Janssen Research & Development

Statistical Analysis Plan (Interim Analysis)

A Randomized Phase 2 Trial to Evaluate Three Daratumumab Dose Schedules in Smoldering Multiple Myeloma

Protocol SMM2001; Phase 2

JNJ54767414 (daratumumab)

Status: Approved
Date: 7 March 2017
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-ERI-139372738

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

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AMENDMENT HISTORY

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CI	confidence interval
CR	complete response
CRF	case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FISH	Fluorescence in situ hybridization
FLC	free light chain
IMWG	International Myeloma Working Group
IRR	infusion related reaction
ITT	intent-to-treat
IWRS	interactive web response system
LDH	Lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	disease progression
PFS	progression-free survival
PR	partial response
SAE	serious adverse event
SAP	statistical analysis plan
SMM	smoldering multiple myeloma
sCR	stringent complete response
SD	stable disease
SOC	system organ class
SPEP	serum M-protein quantitation by electrophoresis
TEAE	treatment emergent adverse event
UPEP	urine M-protein quantitation by electrophoresis
VGPR	very good partial response
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for study JNJ54767414SMM2001. The QTc substudy analysis and reporting will be conducted by an external vendor.

1.1. Trial Objectives

The primary objectives are:

- To evaluate if daratumumab can effectively decrease M protein in subjects with intermediate or high-risk smoldering MM (SMM) as assessed by CR rate
- To determine if daratumumab reduces the progression/death rate in subjects with intermediate or high-risk SMM

The secondary objectives are:

- To evaluate preliminary efficacy, including Overall Response Rate (ORR) and PFS
- To evaluate the MRD negative rate
- To evaluate the pharmacokinetics and immunogenicity of daratumumab
- To assess the safety profile of daratumumab given in 3 different dosing schedules
- To determine if daratumumab has an effect on QT interval

1.2. Trial Design

This is a randomized, open-label, 3-arm, multicenter study in subjects at least 18 years old with intermediate or high-risk SMM. Randomization will be stratified based on the number of risk factors for progression to symptomatic MM (<2 vs ≥2).Approximately 120 subjects will be enrolled in this study with 40 subjects planned per treatment arm.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow up Phase. The Screening Phase will be up to 28 days before Cycle 1, Day 1. Treatment cycles are 8 weeks in length. For subjects randomized to Arm A or Arm B, the Treatment Phase will extend from Cycle 1 to Cycle 20. In Arm A, daratumumab will be administered weekly in Cycle 1, every other week in Cycle 2 and Cycle 3, every 4 weeks in Cycle 4 to Cycle 7, and from Cycle 8 to Cycle 20 on Day 1 of each cycle. In Arm B, daratumumab will be administered weekly in Cycle 1 and then on Day 1 of each cycle from Cycle 2 to Cycle 20. For subjects randomized to Arm C, the Treatment Phase consists of Cycle 1 only, when daratumumab will be administered weekly.

Measures to prevent infusion related reactions will include preinfusion medication with methylprednisolone, paracetamol, and an H1-antihistamine before each daratumumab infusion. Methylprednisolone will also be administered after daratumumab infusions in Cycle 1 to prevent delayed infusion reactions.

The Follow-up Phase will begin once a subject completes the planned number of cycles and completes the End-of-Treatment visit within 4 weeks after last dose. Subjects who discontinue before disease progression must continue to have disease evaluations according to the Time and

Events Schedule. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

Three data cutoff timepoints are planned:

- The first data cutoff is for an interim analysis 6 months after the last subject is randomized. This will be the basis for the analysis of the primary study endpoint of CR. All available data at the time of this data cutoff may be included in the interim analysis.

- The second data cutoff will occur 12 months after the last subject is randomized. This will be the basis for the analysis of the primary study endpoint of PD/death rate. All available data at the time of this data cutoff will be included in the Clinical Study Report.

- A third data cutoff will occur at the end of the study. The data collected will be reported as an addendum to the Clinical Study Report.

The end of the study will occur approximately 4 years after the last subject's first dose.

Assessment of tumor response and progression to multiple myeloma will be conducted in accordance with the International Myeloma Working Group (IMWG) criteria. An assessment of MRD will be conducted on whole blood and bone marrow aspirate samples. 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. A QTc substudy will be conducted in a subpopulation of subjects at selected sites. Blood samples will be drawn for assessment of pharmacokinetic and biomarker parameters.

1.3. Statistical Hypotheses for Trial Objectives

For each treatment arm, the following two hypotheses will be tested independently in each arm:

1. H_0: CR rate $\leq 15\%$
   H_a: CR rate $\geq 35\%$
2. H_0: PD/death rate ≥ 0.346/patient-year (median PFS < 24 months)
   H_a: PD/death rate ≤ 0.185/patient-year (median PFS > 45 months)

1.4. Sample Size Justification

This study will enroll 120 subjects (40/arm) in total. With 40 subjects per arm, each arm will have:

- 90% power to show that the true CR rate is 35% at a one-sided level of 0.05
- 80% power to show that the true PD/death rate is 0.185/patient year at a one-sided level of 0.1

If two or more treatment schedules are deemed to be effective, with 40 subjects per arm this study would have:

- 85% probability of identifying the arm with the higher CR

- 80% probability of identifying the arm with the lower PD/death rate

For the QTc substudy, assuming that the intrasubject standard deviation for change from baseline in QTc (ΔQTc) is 20 milliseconds and that the true difference in means is 5 milliseconds, a sample size of 25 evaluable subjects (completers) will have 80% power to show that the upper limit of the two-sided 90% confidence interval (1 sided upper 95% confidence interval) for the difference in mean QTc (ΔQTc) at each timepoint and baseline will be less than 20 milliseconds. To ensure 25 subjects are evaluable, the QTc substudy will enroll approximately 30 subjects.

1.5. Randomization and Blinding

Subjects will be randomized to treatment in a 1:1:1 ratio to either Treatment Arm A, Treatment Arm B, or Treatment Arm C. The method of randomization is randomly permuted blocks. An interactive web based randomization system (IWRS) will be used. Subjects will be stratified according to the number of risk factors present at screening (<2 versus ≥2) using the criteria of Dispenzieri (2013).[1] These risk factors will include: abnormal free light chain (FLC) ratio (<0.126 or >8), serum M-protein ≥3 g/dL, urine M-protein >500mg/24 hours, IgA subtype, and immunoparesis (at least 1 uninvolved immunoglobulin [IgG, IgA, IgM] decreased more than 25% below lower limit of normal [LLN]). Stratification factors will be based on central laboratory analyses.

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

2. GENERAL ANALYSIS DEFINITIONS

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, which is defined as from randomization to the date of the event, the Kaplan-Meier method will be used for descriptive summaries.

2.1. Visit Windows

Any analysis that uses time-to-event data will be based on exact determination of time from randomization to the date of the event. 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 agent administration data. The start date of a particular cycle is defined as the date of the first scheduled dose, 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 55 days after the last dose if the end of treatment visit date is not available. If data (eg, laboratory and vital sign, etc) are collected by cycle, the nominal cycle will be used to summarize data.

2.2. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken before or at the date of first study agent administration (including time if time is available, with exception of parameters associated with disease-related efficacy assessment such as SPEP, UPEP, kappa, lambda, kappa/lambda ratio, serum calcium, and albumin). If a subject is not treated, the date of randomization will be used.

2.3. Study Agent Dosing Dates

Study agent dosing date is the date on which a subject actually received study agent (partial or complete) and will be recorded in the study agent administration dataset.

The treatment start date for a subject is the date of first daratumumab administration. The last study treatment date is defined as the latest date of non-zero dose of daratumumab administration.

2.4. Imputation for Missing/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) , SMM diagnosis date, prior therapies (start date; end date) and start date of first antimyeloma therapy will be imputed.

2.4.1. 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.

2.4.2. Missing/Partial Adverse Event End Date

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.

After imputation, 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.

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

2.4.4. Partial Smoldering Multiple Myeloma Diagnosis Date

For partial date of original smoldering multiple myeloma diagnosis, the following imputation rules will apply:

- If Year is not missing, either Day or Month or both are missing, assume the first day, first month of the year.
- If Year is missing, no imputation will be applied.

2.4.5. Partial Prior Therapy Start/End Date

For partially missing prior smoldering multiple myeloma therapy 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 imputed start/end date is after first dosing date, further adjust the imputed start/end date as the day prior to first dosing date.

2.4.6. Partial First Anti-myeloma Therapy Start Date

The imputation rules for missing/partial start dates of subsequent therapies:

If year or month 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.

2.5. Analysis Sets

The following analysis sets are defined in this study.

- Intent-to-treat (ITT)
- Response evaluable
- Safety
- Pharmacokinetic evaluable
- ECG evaluable
- Immune response evaluable

2.5.1. Efficacy Analysis Set(s)

There are two primary efficacy analysis sets:

1. Response evaluable analysis set, defined as subjects who have measurable disease at baseline as per IMWG criteria (serum and urine, serum only, urine only, FLC) and received at least 1 dose of daratumumab treatment. In addition, subjects must have at least 1 post-baseline disease assessment. Analyses of the co-primary efficacy endpoint of complete response will be based on this population.

2. ITT analysis set, defined as subjects who have been randomly assigned to one of the 3 daratumumab schedules based on IWRS. Analyses of the co-primary efficacy endpoint of PD/death rate and secondary efficacy endpoints of progression-free survival (PFS), and overall survival (OS) will be based on this population.

2.5.2. Safety Analysis Set

The safety analysis set is defined as subjects who have received at least 1 administration of daratumumab (partial or complete). This population will be used for all safety analyses. The safety analyses grouping will be according to treatment actually received.

2.5.3. Pharmacokinetics Analysis Set

The pharmacokinetics analysis set is defined as subjects who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first infusion. All pharmacokinetics analyses are based on the pharmacokinetic evaluable population.

2.5.4. Immune Response Analysis Set

The immune response analysis set is defined as subjects who have at least 1 immunogenicity sample obtained after their first daratumumab administration.

2.6. Definition of Subgroups

The following pre-specified subgroups will be used to analyze some of the efficacy endpoints

Table 1: Subgroup Analyses for Efficacy Endpoints

Subgroup	Definition	Analysis Type
Sex	Male, Female	E
Age	<65, 65 - < 75 years, ≥75 years	E
Race	White, Others	E
ECOG performance score	0, 1	E

E: efficacy (PFS and ORR)

3. INTERIM ANALYSIS

There will be an interim analysis 6 months after the last subject is randomized. The objective of this interim analysis is to assess the primary endpoint of CR to help guide future development of daratumumab in SMM. For the second primary endpoint of PD/death rate per patient-years descriptive statistics will be provided but a formal statistical analysis will not be conducted at this interim analysis. All available data at the time of this data cutoff may be included in the interim analysis.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

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

Subject enrollment of the study will be summarized for each treatment group according to country. The number of subjects by study treatment assigned versus study treatment received will be tabulated. A list of subject's randomization information will be provided. Subjects who did not meet study inclusion/exclusion criteria will be listed.

Subject demographic variables: age (<65 years, 65- < 75 years, and ≥ 75 years), sex, race, height (cm) and weight (kg) will be summarized by treatment group. Baseline disease characteristics including type of smoldering multiple myeloma, bone marrow plasma cell (%), serum free light chain ratio, and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized and tabulated by treatment group. Time from first date of initial diagnosis of smoldering myeloma to randomization will be summarized by descriptive statistics. Additionally, the number of subjects who meet intermediate or high-risk MM criteria specified in the protocol will be reported for each treatment group, respectively.

Baseline skeletal survey and magnetic resonance imaging test results based on investigator assessment will be tabulated. Serum and urine M-protein and quantitative immunoglobulin (IgG, IgA, IgM, IgD, and IgE) will be summarized and presented for each treatment group.

A summary of hematology and chemistry laboratory values at baseline by descriptive statistics and frequency will be provided. The categorization for each laboratory parameter is based on the threshold specified in the inclusion criteria.

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

The interpretation of 12-ECG test will be classified as 3 categories: within normal limits; abnormal, clinically insignificant; and abnormal, clinically significant, the number and percentage of subjects in each category at baseline will be summarized by treatment group.

For subjects who had either Fluorescence in situ hybridization (FISH) or karyotype testing done, cytogenetic abnormality is classified into 2 categories: high-risk and standard-risk. High-risk abnormality is defined as:

- By FISH: t (4; 14), t (14; 16), amp1q21 and 17p deletion.
- By karyotype: t (4; 14) and 17p deletion.

Otherwise, known cytogenetic abnormality has standard-risk.

Subjects meeting the high-risk cytogenetic abnormality criteria will be summarized by the cytogenetic type. In addition, cytogenetic testing methods based on bone marrow investigation will be summarized by the type of analyses performed. The number and percentage of subjects with numerical/ structural changes will be reported for subjects with karyotype testing. For subjects with FISH testing, the number and percentage of subjects with interphase/metaphase FISH will be reported.

4.2. Disposition Information

The number of subjects who are randomized to each treatment group will be summarized. The number and percentage of subjects who are randomized but not treated will be reported. For subjects in safety analysis set, the number and percentage of subjects who discontinued treatment including reasons for discontinuation will be summarized by treatment group. Similar summaries will be presented for subjects who discontinued study including reasons for discontinuation.

4.3. Extent of Exposure

Extent of exposure to daratumumab will be summarized and presented based on the safety analysis set.

Duration of study treatment, defined as the number of days from the date of the first administration of study agents to the date of the last dose, will be summarized by descriptive statistics. The total dose administered for daratumumab (mg/kg) will be summarized by

treatment arm. In addition, the dose intensity of daratumumab (mg/kg/cycle) will be summarized for each treatment arm.

The number of subjects with dose delay including 1, 2 or >2 dose delays will be summarized by frequency. The reasons (AE or other) for dose delay will be reported.

Duration of follow-up calculated from the date of first dose of administration to the end of follow-up for each subject will be summarized for each treatment group and overall.

4.4. Protocol Deviations

Major protocol deviations will be summarized for the ITT population by the following types of deviations:

- Entered but did not satisfy inclusion/exclusion criteria
- Developed withdrawal criteria but not withdrawn
- Received wrong treatment or incorrect dose
- Received an excluded concomitant treatment
- Efficacy assessment deviation
- Other – protocol non-compliance

A list of subjects with major protocol deviations including subject ID, type of deviation, and protocol deviation coded term will be provided.

4.5. Prior and Concomitant Medications

The number and percentage of subjects who received prior systemic therapy will be summarized. Specifically, the summary will be presented by therapeutic class, pharmacologic class, and medication name.

Concomitant medication use will be summarized separately at baseline and during study treatment by therapeutic class, pharmacologic class, and medication name for each treatment group.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

For the co-primary endpoint of CR rate a 1-sided alpha of 0.05 will be used. For the co-primary endpoint of PD/death rate a 1-sided alpha of 0.1 will be used. No adjustments for multiplicity will be made.

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

There are two co-primary endpoints:

- Complete Response (CR) rate, defined as the proportion of subjects with a CR, as defined in Section 9.2.1.1 of the protocol
- PD/Death rate per patient-year, defined as number of events (PD or death)/total PFS for all subjects.

5.2.2. Analysis Methods

5.2.2.1. Complete Response

The number and percentage of subjects who achieve a complete response including 90% exact CI will be calculated for each treatment group based on response evaluable population. The exact p-value to test the hypothesis, H_0: CR rate $\leq$ 15% will also be calculated.

A similar analysis based on complete response based on investigator assessment will also be conducted.

5.2.2.2. PD/Death Rate

This will be considered as the second primary efficacy analysis and will occur one year after the last subject is randomized. The number of subjects with events (progression or death), total PFS and the PD/death rate per patient-year and the 80% confidence interval for the PD/death rate will be tabulated for each treatment arm. The p-value for testing the hypothesis, H_0: PD/death rate $\geq$ 0.346 will also be calculated using a normal approximation.

5.3. Major Secondary Endpoints

The secondary endpoints include, minimal residual disease negative rate (not analyzed in this interim analysis), time to first treatment for active myeloma, overall response rate, progression-free survival, incidence of symptomatic MM with adverse prognostic features (not analyzed in this interim analysis), response to first active MM treatment and overall survival at 4 years.

5.3.1. Time to First Treatment for Active Myeloma

5.3.1.1. Definition

Time to first treatment for active myeloma is defined as the time from randomization to the start of subsequent antimyeloma treatment. Death due to PD without start of subsequent therapy will be considered as event. Subjects who withdrew consent to study or are lost to follow, or die due to causes other than disease progression will be censored at the date of death or the last date known to be alive.

5.3.1.2. Analysis Methods

Analysis of time to first treatment for active myeloma will be based on the ITT analysis set. The Kaplan-Meier method will be used to estimate the distribution of time to first treatment for active myeloma for each treatment group. Median time to first treatment for active myeloma with 90%

CI will be provided. The Kaplan-Meier time to first treatment for active myeloma curve by treatment group will also be provided.

5.3.2. Overall Response Rate

5.3.2.1. Definition

ORR is defined as the proportion of subjects who achieve a partial response or better (i.e., PR, VGPR, CR or sCR) based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment.

5.3.2.2. Analysis Methods

Analysis of ORR will be based on response-evaluable analysis set The number and percentage of subjects in the following response categories will be presented by treatment group: stringent complete response (sCR), complete response (CR), sCR+CR, very good partial response (VGPR), partial response (PR), overall response (sCR+CR+VGPR+PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 90% exact CI for each response category will also be provided.

A similar analysis based on complete response based on investigator assessment will also be conducted.

5.3.3. Progression-free Survival

5.3.3.1. Definition

Progression-free survival is defined as the time from the date of randomization to the date of initial documented PD according to the SLIM-CRAB criteria, or date of death, whichever occurs first.

5.3.3.2. Analysis Methods

Analysis of PFS will be based on the ITT analysis set. The Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. Median PFS with 90% CI will be provided. In addition, the number and percentage of subjects who had a PFS event or were censored will be reported. The Kaplan-Meier PFS curve by treatment group will also be provided.

A similar analysis of PFS based on investigator assessment will also be conducted.

5.3.4. Response to First Active Multiple Myeloma Treatment

5.3.4.1. Definition

Response rate for first active multiple myeloma treatment is defined as the proportion of subjects who achieve a partial response or better (i.e., PR, VGPR, CR or sCR) as reported by the investigator, to their first active multiple myeloma treatment.

5.3.4.2. Analysis Methods

The number and percentage of subjects who achieve an overall response will be calculated for each treatment group based on population of subject who received active multiple myeloma treatment.

5.3.5. Overall Survival

5.3.5.1. Definition

Overall survival (OS) is defined as the time from the date of randomization to the date of death.

5.3.5.2. Analysis Methods

Analysis of OS will be based on the ITT analysis set. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. Median OS with 90% CI will be provided. In addition, the number and percentage of subjects who had an OS event or were censored will be reported. The Kaplan-Meier OS curve by treatment group will also be provided.

In addition, the 6-month and 12-month overall survival rate will be estimated by the Kaplan-Meier product-limit method for each treatment group based on the ITT population. The corresponding 90% CI of the 6-month and 12-month overall survival rate will be constructed.

5.4. Other Efficacy Variable(s)

5.4.1. BOD Progression-free Survival

5.4.1.1. Definition

Biochemical progression is defined as an increase of 25% from nadir value in any one of the following:

- Serum M-component (absolute increase must be ≥0.5 g/dL)
- Urine M-component (absolute increase must be ≥200 mg/24 hours)
- In subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)

Time to biochemical progression is defined as the time from the date of randomization to the date of the first confirmed biochemical progression as defined above.

BOD progression-free survival is the earlier of time to biochemical progression and PFS.

5.4.1.2. Analysis Methods

BOD progression-free survival will be estimated by the Kaplan-Meier product-limit method for each treatment group based on the ITT analysis set. The corresponding 90% CI of BOD progression-free survival will be constructed.

6. SAFETY

Safety assessment will be evaluated through AEs, clinical hematology and chemistry laboratory tests, physical examinations, ECOG performance status, 12-lead electrocardiogram (ECG), and vital signs. Safety analyses will be based on the safety population and presented by the treatment actually received.

6.1. Adverse Events

AEs will be monitored throughout the study. All 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. Each occurrence of a given AE will be recorded with the NCI-CTCAE grade. Only the most severe grade over the course of a given episode will be reported. For AE reporting, adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs), defined as any AE that occurs after the first administration of study agent through 30 days after the last study agent administration; or any AE that is considered drug-related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug-related by the investigator.

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 agent administration. Specifically, the following AE summaries will be presented:

6.1.1. Overview of Adverse Events

An overview of TEAEs will be provided for each treatment group. The overview will include summaries of subjects with any AE, subjects with any toxicity grade 3 or higher AE, subjects with any SAE, AEs leading to study agent dose interrupted, and AEs leading to study agent discontinuation.

6.1.2. Adverse Events by System Organ Class

- Incidence of TEAEs by MedDRA SOC and preferred term
- Incidence of most common (at least 10% in any arm) TEAEs by MedDRA SOC and preferred term
- Incidence of most common (at least 10% in any arm) TEAEs by preferred term

6.1.3. Adverse Events of Toxicity Grade 3 or 4

- Incidence of toxicity grade 3 or 4 TEAEs, by MedDRA SOC, preferred
- Incidence of most common (at least 5% in any arm) toxicity grade 3 or 4 TEAEs, by MedDRA SOC, preferred term

6.1.4. Study Agent-related Adverse Events

- Incidence of TEAEs considered by the investigator to be reasonably related to study agent, by MedDRA SOC and preferred term

6.1.5. Study Agent-Related Grade 3 or 4 Adverse Events

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

6.1.6. Serious Adverse Events (SAEs)

- Incidence of treatment-emergent SAEs, by MedDRA SOC and preferred term

6.1.7. Infusion-Related Reactions

Infusion-related reactions based on investigator assessment will be summarized by treatment group. In addition, subjects with any infusion reactions associated with daratumumab will be listed. The list will include subject ID, treatment group, MedDRA preferred term/verbatim, study day of event, toxicity grade, relationship to study treatment, action taken with study treatment and outcome.

6.1.8. Discontinuations Due to Adverse Events

The number and percentage of subjects who discontinued study treatment due to AEs will be summarized by MedDRA SOC and preferred term.

6.2. Deaths

The number of subjects who died within 30 days of last dose and the number of subjects who died during the study (exclude subjects who died during long-term survival follow-up) will be summarized for all randomized subjects. The primary cause of death collected on CRF page will also be summarized. If the primary cause of death reported is AE, the number of subjects with at least one reasonably related to AE will be further reported.

A list of subjects who died due to AEs during the study (exclude subjects who died during long-term survival follow-up) will be provided.

In addition, subjects with any TEAEs of toxicity grade 3 or higher, SAEs, subjects who discontinued study agent due to AEs will be listed. .

6.3. Adverse Events of Clinical Interest

6.3.1. Infusion-Related Reactions (IRR)

Subjects with any IRR associated with daratumumab administration will be summarized by MedDRA system-organ class and preferred term. The summaries will be presented by all Grades, and Grade 3 or 4, respectively. In addition, the total number of subjects with IRR in more than 1 infusion will be reported.

6.3.2. Infections and Infestations

Infections and infestations refer to adverse events with MedDRA SOC of infections and infestations. A summary of number of subjects with 1 or more toxicity Grade 3 or 4 treatment-emergent infections and infestations by MedDRA preferred term and relationship to treatment will be provided. In addition, incidences of Grade 3 or 4 treatment-emergent infections and infestation will be summarized by MedDRA preferred term and treatment cycle.

6.3.3. Second Primary Malignancies

A listing of subjects who reported second primary malignancies during the study will be provided. The listing will include subject ID, treatment group, diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and initial diagnosis date etc. information whenever a second primary malignancy is observed,

6.4. Clinical Laboratory Tests

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

- Hematology panel: hemoglobin, WBC count, neutrophils (ANC), absolute lymphocyte count (ALC) and platelet count
- Blood chemistry panel: uric acid, total bilirubin, creatinine, BUN, AST, ALT, and alkaline phosphatase, LDH, potassium, sodium, magnesium, calcium

Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be used to summarize laboratory values and change from baseline at each scheduled visit up to Cycle 24 for each treatment group. Line plots of mean with standard deviation of laboratory values over time up to Cycle 20 will be displayed by treatment group for hemoglobin, neutrophils, platelets, AST, ALT, alkaline phosphatase.

The worst toxicity grade in hematology, chemistry, will be summarized by treatment group and toxicity grade. Shift tables from baseline to worst toxicity grade will be provided for laboratory parameters listed above. These tables will summarize the number of subjects with each baseline CTC grade and changes to the maximum CTC grade.

6.5. Vital Signs and Physical Examination Findings

Vital signs (systolic and diastolic blood pressure, heart rate, and temperature) values and change from baseline will be summarized at Day 1 each treatment cycle. Similar analyses will be performed for weight at Day 1 of each treatment cycle. Box plots of weight, systolic blood pressure, and diastolic blood pressure over time up to Cycle 20 will be displayed.

A complete physical examination will be performed during the Screening Period. The number of subjects with any medical history will be reported; furthermore, the number of subjects with medical history of special interest will be summarized by pre-specified preferred term.

6.6. Electrocardiogram

The number and percentage of subjects with normal or abnormal 12-lead ECG results at baseline will be provided. Subjects with an abnormal 12-lead ECG finding during treatment will be listed.

6.7. Other Safety Parameters

6.7.1. ECOG Performance Score

ECOG performance status and change from baseline in ECOG performance status will be summarized at baseline and at each visit that ECOG is assessed (Weeks 5, 9, 17, 25, 33, 41, 49, 65, 81) by descriptive statistics. In addition, the number and proportion of subjects with ECOG performance score at baseline of 0, 1 will be provided.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Unless specified otherwise, descriptive statistics (e.g., number of observations, mean, standard deviation, median, and range) will be used to summarize pharmacokinetics and pharmacodynamics data.

7.1. Pharmacokinetics

Pharmacokinetic samples will be collected from all subjects for determining daratumumab serum concentration.

Serum daratumumab concentrations at each scheduled sample collection timepoint will be summarized by descriptive statistics for pharmacokinetic evaluable population. In addition, mean serum daratumumab concentration-time profiles will be plotted at Cycle 1, 2, 3, 4, 6 and 8 for Arm A, at Cycle 1, 2, 3, 4 and 6 for Arm B, and at Cycle 1 for Arm C, if sufficient data are available.

With regard to serum daratumumab concentrations from subjects enrolled in the QT sub-study, only those from scheduled sample collection time points not specific to the sub-study will be included in this analysis. Serum daratumumab concentrations specific to the QT sub-study will be summarized in a separate QT report.

REFERENCES

1. Dispenzieri A, Stewart AK, Chanan-Khan A, et al. Smoldering multiple myeloma requiring treatment: time for a new definition? Blood 2013;122:4172-4181.