Daratumumab)

Status: Approved
Date: 16 May 2017
Prepared by: Janssen Research & Development
Document No.: EDMS-ERI-141009715

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

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CR	Complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
DOR	Duration of response
DPS	data presentation specification
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IVRS	interactive voice response system
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
M-protein	monoclonal protein, monoclonal paraprotein
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	principal investigator
PR	Partial response
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAEs	treatment-emergent adverse events
TOR	Time to response
TTP	Time to disease progression
WBC	White blood cells

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the planned interim futility analyses for study JNJ-54767414LYM2001. If futility criteria are met, this interim SAP will serve as the study SAP.

1.1. Trial Design

This is an open-label, multicenter, Phase 2 study in subjects at least 18 years of age with MCL, DLBCL, or FL. Approximately 210 subjects may be enrolled, with up to 100 subjects planned for MCL and up to 55 subjects each for DLBCL and FL.

This study will be conducted and analyzed separately for each subtype of NHL. A biomarker adaptive threshold design is implemented that enables testing of the overall population and the establishment of a biomarker-defined enriched population simultaneously. Two stages are planned.

Stage 1 of the study is designed to provide a preliminary assessment of activity at an early stage. Since CD38 expression level may be associated with daratumumab activity, Stage 1 will enroll subjects who have tumors where at least 50% of the cells are CD38 positive. This requirement seeks to mitigate the possibility that a low response rate observed in Stage 1 might be due to low levels of CD38 expression. The selection of the 50% cut-off is based on the existing CD38 expression level data in these NHL subtypes as well as practical considerations. At the end of Stage 1, which is expected to be 6 months after the last subject is enrolled in each NHL subtype, or earlier if emerging data allows, an interim analysis will be conducted. The purpose of the interim analysis is to evaluate efficacy and safety data in Stage 1. The efficacy assessment will be focused on ORR. In case of low ORR taking into consideration of CD38 expression level, an individual NHL subtype may be terminated for futility. The detailed futility stopping guideline is as follows.

- For MCL, if at least 5 out of 20 subjects have achieved CR or PR after Stage 1, then Stage 2 may be initiated. For DLBCL, if at least 4 out of 15 subjects have achieved CR or PR after Stage 1, then Stage 2 may be initiated. For FL, if at least 7 out of 15 subjects have achieved CR or PR after Stage 1, then Stage 2 may be initiated.
- For MCL, if at most 4 out of 20 subjects have achieved CR or PR after Stage 1, consider terminating MCL for futility. For DLBCL, if at most 3 out of 15 subjects have achieved CR or PR after Stage 1, consider terminating DLBCL for futility. For FL, if at most 6 out of 15 subjects have achieved CR or PR after Stage 1, consider terminating FL for futility.

Alternatively, if the futility criteria are not met and if supported by the totality of the Stage 1 data, Stage 2 for that NHL subtype may be opened for accrual. If the required number of responses is observed prior to completion of enrollment in Stage 1, Stage 2 may be opened immediately upon completion of enrollment to Stage 1, if supported by the totality of data.

Stage 2, if opened, is designed to further evaluate safety and efficacy as well as to determine a threshold for CD38 expression that is associated with enhanced daratumumab activity. Supported by the preliminary activity observed in Stage 1, Stage 2 will enroll any subject in each NHL subtype. To mitigate the possibility that a low response may be observed due to low levels of

CD38 expression in enrolled subjects, the number of Stage 2 subjects with CD38 expression level <50% will be capped within each NHL subtype.

The target number of subjects in each stage by CD38 expression level is shown in table below.

Type of NHL	**Number of Subjects**			
	Stage 1 CD38 expression level [b] ≥50%	**Stage 2 (optional)**		**Overall**
		CD38 expression level [a] <50%	**CD38 expression level [b] ≥50%**	**Total**
MCL	20	≤30	≥50	**100**
DLBCL	15	≤20	≥20	**55**
FL	15	≤20	≥20	**55**

DLBCL=diffuse large B cell lymphoma ; FL=follicular lymphoma; MCL= mantle cell lymphoma

a. These subjects have tumors where <50% of the cells are positive for CD38 by immunohistochemistry.

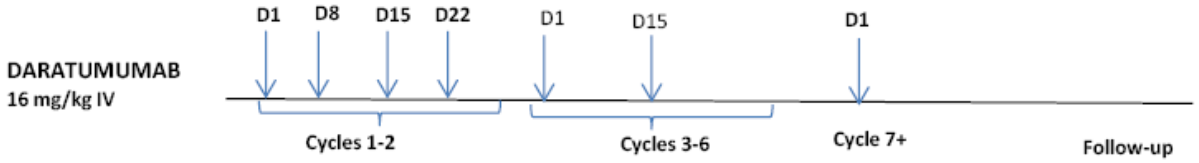
b. These subjects have tumors where ≥50% of the cells are positive for CD38 by immunohistochemistry.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase.

The Screening Phase will be up to 28 days prior to Cycle 1, Day 1. Prior to enrollment, subjects are required to provide tumor tissue to determine CD38 expression level by immunohistochemistry (IHC) at a central laboratory. An additional fresh biopsy should be obtained whenever possible even if an archival sample is provided.

The Treatment Phase will extend from Cycle 1, Day 1 until study drug discontinuation. After first dose, disease evaluations will occur every 8 weeks for the first 3 evaluations, then every 16 weeks for the next two evaluations and then every 24 weeks thereafter. Subjects will be treated until disease progression, unacceptable toxicity, or other reasons as listed in the protocol.

A schematic overview of the dosing schedule is presented as follows.



The Follow-up Phase will begin once a subject discontinues study drug, and will continue until death, loss to follow up, consent withdrawal for study participation, or end of study, whichever occurs first.

The end of the cohort for each NHL subtype is defined as 18 months after the last subject in the particular NHL subtype receives the first dose of daratumumab. After each NHL subtype

completes the study, the sponsor will ensure that subjects, who are currently on treatment and receiving benefit, as determined by the investigator, will continue to receive daratumumab. The end of the study is defined as the completion of all three NHL subtypes.

Throughout the Treatment Phase and Follow-up Phases, assessment of tumor response and disease progression will be conducted by investigators in accordance with the Cheson 2014[1] response criteria. Identical methodology should be used for disease assessment at screening and throughout the course of the study. Radiological and PET scans should be performed and collected according to instructions from the independent imaging laboratory. A central review of the response assessments may be performed if deemed necessary.

Safety evaluations will include AE monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Measures to prevent infusion-related reactions will include preinfusion medication with methylprednisolone, acetaminophen (or paracetamol), and an antihistamine before each daratumumab infusion.

Blood samples will be drawn for assessment of serum concentration (pharmacokinetics) of daratumumab and the generation of antibodies to daratumumab (immunogenicity) from all subjects according to the Time and Events Schedule. In addition, biomarker samples will be collected to identify markers predictive of response (or resistance) to daratumumab.

The primary efficacy endpoint, is Overall Response Rate (ORR) defined as the proportion of subjects who achieve CR or PR.

Major secondary efficacy endpoints are duration of response (DoR), PFS, overall survival (OS), and time to response (TTR).

1.2. Sample Size Justification

Within each subtype of NHL, a biomarker adaptive threshold design (Jiang 2007)[2] is to be utilized, which allows identification of a biomarker threshold based on data analysis in parallel with the statistical testing of the ORR for proof-of-concept. That is, the proof-of-concept could be established either in the overall population or in the subpopulation of subjects as identified by the biomarker (CD38 expression level) threshold. In order to provide an early futility check within each NHL subtype, a two-stage procedure is also incorporated.

Given that there are two potential pathways for proof-of-concept and the inherent multiple testing issues associated with the selection of the biomarker threshold, per the recommendation by Jiang (2007)[2], the powering for MCL will be based on the overall population with an overall alpha of 0.04, which preserves the power of the overall test while providing a reasonable power against a strong subset effect at the same time with the remaining alpha of 0.01. Since further randomized Phase 2 proof-of-concept studies in combination with other agents are likely required for DLBCL and FL, an alpha of 0.05 is used for the overall population in these two subtypes.

In Stage 1, a total of 50 subjects will be enrolled for all 3 NHL types combined. In Stage 2, a maximum of 160 subjects may be enrolled if all three tumor types are expanded, bringing the maximal sample size to 210 with all tumor types combined.

For MCL, the null hypothesis is that the ORR is at most 20%, and the alternative hypothesis is that the ORR is at least 35% for all subjects, or at least 40% for those subjects whose CD38 expression level is above a to-be-determined level. These are based on the fact that some recent approvals in previously treated MCL were based on an ORR of approximately 31% for bortezomib and 26% for lenalidomide. Up to 100 MCL subjects with positive CD38 expression may be enrolled. Seventy (70) of those must have tumors with 50% or more cells positive for CD38 expression at baseline in order to rule out that any lack of activity is mostly due to low CD38 expression level in the enrolled subjects.

For DLBCL, the null hypothesis is that the ORR is at most 15%, and the alternative hypothesis is that the ORR is at least 30% for all subjects, or at least 40% for those subjects whose CD38 expression level is above a to-be-determined level. These were based on the clinical observation that relapsed DLBCL subjects who are not eligible for HDT/ASCT have a very poor prognosis and no established therapeutic options.

For FL, the null hypothesis is that the ORR is at most 30%, and the alternative hypothesis is that the ORR is at least 50% for all subjects, or at least 60% for those subjects whose CD38 expression level is above a to-be-determined level. These are based on the published ORRs of idelalisib (54%, which was the basis of an accelerated approval is the U.S.) and rituximab monotherapy (49%, Coiffier 2011)[5].

For both DLBCL and FL, 55 subjects may be enrolled. Thirty-five (35) of those must have tumors with 50% or more cells positive for CD38 expression at baseline in order to rule out that any lack of activity is mostly due to low CD38 expression level in the enrolled subjects.

The trial will be carried out in two stages within each NHL subtype, as in a Simon's two-stage design. Each NHL subtype, independent of the other subtypes, may be discontinued after Stage 1 due to futility. To exclude the possibility that an observed low response rate is due to low CD38 expression level at baseline, the trial will enroll sufficient number of subjects with tumors where ≥50% of cells are CD38 positive in both stages. The detailed procedure will proceed as follows.

For MCL, Stage 1 will accrue 20 subjects with tumors where ≥50% of cells are CD38 positive. If the futility criteria are met (at most 4 responses overall), no further expansion is planned. Otherwise, an additional 80 subjects will be enrolled to Stage 2; at least 50 of these subjects will have tumors where ≥50% of cells are CD38 positive. The sample size will provide approximately 85% power to reject the null hypothesis for the overall population with a one-sided significance level of 0.04.

For DLBCL, Stage 1 will accrue 15 subjects with tumors where ≥50% of cells are CD38 positive. If the futility criteria are met (at most 3 responses overall), no further expansion is planned. Otherwise, an additional 40 subjects will be enrolled to Stage 2; at least 20 of these

subjects will have tumors where ≥50% of cells are CD38 positive. The sample size will provide approximately 80% power to reject the null hypothesis for the overall population with a one-sided significance level of 0.05.

For FL, Stage 1 will accrue 15 subjects with tumors where ≥50% of cells are CD38 positive. If the futility criteria are met (at most 6 responses overall), no further expansion is planned. Otherwise, an additional 40 subjects will be enrolled to Stage 2; at least 20 of these subjects will have tumors where ≥50% of cells are CD38 positive. The sample size will provide approximately 80% power to reject the null hypothesis for the overall population with a one-sided significance level of 0.05.

At the end of the study, all available data for each particular NHL subtype will be analyzed to determine a CD38 expression threshold for that subtype, which will be used to define an enriched population, via statistical inference.

1.3. Interim Analysis

The objective of the interim analysis is to evaluate efficacy and safety data in Stage 1 for all 3 cohorts. The interim analysis will be conducted at the end of Stage 1, which is expected to be 6 months after the last subject is enrolled in each NHL subtype, or earlier if emerging data allows.

At the interim analysis, the primary efficacy endpoint of ORR will be evaluated and the major secondary endpoints of DoR, PFS, OS and time to response will be assessed. The detailed analyses of efficacy are described in Section 4. Safety evaluation at the interim analysis will focus on assessment of cumulative interim safety data, specifically on assessment of study treatment discontinuation, adverse events, Grade 3 or 4 adverse events, adverse events related to study treatment, serious adverse events, adverse events leading to study treatment discontinuation, infusion-related reactions, deaths due to adverse event, and clinical laboratory parameters (hematology and chemistry). The detailed analyses of safety are described in Section 5.

1.4. Treatment Allocation and Blinding

After determination of eligibility, subjects will be enrolled to the study. No randomization will be used in this study.

As this is an open study, blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

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 daratumumab 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 dose of daratumumab of that cycle, 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 (eg, 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 participating centers in the study will be pooled together for analyses.

2.3. Analysis Sets

The following analysis sets are defined.

- All treated analysis set: is defined as subjects who received at least one non-zero dose of daratumumab.
- Pharmacokinetics-evaluable: is defined as subjects who received at least one non-zero dose of daratumumab and had at least 1 pharmacokinetic sample concentration value after the first infusion. All pharmacokinetics analyses are based on the pharmacokinetic evaluable population.

2.4. Study Treatment and Study Drug

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

2.5. 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.

2.6. Treatment Cycle

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

2.7. 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.

2.8. 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.

2.8.1. Missing/Partial Adverse Event Onset Date

If the onset date of an adverse event is missing completely or 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.

2.8.2. Missing/Partial Adverse Event End Date

If the end date of an adverse event is missing completely or 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.

2.8.3. 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.

2.8.4. Partial Prior Therapy Start/End Date

In case of partially missing dates, the imputation will be needed as follows. If the date is completely missing, no imputation will be performed.

Impute partially missing dates (start date, stop date) by using the following rules:

- 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 imputed start/end date is after first doing date, further adjust the imputed start/end date as the day prior to 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.

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

2.8.6. 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.

2.9. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

Unless specified otherwise, all demographic and baseline characteristics variables will be summarized for the all treated analysis set. No statistical comparisons between the 3 NHL subtypes are planned.

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

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

Baseline disease diagnosis including % CD38 and CD59 expression level, CD38 H-score, ratio of CD38 and CD59 expression level, ß2-microglobulin, bone marrow % lymphoma cell infiltration, CD5, CD10, CD19, CD20 and months since initial diagnosis will be summarized by NHL subtype and overall. Subtype of Follicular lymphoma (Grade 1, 2, 3A) will be summarized for FL cohort, and subtype of DLBCL molecular (Non-GCB, GCB, Unknown) will be summarized for DLBCL cohort. 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 for each NHL subtype and overall.

3.2. Disposition Information

An overview of subject disposition by NHL subtype will be provided. The overview includes a summary of total number of subjects who are treated in each NHL subtype. For all treated subjects, 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.

In addition, a summary of all screened subjects per analysis set will be reported and a listing of subjects who discontinued study treatment or study participation including reasons for discontinuation will be provided.

3.3. 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 by NHL subtype and overall. 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 by NHL subtype and overall.

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 by NHL subtype 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.

3.4. Protocol Deviations

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

3.5. Prior and Concomitant Medications

A summary of prior therapies (systemic therapy, radiotherapy, or cancer-related surgery/ procedure) will be provided by NHL subtype. 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 for each NHL subtype.

For FL cohort, the number of subjects who had prior anti-CD20 medication (rituximab or obinutuzumab) will be provided.

For MCL cohort, the number of subjects who had prior ibrutinib will be provided. A descriptive summary of total number of cycles received for prior ibrutinib will be provided. The incidence of

subjects who received prior ibrutinib in their last line of therapy will be reported. Best response to prior ibrutinib and number of subjects who had progression/relapse from prior ibrutinib will also be summarized.

Concomitant medications collected in the CRF page during the study will be summarized by therapeutic class, pharmacologic class, and drug name for each NHL subtype. 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.

3.6. Subsequent Anticancer Therapy

The total number of subjects who received subsequent anticancer therapy will be reported for each NHL subtype. A summary of subsequent anticancer therapy will be presented by therapeutic class, pharmacologic class and drug name. Specifically, the number of lines of subsequent anticancer therapy will be calculated and summarized by the following categories: 1, 2, or ≥ 3 through frequency and descriptive statistics.

4. EFFICACY

Response and disease progression were assessed by investigators, based on Revised Criteria for Response Assessment (Cheson 2014)[1]. The detailed documentation can be found in Attachment 1 in Protocol. Efficacy analyses will be based on all treated population and presented by each NHL subtype.

4.1. Analysis Specifications

4.1.1. Level of Significance

All 95% confidence interval presented will be 2-sided.

4.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

4.2. Primary Efficacy Endpoint(s)

4.2.1. Definition

The major efficacy endpoint, ORR, is defined as the proportion of subjects who achieve CR or PR.

4.2.2. Analysis Methods

For each NHL subtype, 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 by NHL subtype: 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).

4.3. Major Secondary Endpoints

The major secondary endpoints include PFS, OS, DoR and time to response.

4.3.1. Progression-free Survival (PFS)

Definition

PFS is defined as the duration from the date of the first daratumumab dose to the date of progression/relapse or death (prior to subsequent systemic anticancer therapy or withdrawal of consent to study participation or lost to follow-up) due to any cause, whichever comes first.

If a subject started subsequent therapy or withdrew consent to study participation or lost to follow-up, PFS will be censored at last disease assessment prior to the date of the start of subsequent therapy or date of withdrawal of consent or lost to follow-up. Subjects who have not progressed and are still alive at the cut-off date for analysis will be censored at the date of last disease assessment. Subjects without any post-baseline disease assessment will be censored at the date of first Dara dosing.

Analysis Methods

Analysis of PFS will be based on all treated population. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each NHL subtype. The median PFS will be provided. In addition, the number and percentage of subjects who had progression disease or were censored will be reported. The Kaplan-Meier PFS curve will also be plotted by NHL subtype.

Additionally, reasons for PFS and censoring will be summarized for all treated subjects.

4.3.2. Overall Survival (OS)

Definition

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. Subjects who are still alive at the cut-off date for the analysis will be censored at the last known alive. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

Analysis Methods

Analysis of OS will be based on all treated population. The Kaplan-Meier method will be used to estimate the distribution of overall OS for each NHL subtype. The median OS will be provided. In addition, the number and percentage of subjects who had died or were censored will be reported.

4.3.3. Time to Response (TTR)

Time to response is defined as the duration from the date of the first dose of daratumumab to the earliest date that a response (CR/PR) is first documented. Time to response will be listed for responders.

4.3.4. Duration of Response

Duration of response (DoR) will be calculated and listed only for responders. It is defined as the duration from the date of the initial documentation of a response (PR or better) to the date of first documented evidence of PD (or relapse for subjects who experience CR) or death due to PD, whichever comes first.

A listing of subjects' first response, best response, TTR, DoR disease progressions and overall survival including NHL subtype, subject ID, baseline beta-microglubin and CD38 expression level will be provided.

5. SAFETY

Safety assessment will be evaluated through AEs, clinical hematology and chemistry laboratory tests, ECGs, vital signs measurements, physical examination findings, and assessment of ECOG performance status score. All toxicities will be graded according to the NCI CTCAE Version 4.03. Safety analyses will be based on all treated population and presented by each NHL subtype.

5.1. Adverse Events

All adverse events whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment, until the subject withdraws consent for study participation, or until the subject starts subsequent anticancer therapy, whichever occurs first. AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. For AE reporting, the verbatim term used in the CRF by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Unless otherwise specified, at each level (e.g., system organ class and/or preferred term) of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs). TEAEs are defined as any AE that occurs after start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent anticancer therapy, whichever is earlier; or any AE that is considered drug-related (very likely, probably, or possibly related) regardless of the start date of the event.

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 AE summaries will be presented by NHL subtype:

5.1.1. Overview of TEAEs

An overview of TEAEs reported through the study will be provided for each NHL subtype. The overview will include summaries of subjects with TEAEs, TEAEs related to study treatment, TEAEs of maximum toxicity grade of 1 to 5, SAEs, TEAEs leading to discontinuation of study treatment and summary of TEAEs result in death.

5.1.2. All TEAEs

- Incidence of TEAEs by MedDRA SOC and preferred term
- List of subjects with any TEAEs

5.1.3. Toxicity Grade 3 or 4 TEAEs

- Incidence of toxicity grade 3 or 4 TEAEs, by MedDRA SOC and preferred term

5.1.4. Treatment-emergent Infusion related reactions

- Incidence of treatment-emergent infusion related reactions, by MedDRA SOC and preferred term
- Toxicity grade of treatment-emergent infusion related reactions
- List of infusion related reactions

5.1.5. Study Treatment-Related TEAEs

- Incidence of TEAEs considered by the investigator to be related to study treatment, by MedDRA SOC, and preferred term
- Incidence of TEAEs with toxicity grade 3 or 4 considered by the investigator to be related to study treatment, by MedDRA SOC and preferred term

5.1.6. Serious Adverse Events (SAEs)

- Incidence of treatment-emergent SAEs, by MedDRA SOC and preferred term
- Incidence of treatment-emergent SAEs considered by the investigator to be related to study treatment, by MedDRA SOC, and preferred term

5.1.7. TEAEs Leading to Discontinuation of Study Treatment

A summary of number of subjects who discontinued study treatment because of 1 or more TEAEs by MedDRA system-organ class and preferred term will be provided. This table includes AEs leading to discontinuation of study treatment for those subjects indicated as having discontinued study treatment due to an adverse event on the end of treatment CRF page.

5.1.8. TEAEs Leading to Cycle Delays or Dose Modifications

Incidence of TEAEs leading to treatment cycle delays or dose modifications will be summarized by MedDRA SOC and preferred term. This table will includes TEAEs leading to cycle delays or at least 1 of study treatments dose modifications, the dose modifications include dose delays or dose skipping.

5.1.9. AEs with Outcome Death

Incidence of AEs with outcome of “FATAL” or toxicity grade of 5 from AE page will be summarized by MedDRA SOC and preferred term.

5.2. Deaths

5.2.1. All Deaths

A summary of death within 30 days of last study treatment and cause of death will be tabulated overall and by NHL subtype. Specifically, the number of subjects who died during the study will be summarized for all treated population. The primary cause of death collected on CRF page will be reported. If the primary cause of death reported is an AE, the number of subjects who have a treatment related AE and unrelated AE will be further reported. Similar summaries will be presented for all death.

A listing of death information will be provided.

5.3. Clinical Laboratory Tests

The evaluation of clinical laboratory tests will focus on the following selected laboratory analytes:

Hematology panel:

-hemoglobin
-platelet count
-white blood cell (WBC) count with absolute neutrophils and lymphocytes

Blood chemistry panel:

-sodium
-potassium
-creatinine
-total bilirubin
-direct bilirubin
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)
-alkaline phosphatase
-lactate dehydrogenase
-uric acid
-calcium
-total Protein
-albumin
-Creatinine clearance

Blood samples for serum hematology are taken at the screening visit, on Days 1, 8, 15 and 22 of Cycles 1-2, Days 1 and 15 of Cycles 3-6, Day 1 of Cycles 7+ and at the End-of-Treatment visit. Results of hematology tests must be evaluated before study drug administration. Blood samples for biochemistry are taken at the screening visit, on Day 1 of each treatment cycle and at the End-of-Treatment visit.

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit for each NHL subtype.

The worst toxicity grade in hematology and chemistry during the treatment will be summarized by NHL subtype and toxicity grade.

5.4. Vital Signs and Physical Examination Findings

Vital signs (systolic and diastolic blood pressure, pulse, and temperature) values collected immediately before Day 1 of each cycle and change from baseline will be summarized.

Similar analyses will be performed for weight at Day 1 of each treatment cycle.

Post baseline physical examination findings were collected as AEs, and therefore will not be summarized.

5.5. Electrocardiogram (ECG)

Electrocardiograms (ECG) will be performed at Screening, Day 1 of Cycle 3 and Cycle 6, and End-of-Treatment visit. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, then the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

The number and percentage of subjects with normal, clinically significant or clinically non-significant abnormal 12-lead ECG results will be summarized at each scheduled visit by NHL subtype.

5.6. Other Safety Parameters

5.6.1. ECOG Performance Score

ECOG performance status, which evaluates the effect of the disease status on the activities of daily living, will be assessed at Screening, Day 1 of Cycle 1, 3, 5, 7, every 12 weeks after Cycle 7 and 16 weeks post PD. Descriptive statistics will be used to summarize ECOG performance status at baseline and post-baseline (including change from baseline) for each NHL subtype.

6. PHARMACOKINETICS/PHARMACODYNAMICS

Unless specified otherwise, descriptive statistics (eg, number of observations, mean, standard deviation, median, and range) will be used to summarize pharmacokinetics and pharmacodynamics data. In addition, coefficient variation and geometric mean will be provided in the pharmacokinetic concentration summary.

6.1. Pharmacokinetics

6.1.1. Sampling Time Points

For all subjects, pharmacokinetic samples to determine serum concentration of daratumumab will be obtained on Day 1 of Cycle 1, 3, 5, 7, 11, 15, and 4 weeks and 8 weeks after last daratumumab dose. On a daratumumab dosing day, blood samples need to be collected before (up to 2 hours but not after the start of infusion) and immediately after (up to 2 hours but not before the end of infusion) daratumumab administration.

6.1.2. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:
Cmax Maximum observed concentration
Cmin Minimum observed concentration

Pharmacokinetic samples to determine serum concentration of daratumumab will be obtained from all subjects. Pharmacokinetic endpoints include:

- Minimum observed concentration (C_{min})
- Maximum observed concentration (C_{max})

If sufficient data are available, then other pharmacokinetic parameters may be calculated.

6.1.3. Analysis Methods

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population, defined as subjects who have received at least 1 dose of daratumumab and have at least one postinfusion sample.

All serum concentrations below the lowest quantifiable concentration in a sample or missing data will be labelled as such in the concentration data listings. 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 timepoint and pharmacokinetic parameters of daratumumab. C_{min} is defined as the concentration observed immediately before infusion and C_{max} is defined as the concentration observed at the end of infusion, as presented in the summary of serum concentration by sampling time point. Other pharmacokinetic parameters may also be summarized.

If sufficient data are available, then population pharmacokinetic analysis of serum concentration time data of daratumumab may be performed and may include data from other studies. If the population pharmacokinetic analysis is conducted, then details will be given in a population pharmacokinetic analysis plan and the results of the analysis will be presented in a separate report.

6.2. Immunogenicity

6.2.1. Sampling Time Points

Samples to assess the generation of antibodies to daratumumab (immunogenicity) will be obtained from all treated subjects at Cycle 1 Day 1 predose, Post-Treatment Week 4, and Post-Treatment Week 8. In addition, any time an infusion-related reaction is observed during the study, an unscheduled blood sample should be drawn as soon as possible after the reaction for potential immune response analysis. No additional sample needed for these planned timepoints; will be taken from PK samples.

6.2.2. Analysis Methods

The incidence of antibodies to daratumumab will be summarized for all subjects who receive at least one dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab. A listing of sample status for antibodies to daratumumab at any time during the study for pharmacokinetic evaluable population will be provided. In addition, subjects who are positive for antibodies to daratumumab will also be listed.

7. BIOMARKER

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab, as well as to gain deeper understanding of NHL. During screening, subjects will be required to provide tumor samples for assessment of CD38 expression based on central testing using investigational IHC methodology under development. In addition to CD38, CD59 expression will be measured by IHC in a designated laboratory as an exploratory biomarker. CD59 is a complement inhibitory protein and can contribute to resistance to CDC, which may be important for daratumumab response.

CD38 and CD59 expression will be summarized for all screened subjects.

A listing of subject CD38 and CD59 expression levels correlated with clinical parameters will be provided for all treated subjects.

REFERENCES

1. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059-3067.
2. Jiang W, Freidlin B, Simon R. Biomarker-Adaptive Threshold Design: A Procedure for Evaluating Treatment With Possible Biomarker-Defined Subset Effect. J Natl Cancer Inst 2007; 99:1036-1043.