Janssen Research & Development

Statistical Analysis Plan

A Randomized Study of Daratumumab Plus Lenalidomide Versus Lenalidomide Alone as Maintenance Treatment in Patients with Newly Diagnosed Multiple Myeloma Who Are Minimal Residual Disease Positive After Frontline Autologous Stem Cell Transplant

Protocol 54767414MMY3021; Phase 3

JNJ-54767414 (daratumumab)

Status:	Final Amendment
Date:	9 May 2024
Prepared by:	**Janssen Research & Development**
Document No.:	EDMS-ERI-185621295

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

TABLE OF CONTENTS

VERSION HISTORY

SAP Version	Approval Date	Description of Changes
1.0	5/8/2019	Signed by the time the first patient enrolled
2.0	5/9/2024	The following amendments were made: • Study design update per 3 protocol amendments • Sensitivity and supplemental analyses added for MRD and PFS • Additional other efficacy endpoints to be evaluated (PFS2 and time to subsequent therapy) • AEs of special interest are added

ABBREVIATIONS

AE	adverse event(s)
ASCT	autologous stem cell transplant
C_{min}	minimum observed concentration
C_{max}	maximum observed concentration
C_{trough}	lowest drug concentration reached before the next dose is administered
CR	complete response
CTC	Common Terminology Criteria
DR	daratumumab plus lenalidomide
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-MY20	European Organization for Research and Treatment of Cancer Multiple Myeloma Module
EQ-5D-5L	EuroQol Group Five Dimensions Five Levels
FLC	free light chain
HDT	High-dose therapy
HR	hazard ratio
HRQoL	health related quality of life
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IMWG	International Myeloma Working Group
IRR	injection-related reaction
ISS	International Staging System
IV	intravenous
IWRS	interactive web response system
MoA	mechanism of action
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NGF	next-generation flow
NGS	next-generation sequencing
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival on the next line of therapy
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PRO	patient-reported outcome(s)
R	lenalidomide
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SC	subcutaneous
sCR	stringent complete response
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VGPR	very good partial response

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of the analysis sets, derived variables and statistical methods for the planned analysis for the clinical study report (CSR) of the Phase 3 study protocol JNJ-54767414MMY3021, comparing daratumumab plus lenalidomide (DR) versus lenalidomide (R) alone as maintenance treatment in patients with newly diagnosed multiple myeloma who are minimal residual disease (MRD) positive after frontline autologous stem cell transplant (ASCT).

1.1. Trial Objectives

The primary objective is to evaluate conversion rate to MRD negativity following the addition of daratumumab to lenalidomide relative to lenalidomide alone, when administered as maintenance treatment to anti-CD38 treatment naïve patients with newly diagnosed multiple myeloma who are MRD positive as determined by next generation sequencing (NGS), following high-dose therapy (HDT) and ASCT, with or without consolidation therapy.

The secondary objective is to further evaluate the efficacy, health-related quality of life and safety of daratumumab in combination with lenalidomide as maintenance treatment for patients with newly diagnosed multiple myeloma.

Major secondary endpoint is PFS.

Other secondary endpoints include:

- The overall MRD negative conversion rate at any time after the date of randomization.
- Durable MRD negativity rate, defined as the proportion of patients who have achieved MRD negative status (at 10^{-5}) in 2 bone marrow aspirate examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between assessments.
- Response rates by IMWG 2016 criteria including rate of CR and sCR.
- Overall survival (OS).
- Duration of CR.
- Change in HRQoL based on the patient reported outcomes (PROs) utilized in the study
- Safety/tolerability

1.2. Trial Design

This is a Phase 3, randomized, open-label, active-controlled, multicenter study to be conducted at sites in the United States (US) and Canada to primarily evaluate the conversion rate to MRD negativity following 12 months of maintenance treatment with SC daratumumab in combination with lenalidomide relative to treatment with lenalidomide alone in patients with newly diagnosed multiple myeloma who have received at least 4 cycles of induction with or without consolidation, have undergone HDT and ASCT within 12 months of the start of induction, are within 6 months of the ASCT date at the time of randomization, have very good partial response or better at the time of randomization, are MRD positive at the time of screening, and are anti-CD38 treatment naïve.

The study includes a Screening Period; a Maintenance Phase; an End of Treatment (EOT) Visit; and a Follow-up Phase as described below.

- Screening Period: Screening is to be conducted within 60 days prior to randomization; randomization must be within 6 months of the transplant date. Patients must have undergone HDT and ASCT within 12 months of the start of induction therapy.

- Maintenance Phase: Comprised of up to thirty-six, 28-day cycles. Patients will be randomized to receive maintenance treatment with SC daratumumab in combination with lenalidomide or lenalidomide alone. Study treatment will continue until confirmed progressive disease (PD), unacceptable toxicity, withdrawal from study or the end of study maintenance phase.

- EOT Visit: An EOT visit is to be scheduled 30 days (± 7 days) after the last dose of study treatment(s) or, if a patient begins new therapy for multiple myeloma, as soon as possible prior to the start of next-line therapy.

- Follow-up Phase: After the EOT visit, patients will continue to be followed until the end of the study. The end of the study is defined as 36 months from the date of randomization of the last patient. If a patient has died, the date and cause of death will be collected and documented in the eCRF.

Planned enrollment includes a total of 214 patients to be randomly allocated in a 1:1 ratio to one of the two treatment arms, with randomization stratified by cytogenetic risk at screening as determined by the investigator (high risk versus standard/unknown risk).

Study evaluations will include evaluation of the following:

- Standard baseline screening evaluations for this patient population, including assessment of MRD status by NGS assay (Adaptive Biotechnologies' NGS-based MRD assay), and treatments to be administered.
  - Calibration by NGS on archived bone marrow sample collected before induction treatment or before transplant.
  - Efficacy: MRD assessment by NGS at the end of 12, 18, 24, and 36 months after the start of study treatment(s) (ie, after C1D1), myeloma proteins (M-proteins), bone marrow examinations, skeletal surveys, and extramedullary soft tissue plasmacytomas. Disease status will be assessed in accordance with IMWG 2016 response criteria.
- Patient-reported outcomes (PROs): European Organization for Research and Treatment of Cancer Quality of Life Questionnaires-C30 (EORTC QLQ-C30) and Multiple Myeloma Module (EORTC QLQ-MY20), and the European Quality of Life Five Dimensions Questionnaire-5-level (EQ-5D-5L) scale (questionnaire).
- Safety/tolerability: Adverse events, clinical laboratory evaluations, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status.

In addition, patients will be followed for onset of other malignancy, next-line therapy including date of PD on next-line therapy, and survival.

1.3. Statistical Hypotheses for Trial Objectives

The primary endpoint of this study is the MRD conversion rate from baseline to 12 months after maintenance treatment. The null hypothesis is that there is no difference in overall MRD conversion rate between daratumumab in combination with lenalidomide and lenalidomide alone in patients with newly diagnosed multiple myeloma who are MRD positive after frontline ASCT.

1.4. Sample Size Justification

Based on previous reports of MRD negativity rate in lenalidomide-treated myeloma patients, the anticipated MRD (at 10^{-5}) negativity conversion rate is estimated to be 20% for patients treated with lenalidomide alone following post ASCT. Assuming a 20% absolute increase in MRD negativity rate (40% daratumumab plus lenalidomide versus 20% lenalidomide alone) by the end of 12-month maintenance treatment, a sample size of 214 patients (ie, 107 patients per treatment group at 1:1 randomization) will be needed to achieve at least 85% of power to detect such a treatment difference at a 2-sided alpha of 0.05 using continuity corrected chi-squared test.

Disease assessments for each patient will continue until 36 months from the date of randomization of the last patient. It is anticipated that this will yield 64 PFS events and provide approximately 79% power to detect a 50% reduction in the risk of progression or death (HR=0.50, translating to an improvement in median PFS from 60 months to 120 months) with a log-rank test at a 2-sided alpha of 0.05 with an accrual period of 1 year. One interim analysis using Obrien-Fleming alpha spending function is planned at the time of primary endpoint analysis when approximately 32 events are anticipated.

1.5. Randomization and Blinding

This is an open-label study. Patients will be assigned in a randomized manner in a 1:1 ratio to receive either 1800 mg daratumumab SC in combination with lenalidomide or lenalidomide alone as maintenance therapy. Randomization will be stratified by cytogenetic risk (standard risk/unknown versus high risk) at screening as determined by the investigator.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

The primary endpoint of this study is the MRD conversion rate from baseline to 12 months after initiation of maintenance treatment. As subjects do not always adhere to the protocol visit schedule, a 2-month window is extended to 12-month MRD assessment for the primary endpoint.

For analyses of data by cycle, if data are collected by date (e.g., 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 certain cycle is defined as the date of the first scheduled dose of any component of the study treatment, 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 and subsequent antimyeloma therapy minus 1 day if the end of treatment visit date is not available.

In general, if data (e.g., laboratory, vital sign and PRO etc.) are collected by cycle, the nominal cycle will be used to summarize data. However, due to possible cycle delays, assessment performed in the same cycle may not be well aligned in time scale for different subjects. If a subject has 2 or more actual visits in the visit window, the visit closest to the target day will be used as the protocol visit for that visit window.

2.2. Pooling Algorithm for Analysis Centers

All participating centers in the study will be pooled together for analyses.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set(s)

The full analysis set (FAS), following the intent-to-treat principle, includes all subjects randomly assigned to daratumumab in combination with lenalidomide or the lenalidomide alone. Analyses of demographics, baseline characteristics, and efficacy endpoints will be analyzed based on this analysis set.

MRD evaluable analysis set includes all randomized subjects who have MRD assessment at baseline and have at least one post-baseline MRD evaluation. The MRD evaluable analysis set will be used for supplementary analysis of the primary endpoint MRD conversion by 12 months.

2.3.2. Safety Analysis Set

The safety analysis set includes all randomized subjects who received at least 1 dose of study agent.

2.4. Definition of Subgroups

The pre-specified subgroups are summarized in **Error! Reference source not found.**. Additional exploratory subgroup analyses may be performed, if requested and deemed necessary by IDMC for their analyses and decision making.

Table 1: Subgroup Definition

Subgroup	Definition of Group	Analysis Type
Sex	• Male • Female	E, S
Age	• <65, 65-<70, ≥70 years	E, S
Race	• White, Black or African American, Other	E, S
Baseline renal function	• <60 mL/min • 60 to <90 mL/min • ≥90 mL/min Based on creatinine clearance (mL/min) values	S
Baseline body weight	• ≤70 kg • >70 kg	E
Baseline ECOG performance score	• 0 • ≥1	E
International Staging System (ISS) at diagnosis	• I • II • III	E
Cytogenetic risk at screening	• High-risk [a] • Standard-risk/unknown	E
Revised cytogenetic risk at screening	• High-risk [b] • Standard-risk/unknown	E
Cytogenetic risk at MM diagnosis	• High-risk [a] • Standard-risk/unknown	E
Revised Cytogenetic risk at MM diagnosis	• High-risk [b] • Standard-risk/unknown	E

E= efficacy (MRD negativity rate, PFS, CR or better rate), ECOG= Eastern Cooperative Oncology Group, S=Safety

[a] Cytogenetic high risk is defined as positive by FISH/Karyotype testing of subjects having t(4; 14); t(14; 16) and/or 17p deletion.

[b] Revised cytogenetic high risk is defined as positive by FISH/Karyotype testing of subjects having t(4; 14); t(14; 16), 17p deletion, t(14; 20) and/or gain/amp1q.

Note: t(14; 20) is only available for local lab, and unavailable for central lab.

2.5. Study Day and Relative Day

Study Day 1 refers to the date of first study treatment administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (Date of Study Day 1) +1, if visit date is ≥ date of Study Day 1
- Visit date - Date of Study Day 1, if visit date is < date of Study Day 1

2.6. Baseline

The baseline value is defined as the closest non-missing value on or prior to the first study treatment administration (including time if time is available, with exception of parameters associated with disease-related efficacy assessment).

2.7. Unique Lab Value

In general, in instances when there are multiple records at a given visit date for laboratory parameters, the following rules are applied to select the unique laboratory value for analysis:

a) When there are multiple records from both central and local labs, central lab value always takes precedence over local lab value

b) When there are multiple records from central lab for a treatment phase, select the latest value as the unique lab value within the treatment phase

c) When there are multiple records from local lab for a treatment phase, select the latest lab value as the unique lab value within the treatment phase with the exception of cytogenetic risk at diagnosis where the earliest local lab data is used.

Cytogenetic risk is to be determined using data from central or local labs. Local lab data was only used in case of unavailability of central lab data for all the genes defining high risk. No mixture of central and local cytogenetic data was done to define high cytogenetic risk status for a subject.

2.8. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study treatment
  - The day of study treatment, if the month/year of the onset of AE is the same as month/year of the study treatment start date and month/year of the AE resolution date is different
  - The day of study treatment or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study treatment start date and month/year of the AE resolution date are the same
- If the onset date of an AE is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study treatment start date
  - Month and day of the study treatment start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study treatment start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an AE is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analysis is planned for the study primary endpoint. The primary endpoint analysis will be performed after all randomized patients have completed 12 months of maintenance treatment, have disease progression, died, or have been discontinued/withdrawn from study treatment by this time point.

One interim analysis, at the time of primary endpoint analysis, and a final analysis, is to be conducted for PFS. Obrien-Fleming alpha spending function will be used to control overall 2-sided alpha at 0.05.

Final analysis will occur at the end of study which is 36 months from the date of randomization of the last patient, disease progressed, died, or withdrawal of consent, whichever occurs first.

An Independent Data Monitoring Committee, consisting of at least 2 clinicians and 1 statistician, is to be established to review safety data before the primary analysis of the MRD negativity rate, which is to be conducted by the sponsor. The Independent Data Monitoring Committee is to start their review after the first 100 patients have been treated for at least 4 cycles or discontinued and subsequently perform their review every 6 months. Details were provided in a separate Independent Data Monitoring Committee charter.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized by treatment group, and overall. A listing will be provided with subjects' demographic information.

4.1. Demographics and Baseline Characteristics

Table 2 presents a list of the demographic variables that will be summarized by treatment group and overall for the FAS.

Table 2: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Baseline weight (kg)	
Height (cm)	
Baseline body surface area (BSA) (m^2)	
Categorical Variables	
Age (<65, 65-70, ≥70 years)	

Sex (male, female, undifferentiated)	Frequency distribution with the number and percentage of subjects in each category.
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Baseline weight (≤70, >70 kg)	

Table presents a list of the baseline characteristics variables that will be summarized by treatment group and overall.

Table 3: Baseline Characteristics Variables

Continuous Variables	**Summary Type**
Time from diagnosis of multiple myeloma to date of randomization (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Time from the ASCT day to the randomization (months)	
Number of induction cycles	
Received consolidation treatment? (Yes/No)	
Categorical Variables	
Presence of diffuse myeloma-related osteopenia at baseline	Frequency distribution with the number and percentage of subjects in each category.
Baseline number of lytic bone lesions (none, 1-3, 4-10, >10)	
Number of extramedullary plasmacytomas (0, ≥1)	
Baseline ECOG (0, 1, 2, >2)	
ISS stage at diagnosis (I, II, III)	
Medical history collected at baseline or screening visit (by system organ class, preferred term)	
Cytogenetic risk at screening by del(17p), t(4; 14), t(14; 16) (standard risk, high risk)	
Revised cytogenetic risk at screening by del(17p), t(4; 14), t(14; 16), t(14; 20), gain/amp1q21 (standard risk, high risk)	
Cytogenetic risk at MM diagnosis by del(17p), t(4; 14), t(14; 16) (standard risk, high risk)	
Revised cytogenetic risk at MM diagnosis by del(17p), t(4; 14), t(14; 16), t(14; 20), gain/amp1q21 (standard risk, high risk)	

4.2. Disposition Information

For screen failed subjects, reasons for screen failures will be listed.

The number and percentage of subjects in the following disposition categories will be summarized throughout the study by treatment group and overall:

- Subjects randomized
- Subjects randomized and received at least one dose of study treatment
- Subjects randomized and not treated by study treatment

- Subjects who completed all randomized study treatment(s)

- Subjects who discontinued all randomized study treatment(s)
- Subjects who discontinued any randomized study treatment

- Subjects who completed lenalidomide treatment
- Subjects who discontinued lenalidomide treatment
- Reasons for discontinuation of lenalidomide treatment

- Subjects who completed daratumumab treatment
- Subjects who discontinued daratumumab treatment
- Reasons for discontinuation of daratumumab treatment

- Subjects completed the study
- Subjects who discontinued study prematurely
- Reasons for study discontinuation

Duration of follow-up time in months will be summarized descriptively as well as reverse Kaplan-Meier method.

A listing of subjects will be provided for the following categories:

- Study disposition
- Treatment disposition
- Randomization information
- Subjects who were randomized but were not treated.

4.3. Extent of Exposure

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

The dose intensity, which is defined as the sum of total dose administered in all cycles divided by the number of treatment cycles, will be calculated for each study treatment and summarized accordingly.

The relative dose intensity (%) defined as the ratio of total dose actually received and total planned dose (planned dose level times the number of administered injections/medications) will be calculated for each study treatment and summarized by treatment group using descriptive statistics. The planned dose for daratumumab is 1800 mg and 10 mg for lenalidomide per administration.

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

Duration of study treatment, defined as the number of months 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 subjects with treatment cycle delay, dose delay, dose skipped and dose adjusted for each study treatment will be summarized, respectively. The reasons (AE or other) for treatment cycle delay, dose skipped and dose adjusted for each study treatment will also be summarized.

4.4. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category for the FAS including:

- Entered study but did not satisfy inclusion or exclusion criteria
- Developed withdrawal criteria but not withdrawn
- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment
- Efficacy assessment deviation
- Safety assessment deviation, whether it is COVID-19 related
- Other

A listing of all major protocol deviations including COVID-19 will be provided by displaying subject ID, type of deviation, and reasons for deviation.

Subjects with protocol deviations related to COVID-19 will be summarized. A listing of subjects with minor protocol deviations related to COVID-19 will be provided.

4.5. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that continue on after the first dose of study agent.

Summaries of concomitant medications will be presented by therapeutic class, pharmacologic class, drug name and treatment group. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least 1 concomitant medication.

Prior therapies used for induction will be summarized by the drugs captured on the CRF pages.

4.6. Subsequent Antimyeloma Therapy

The total number of subjects who received subsequent antimyeloma therapy will be reported for safety analysis set in each treatment group. A summary of all subsequent antimyeloma therapies as well as the first line of subsequent therapies will be presented by therapeutic class, pharmacologic class and drug name, coded using the WHO Drug Dictionary.

In addition, for subjects who received subsequent antimyeloma therapy, their best response based on investigator's assessments to the first subsequent antimyeloma therapy will be summarized.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical hypothesis tests and 95% confidence intervals presented will be 2-sided.

The primary hypothesis is to be tested at the 0.05 significance level (overall).

If the primary endpoint of the MRD negativity (10^{-5}) conversion rate from baseline to 12 months after initiation of maintenance treatment is statistically significant, the key secondary endpoint PFS will be sequentially tested with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller (1999)[3] that strongly controls Type I error rate.

One interim analysis on the key secondary endpoint, PFS, using the Obrien-Fleming alpha spending function is planned at the time of primary endpoint analysis.

Analyses on all other efficacy endpoints are exploratory and will be tested at 2-sided 0.05 significant level without multiplicity adjustment.

5.1.2. Data Handling Rules

Data handling rules for the primary efficacy endpoint is given in section 5.2.1. There is no imputation planned for the other missing efficacy endpoint values.

5.2. Primary Efficacy Endpoint(s)

The MRD conversion rate from baseline to 12 months after maintenance treatment (defined as the proportion of patients who have achieved MRD negative status [at 10^{-5}] by 12 months after the start of maintenance treatment) as determined by NGS.

5.2.1. Definition

The primary endpoint of this study is the MRD conversion rate from baseline to 12 months after start of maintenance treatment. It is defined as the proportion of subjects who were MRD [at 10^{-5}] positive at baseline and have achieved MRD negative status [at 10^{-5}] as determined by NGS by 12 months of maintenance treatment. The primary endpoint will be analyzed based on FAS.

Subjects' MRD positive status at baseline should be verified. Since subjects do not always adhere to the protocol visit schedule, the post-baseline MRD records from randomization up to 12-month + 2 months will be selected for MRD negativity status evaluation. Subjects with missing or unevaluable MRD status will be considered as MRD positive. Subjects who have achieved MRD negative status on or after PD or switch to subsequent anti-myeloma therapy before PD, will not be considered MRD negative in the primary endpoint analysis.

5.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 5 components:

- Population: subjects with newly diagnosed multiple myeloma eligible for transplant who are ≥VGPR post ASCT and MRD [at 10^{-5}] positive
- Treatment: subjects randomized at 1:1 to DR or R for 36 cycles maintenance treatment
- Variable: a binary variable for the MRD conversion rate from baseline to 12 months after maintenance treatment (defined as the proportion of patients who have achieved MRD negative status [at 10^{-5}] by 12 months after start of maintenance treatment prior to the intercurrent events of subsequent antimyeloma therapy or PD) as determined by NGS.
- Intercurrent event (ICE):
    - subsequent antimyeloma therapy
    - PD
    - composite strategy will be used to count for the intercurrent events as reflected in the variable definition
- Population-level summary: odds ratio of MRD conversion rate for DR vs. R treatment groups

5.2.3. Analysis Methods

The MRD conversion rate will be calculated for each treatment group based on the FAS. The corresponding 95% exact CI will be provided.

The stratified Cochran-Mantel-Haenszel (CMH) method will be used to test if the MRD conversion rate is the same between the two treatment groups. Stratification factor included in the analysis is baseline cytogenetic risk per investigator's assessment (high risk versus standard/unknown risk) as used for randomization of the study. The estimate of odds ratio and its 95% confidence interval will be provided. P-value will be provided by Fisher's exact test.

The following supplemental analyses may be performed in a similar manner as described above:

- MRD negativity conversion rate (10-5) by 12-months for the MRD-evaluable analysis set
- MRD negativity conversion rate (10-5) by 12-months for subjects in FAS who achieved CR or better response per computerized algorithm at any time during the study
- MRD negative (10^{-5}) CR conversion rate by 12 months of maintenance treatment in FAS where MRD negative CR conversion rate is defined as the proportion of subjects achieved MRD negativity and CR or better response by 12-months of maintenance treatment according to IMWG criteria per computer algorithm
- MRD negativity rate at 10^{-4}, 10^{-5} and 10^{-6} by 12 months of maintenance treatment in FAS
- MRD negativity (10^{-5}) conversion rate by 12-months of maintenance treatment by subgroups of subjects according to Section 2.4. Analysis will be performed similarly as

the primary analysis except that randomization stratification factor will be excluded from CMH test. Forest plot will be generated.

5.3. Major Secondary Endpoints

The major secondary efficacy endpoint is progression-free survival (PFS).

5.3.1. Definition

PFS, defined as the duration from the date of randomization to either PD or death, whichever occurs first. Disease progression will be determined according to IMWG 2016 criteria per computer algorithm. For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy. Subjects who withdrew consent from the study before disease progression will be censored at the last disease assessment. Subjects who are lost to follow-up will be censored at the last disease assessment before subjects are lost to follow-up. Subjects who have not progressed and are still alive at the cutoff date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at the date of randomization.

Table 4: PFS Event and Censoring Method

Situation	Outcome	Date of Event or Censoring
Disease progression prior to start of subsequent antimyeloma therapy	PFS event	Earliest date that indicates disease progression
Death without subsequent antimyeloma therapy and without disease progression *	PFS event	Date of death
No postbaseline disease assessment after randomization	Censored	Date of randomization
Disease progression or death immediately after 2 or more missing consecutive disease evaluations	Censored	Date of last disease assessment
Others, such as: • Withdrawal of consent to study participation • Lost to follow-up • Start of subsequent antimyeloma therapy prior to disease progression or death	Censored	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, or start of subsequent antimyeloma therapy

*Subjects who died after consent withdrawal will be censored at the date of consent withdrawal from PFS analysis

5.3.2. Analysis Methods

Analysis of PFS will be based on the FAS. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment group. The median PFS with 95% CI will be provided. In addition, the number and percentage of subjects who had a PFS event or were censored will be reported. The reasons for PFS censoring will be summarized accordingly. The Kaplan-Meier PFS curve will also be plotted by treatment group.

The treatment comparison of the distribution of overall PFS will be based on a stratified log-rank test. The p-value from a stratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on a stratified Cox's regression model with treatment

as the sole explanatory variable. Stratification factor used in the analyses include baseline cytogenetic risk (high risk versus standard/unknown risk) as used for randomization of the study.

In addition, PFS rate with 95% CI will be estimated at various time points by Kaplan-Meier method for each treatment group.

To evaluate the robustness of PFS analysis, the following sensitivity and supplementary analyses may be performed in a similar manner as described above:

Sensitivity

- Unstratified analysis of PFS by using unstratified log-rank test and unstratified Cox's regression model
- Progressive disease based on investigator assessment according to the IMWG response criteria
- Not censoring for death or disease progression after 2 or more missing consecutive disease evaluations: For any disease progression identified by the computer algorithm or death, if there are 2 or more consecutive missing scheduled disease evaluations between the event date and the latest date of scheduled disease evaluation (includes serum M-protein, urine M-protein, and serum FLC only) immediately preceding the event, this event will be considered as a PFS event in the analysis

Supplementary

- Not censor the events after the start of subsequent antimyeloma therapies; Progression or death occurred after the start of subsequent anti-myeloma therapies will NOT be censored at the last disease assessment before the start of subsequent therapies. If there is no confirmed progressive disease, the subjects will be censored at the last disease assessment before subjects are lost to follow-up or withdrawal of consent to study
- Censor the death due to COVID-19 at the date of last disease evaluation before the date of death for those who have not developed a confirmed PD
- Censor the subjects who permanently discontinue treatment/study due to COVID-19 (censor at last disease evaluation before treatment/study discontinuation)
- PFS subgroup analysis by overall MRD conversion status (at 10^{-5}) for subjects who achieved MRD (at 10^{-5}) conversion from positive at baseline to negative at any time during treatment period, and for subjects who did not achieve the MRD negative conversion.
- PFS subgroup analysis according to Section 2.4. Analysis will be performed similarly as the main PFS analysis except that randomization stratification factor will be excluded from Cox model and log-rank test. Forest plot will be generated.

5.4. Other Efficacy Endpoints

Other efficacy endpoints include the overall MRD conversion rate at any time after randomization, durable MRD negativity rate, response rates including CR or better rate and sCR rate, OS, and duration of CR.

5.4.1. Definition

MRD by NGS are evaluated post-baseline at the end of 12, 18, 24, and 36 months after the start of study treatment(s). The overall MRD negativity (10^{-5}) conversion rate at any time after randomization is defined as the rate of MRD converted from positive at baseline to negativity at the threshold 10^{-5} achieved at any time after randomization.

In addition, MRD negativity (10^{-5}) conversion rate at 12, 18, 24 and 36-months landmark time with +/- 2 months window, as well as accumulative rate up to these timepoints will be summarized. MRD negativity (10^{-5}) CR conversion rates for FAS patients, and MRD negativity (10^{-5}) conversion rates for those achieved CR or better response per computerized algorithm will be summarized in a similar manner.

Durable MRD (≥1 year) negativity rate, defined as the proportion of subjects who have achieved MRD negative status (at 10^{-5}) in 2 bone marrow aspirate examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between assessments. Subjects who have achieved MRD negative status on or after PD or switch to subsequent anti-myeloma therapy before PD, will not be considered MRD negative. Subjects with missing or unevaluable MRD status will be considered as MRD positive.

Similar analysis will be performed for durable MRD (≥6 months) negativity rate.

OS, measured from the date of randomization to the date of the subject's death due to any cause. Subjects who died after consent withdrawal will be considered as having an OS event. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. If the patient is alive and vital status is unknown, then the patient's data will be censored at the date the patient was last known to be alive determined by the maximum collection/assessment date from among selected data domains within the clinical database.

Response rates by IMWG 2016 criteria including CR or better rate and sCR rate, defined as the proportion of subjects who achieve the respective responses prior to the first subsequent anti-myeloma therapy per computer algorithm in accordance with the IMWG criteria, during or after the study treatment. All subjects are assumed to be VGPR at baseline to enter the study per inclusion criteria. Subgroup analysis will be performed for CR or better rate per computer algorithm with forest plot provided. In addition, responses per investigator assessment by IMWG 2016 criteria will be summarized. Shift tables will be provided to summarize the best responses from baseline vs. post-baseline for each treatment group.

Duration of CR, calculated from the date of initial documentation of a response of CR or sCR at or after randomization to the date of first documented evidence of PD (as defined in the IMWG criteria), or death due to PD, whichever occurs first, for subjects who have CR or better as their best response. Subjects who have not progressed or who die due to causes other than disease progression will be censored at the last disease evaluation before the start of subsequent antimyeloma therapy. Subjects who achieved CR or sCR prior to randomization will use randomization date as their starting time of CR or sCR for calculating duration of CR.

Time to the first response of CR or better is defined as the time between randomization and the first efficacy evaluation at which the subjects meet all criteria for CR or better based on computerized algorithm, according to IMWG response criteria. For subjects who achieved CR or sCR prior to randomization, time to CR or better will be set as 0 day.

In addition to protocol specified other secondary efficacy endpoints, progression-free survival on next line of therapy (PFS2) and time to subsequent therapy will be evaluated.

PFS2 is defined as the time from randomization to progression on next line of therapy or death, whichever comes first. Disease progression on the next line of treatment will be based on investigator assessment. Any deaths are considered as PFS2 events. Subjects who start next line of therapy without disease progression on study treatment will be censored at the last disease assessment before starting next line of therapy. For subjects who start next line of therapy after progression on study treatment, are still alive and not yet progress on next line of therapy or progressed on or after a 2nd line of next therapy, they will be censored on minimum of the last date of follow-up and start date of 2nd line of next therapy minus 1. Subjects without any post-baseline follow-up will be censored at the randomization. Time to subsequent antimyeloma therapy 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.

5.4.2. Analysis Methods

The analysis of the overall MRD (10^{-5}) conversion rate at any time after randomization, durable MRD negativity rate, the CR or better rate, and sCR rate will be performed similarly to that for the primary endpoint on the FAS, as described in Section 5.2.3. Similarly, for thresholds 10^{-4} and 10^{-6}, the overall MRD negativity rate at any time after randomization will be analyzed similarly as for the threshold 10^{-5}.

The time-to-event variables (ie., OS, duration of CR, PFS2 and time to subsequent antimyeloma therapy) will be performed using the approach for PFS, as described in Section 5.3.2.

Time to the first response of CR or better will be summarized using descriptive statistics for those who reached CR or better response.

6. SAFETY

All safety analyses will be based on the safety analysis set based on actual treatment received, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

6.1. Adverse Events

All adverse events whether serious or non-serious, will be reported from the time a signed and dated informed consent form (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 antimyeloma therapy, whichever occurs first. Adverse Events will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0. The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the latest 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 antimyeloma 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; or any AE that is present at baseline but worsens in toxicity grade during the TEAE reporting period, or after the TEAE reporting but is considered drug-related by the investigator. If the event occurs on the day of the first study treatment and either event time or time of study drug are missing, then the event will be assumed to be treatment-emergent. If the event date is recorded as partial or completely missing, then the event will be considered as treatment-emergent unless it is known to be prior to the first study treatment based on partial onset date or resolution date.

The following AE summaries will be presented by treatment group.

- An overview of TEAEs, including the number and percentage of subjects with
  - TEAEs
  - treatment-emergent SAEs
  - TEAEs related to study treatment
  - TEAEs leading to discontinuation of study treatment which includes those subjects indicated as having discontinued treatment due to an AE on the End of Treatment Disposition CRF page
  - TEAEs leading to discontinuation of any study treatment with action taken of drug withdrawn on AE CRF page
  - TEAE by maximum toxicity grade of 1 to 5
  - deaths due to TEAE

- TEAEs by SOC and PT, and by maximum toxicity grade of 1 to 5
- Most common (>10% in either DR or D) TEAEs by SOC and PT

- TEAEs related to study treatment by SOC and PT

- TEAEs related to study treatment with toxicity grade 3 or 4 by SOC and PT

- TEAEs with toxicity grade 3 or 4 by SOC and PT
- Most common (>5% in either DR or D) TEAEs with toxicity grade 3 or 4 by SOC and PT
- TEAEs with toxicity grade 3 or 4 by SOC, PT and by treatment cycle of first onset

- TEAEs leading to dose modifications or drug interruptions of any study treatment(s) by SOC and PT where dose modifications refer to action taken of the AEs with dose reduced, dose increased, or dose delayed according to AE CRF page
- TEAEs leading to dose modifications or drug interruptions of lenalidomide by SOC and PT
- TEAEs leading to dose modifications or drug interruptions of daratumumab by SOC and PT

- Treatment-emergent SAEs by SOC and PT
- Treatment-emergent SAEs related to study treatment by SOC and PT
- Treatment-emergent SAEs by SOC, PT, and toxicity grade
- Most common (>2% in either DR or D) Treatment-emergent SAEs by SOC, and PT
- Treatment-emergent SAEs by SOC, PT and by treatment cycle of first onset (Cycles 1-2, Cycles 3-6. Cycles 7+)

- TEAEs leading to discontinuation of any study treatment by SOC, and PT. The AEs leading to discontinuation of any study treatment are based on AEs recorded in the AE CRF page with an action taken of drug withdrawal for any study treatment.

- TEAEs leading to discontinuation of study treatments per treatment disposition by SOC, PT, and toxicity grade 3/4. This summary includes TEAEs 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.

6.2. Deaths

6.2.1. Death Due to TEAEs

TEAEs with outcome of death will be summarized by SOC and PT and a listing is to be provided. TEAEs with outcome of death due to COVID-19 will also be summarized by SOC and PT.

6.2.2. All Deaths

A summary of all death and cause of death will be tabulated overall and by treatment group. Specifically, the number of subjects who died during the study will be summarized for the safety analysis set. The primary cause of death collected on the death information CRF page will be reported. If the primary cause of death is an AE, the number of subjects who have a related AE and unrelated AE will be further summarized. The similar summaries will be presented for subjects who died within 30 days of last study treatment dose and within 60 days of first study treatment dose, respectively.

6.3. Adverse Events of Clinical Interest

6.3.1. Injection-Related Reactions (IRR) and Injection Site Reaction

Subjects with any treatment-emergent IRR and injection site reaction associated with daratumumab administration will be summarized by MedDRA SOC and PT. The summaries will be presented for all grades, Grade 3 or 4, Grade 5, and SAEs.

The number and percentage of subjects with IRRs will be summarized by time of injections (first injection, second injection or subsequent injections) and by MedDRA SOC and PT.

A listing of subjects with treatment-emergent IRR and injection site reaction associated with daratumumab administration will be provided.

6.3.2. Infections and infestations

Infections and infestations refer to adverse events with SOC of infections and infestations. A summary of number of subjects with 1 or more treatment-emergent infections and infestations will be summarized by MedDRA PTs for all grades, Grade 3 or 4, Grade 5, and SAEs. Additional summary analysis will be performed by onset time (i.e., ≤6 months vs. 6- ≤12 months vs. >12 months) based on the first onset of the infections and infestations.

6.3.3. Opportunistic Infection

Opportunistic infection events refer to the adverse events defined by SMQ search of "opportunistic infections (SMQ)". These TEAEs will be summarized by SOC and PT for all grades, Grade 3 or 4, Grade 5, and SAEs.

6.3.4. COVID-19 Infections

To evaluate COVID-19 pandemic's impact on the study, TEAEs of COVID-19 infections will be summarized by MedDRA SOC and PTs for all grades, Grade 3 or 4, Grade 5, and SAEs. The COVID-19 TEAEs will be identified through PTs which contain text string of "COVID-19".

All COVID19 TEAEs will be listed with subjects vaccination status displayed for COVID-19.

6.3.5. Hemorrhage Events

Hemorrhage events refer to the adverse events defined by Standardized MedDRA Queries (SMQ) with the first subcategory SMQ of hemorrhage terms (exclude laboratory terms). Incidences will be summarized by MedDRA SOC and PT for all grades, Grade 3 or 4, Grade 5, and SAEs.

6.3.6. Cytopenia

Cytopenia will be identified by the following PTs and grouped into 4 categories. They will be summarized by MedDRA SOC and PT for all grades, Grade 3 or 4, Grade 5, and SAEs:

- Neutropenia
  - Agranulocytosis

  - Granulocyte count decreased
  - Granulocytopenia
  - Neutropenic infection
  - Neutrophil count abnormal
  - Neutrophil count decreased
  - Neutropenia
  - Febrile neutropenia

- Anaemia
  - Anaemia
  - Anaemia macrocytic
  - Anaemia megaloblastic
  - Autoimmune haemolytic anaemia

- Thrombocytopenia
  - Megakaryocytes decreased
  - Platelet count decreased
  - Platelet production decreased
  - Thrombocytopenia
  - Thrombotic thrombocytopenic purpura
  - Acquired amegakaryocytic thrombocytopenia
  - Amegakaryocytic thrombocytopenia
  - Congenital thrombocytopenia
  - Heparin-induced thrombocytopenia
  - Immune thrombocytopenic purpura
  - Non-immune heparin associated thrombocytopenia
  - Neonatal alloimmune thrombocytopenia
  - Severe fever with thrombocytopenia syndrome
  - Spontaneous heparin-induced thrombocytopenia syndrome
  - Thrombocytopenic purpura

- Lymphopenia
  - Lymphocyte count decreased

- B-lymphocyte count decreased
- T-lymphocyte count decreased
- Lymphopenia

6.3.7. Hepatitis B virus reactivation

Hepatitis B virus reactions TEAEs will be summarized by SOC and PT for all grades, Grade 3 or 4, Grade 5, and SAEs. Hepatitis B virus reactions can be identified by PT as below:

- Hepatitis viral
- Acute Hepatitis B
- Hepatitis B
- Hepatitis B reactivation
- Chronic Hepatitis B
- Hepatitis B DNA assay positive
- Hepatitis B DNA increased

6.3.8. Other Malignancy

Other malignancies will be grouped and summarized by treatment groups. A listing of subjects who reported other malignancies during the study will be provided. This listing will include diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no), pathology diagnosis (biopsy, aspirate, etc.), outcome, treatment for malignancies and other information whenever a new malignancy is observed.

6.4. Adverse Events by Subgroups

The following subgroup analysis of AEs will be performed based on subgroups specified in Section 2.4:

- Overview of TEAEs
- All TEAEs

6.5. Clinical Laboratory Tests

On-site or accredited local laboratory must be used for hematology laboratory assessments. Results of local hematology tests must be evaluated before each study treatment administration to guide treatment decisions.

Applicable laboratory results will be graded according to NCI-CTCAE version 5.0. The worst toxicity grade in hematology and chemistry during the treatment will be summarized by treatment group and toxicity grade. Shift tables from baseline to worst toxicity grade during the treatment will be provided for each laboratory analyte listed below. These tables will summarize the number of subjects with each baseline CTC grade and changes to the maximum CTC grade.

Hematology parameters include:

- hemoglobin
- neutrophils
- lymphocytes
- platelet
- white blood cell (WBC)

Chemistry parameters include:

- sodium
- potassium
- creatinine
- corrected calcium
- bilirubin
- alkaline phosphatase
- albumin
- glucose
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)

6.6. Vital Signs and Physical Examination Findings

Vital signs (systolic and diastolic blood pressure, pulse, and body weight) are measured at screening visit. Vital signs are taken at a different schedule for the two treatment groups at post-baseline. For the lenalidomide only group on Day 1 of odd cycles (ie, cycles 1, 3, 5, 7, and so on). For the daratumumab plus lenalidomide group on Day 1 of cycle 1 immediately before administration, at end of administration; and at 0.5 and 1 hour after end of administration; from cycle 2 onwards: Immediately before and at the end of daratumumab administration on Day 1 of odd cycles (ie, Day 1 of cycles 3, 5, 7, and so on). The values and change from baseline of each parameter will be summarized at each scheduled time point by treatment group.

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

6.7. Electrocardiogram

The interpretation of the electrocardiograms (ECGs) as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of subjects meeting the normality criteria. The interpretation will be summarized at baseline and the post-baseline timepoints by treatment group.

6.8. ECOG Performance Score

ECOG performance status evaluates the effect of the disease status on the activities of daily living will be assessed at screening visit, at Day 1 of old cycles. Descriptive statistics will be used to summarize ECOG performance status at baseline, scheduled post-baseline timepoints (including change from baseline) for each treatment group. Shift table from baseline to the worst score during the treatment period will be provided.

6.9. Transfusions

The number of subjects with transfusions during the study will be summarized by the type of transfusions. Also, the number of transfusions will be summarized similarly.

7. FUNCTIONAL STATUS AND WELL-BEING

7.1.1. Definition

Functional status and well-being will be assessed using three patient-reported outcomes (PROs) measure: the EORTC-QLQ-C30, EORTC-QLQ-MY20, and the EQ-5D-5L, which will be measured at baseline, 6 months, 12 months, 24 months, and 36 months. They will be scored based on the instrument developer guidelines. No imputation will be done for the PRO data.

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale (GHS), 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The instrument contains 28 items using a Likert scale with 4 response options: “Not at All,” “A Little,” “Quite a Bit,” and “Very Much” (scored 1 to 4). Two additional items use response options (1 to 7): 1 = Very Poor, to 7 = Excellent. All scale and item scores will be linearly transformed to be in the range from 0 to 100 according to the algorithm in EORTC QLQ-C30 scoring manual, version 3.0 (Fayers et al, 2001). A higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

The EORTC Multiple Myeloma Module (QLQ-MY20) has 20-items that make up 4 scales: disease symptoms, side effects of treatment, future perspective, and body image. Scoring and interpretation are similar to the EORTC QLQ-C30.

The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale (VAS) rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual.

7.1.2. Analysis Methods

Analysis of PRO data will be performed on the FAS. For subjects with multiple records at the same visit, the closest one to the scheduled visit date will be selected for analysis. Compliance rates for completion of EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L at each time point will be generated based on number of received and expected. Compliance is defined as the actual number of assessments received for a visit divided by the expected number of assessments for that visit, the expected number of assessments per visit will be determined by subject-level study completion status.

The PRO endpoints are secondary and not part of the statistical hierarchy. Type 1 error control will not be applied to PRO data.

Key PRO endpoints

- EORTC-QLQ-C30 GHS, Physical Functioning, Fatigue, Pain subscales
- EORTC QLQ-MY20 Disease symptoms scale
- EQ-5D-5L utility score and VAS

Descriptive statistics (n, mean, standard deviation, median, and range) at each time point and the change from baseline will be summarized by treatment group. Line plots of mean change from baseline, with standard error, over time will be displayed by treatment group.

A mixed effects model with repeated measures analysis will be conducted estimating change from baseline at each time point between two treatments. FAS subjects who have a baseline value and at least one post-baseline value are included in the analysis. Change from baseline will be fitted to a mixed effects model including subjects as a random effect, and baseline value, treatment group, time in treatment cycles, treatment-by-time interaction, and randomization stratification factor as fixed effects. A mean change between 5 and 10 points on the 1 to 100 scales of the EORTC QLQ-C30 and EORTC QLQ-MY20 has been defined as noticeable by subjects and regarded as a significant change or a meaningful change (EORTC Quality of Life Group).

For the key PRO endpoints, time to worsening and time to improvement will be derived. A distribution-based method will be used to define improvement/worsening in scores, i.e., half standard deviation away from the mean score at baseline combining both treatment groups.

Time to improvement will be summarized by using descriptive statistics such as mean, standard deviation, median and range.

Time to worsening will be estimated using Kaplan-Meier methods. The hazard ratio for daratumumab plus lenalidomide relative to lenalidomide and its associated 95% confidence interval (CI) will be calculated based on the stratified Cox proportional hazards model by the stratification factor at randomization. Death due to disease progression will be considered as worsening. Subjects who have not met the definition of worsening will be censored at the last PRO assessment. Subjects without baseline assessment or post-baseline assessment will be censored at date of randomization. A Kaplan-Meier figure for the key PRO endpoints will be generated to show time to worsening and censored subjects.

Other PRO endpoints

Other scales of EORTC QLQ-C30 and QLQ-MY20 include:

- EORTC QLQ-C30
  - functional scales: role, cognitive, emotional, and social
  - symptom scales: nausea and vomiting
  - single-item score: dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties
- QLQ-MY20

- side effects of treatment
- future perspective
- body image.

The change from baseline at each time point will be summarized descriptively by treatment group.

REFERENCES

1. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20(9):1467-1473.

2. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011; 117(18):4691-4695.

3. Tang DI, Geller NL. Closed testing procedures for group sequential clinical trials with multiple endpoints. Biometrics. 1999; 55(4):1188-1192

4. Fayers, P., Aaronson, N. K., Bjordal, K., Groenvold, M., Curran, D., & Bottomley, A. (2001). EORTC QLQ-C30 Scoring Manual (3rd edition). (3rd ed.) Brussels: European Organisation for Research and Treatment of Cancer.

5. Cocks K, Cohen D, Wisløff F, et. al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. Eur. J. Cancer. 2007; 43:1670-1678.

Signature

User	Date	Reason