Janssen Research & Development

Statistical Analysis Plan

A Multicenter Phase 2 Study to Evaluate Subcutaneous Daratumumab in Combination with Standard Multiple Myeloma Treatment Regimens

Protocol 54767414MMY2040; Phase 2

JNJ-54767414 (daratumumab)

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

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AMENDMENT HISTORY

SAP Version	Issue Date
Original SAP	20 March 2019
Amendment 1	08 September 2020

The following is a summary of the major changes from the original version of the SAP:

1. Primary analysis about the safety and efficacy of daratumumab SC in combination with carfilzomib and dexamethasone (D-Kd) was added.
2. Updated the intercurrent event in estimand (section 5.2.2)

ABBREVIATIONS

AE	adverse event
ALB	albumin
ALKY	alkylating agent
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
B2MG	beta2 microglobulin
BUN	blood urea nitrogen
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CT	cancer therapy
CTSQ	Cancer Therapy Satisfaction Questionnaire
Dara-IV	daratumumab for intravenous infusion
Dara-SC	daratumumab administered subcutaneously
DMC	Data Monitoring Committee
DOR	duration of response
DPS	Data Presentation Specifications
ECG	electrocardiograms
ECOG	European Cooperative Oncology Group
eCRF	electronic case report form
FLC	free light chain
FM	Farrington-Manning
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GM	geometric mean
HLT	high level term
ICH	International Conference on Harmonization
LDH	lactic acid dehydrogenase
LLN	lower limit normal
IMiD	immunomodulatory drug
IMWG	International Multiple Myeloma Working Group

IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
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	progressive disease
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PN	peripheral neuropathies
PP	per-protocol
PR	partial response
PT	preferred term
RBC	red blood cell
rHuPH20	recombinant human hyaluronidase
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SET	study evaluation team
SMQ	standardized MedDRA queries
SOC	system organ class
SWT	satisfaction with therapy
TEAE	treatment-emergent adverse event
TLFs	tables, listings and figures
TLS	tumor lysis syndrome
TNT	time to next therapy
TTP	time to disease progression
TTR	time to response
ULN	upper limit normal
VGPR	very good partial response
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of the analysis set(s), derived variables and statistical methods for the primary analysis of the open-label, multicenter, Phase 2 study to demonstrate that daratumumab administered by subcutaneous (SC) injection in combination with standard treatment regimens is safe and efficacious in subjects with newly diagnosed multiple myeloma (MM) or in subjects with relapsed or refractory disease.

1.1. Trial Objectives

Primary Objectives

- To evaluate the clinical benefit of SC daratumumab administered in combination with standard MM regimens in subjects with MM as measured by overall response rate (ORR) or very good partial response (VGPR) or better rate

Secondary Objectives

- To evaluate safety and pharmacokinetics (PK) of SC administration of daratumumab in combination with standard MM regimens
- To evaluate additional clinical benefit of SC daratumumab administered in combination with standard MM regimens in subjects with MM
- To characterize the immunogenicity of daratumumab and rHuPH20 following SC administration
- To evaluate minimal residual disease (MRD) negativity rate in the D-VMP (daratumumab in combination with bortezomib, melphalan and prednisone), D-Rd (daratumumab in combination with lenalidomide and dexamethasone) cohorts, and D-Kd (daratumumab in combination with carfilzomib and dexamethasone)

1.2. Trial Design

This is a multicenter, open-label, phase 2 study to investigate the efficacy and safety of Dara SC in combination with bortezomib, lenalidomide, and dexamethasone (VRd) in subjects with newly diagnosed MM who are transplant eligible; or in combination with bortezomib, melphalan, and prednisone (VMP) in subjects with newly diagnosed MM who are ineligible for transplant; or in combination with lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory MM; or in combination with carfilzomib and dexamethasone (Kd) in subjects in first relapse or refractory MM after initial treatment with a lenalidomide-containing regimen. Approximately 60 subjects will be treated in each cohort. Subjects enrolled in the daratumumab, bortezomib, lenalidomide, and dexamethasone cohort (D-VRd) will be treated for 4 cycles and will be evaluated for a VGPR or better rate thereafter. Hematopoietic stem cell collection and autologous transplant will be performed off protocol. Subjects enrolled in the D-VMP, D-Rd and D-Kd cohorts will be treated until disease progression.

The data cutoff for the primary analysis will occur at least 6 months after approximately the sixtieth subject is enrolled in the last treatment cohort (D-VRd, D-VMP, or D-Rd). All available

data at the time of this data cutoff will be included in the Clinical Study Report. The cutoff for the primary analysis for the D-Kd cohort will occur at least 6 months after approximately the 60th subject is enrolled in the D-Kd cohort. The study will end 18 months after the last subject is enrolled in the D-Kd cohort. Data collected through the end of the study will be reported as an addendum to the Clinical Study Report.

A study evaluation team (SET) consisting of the participating investigators the sponsor's medical monitor, the sponsor's clinical pharmacologist (if PK data are being evaluated), the sponsor's statistician the sponsor's safety officer, and the sponsor's study manager will evaluate safety data after at least 6 toxicity-evaluable subjects complete Cycle 1 in each cohort.

1.3. Statistical Hypotheses for Trial Objectives

The hypothesis is that the addition of daratumumab administered SC to standard MM regimens will improve responses compared to response data observed in completed phase 3 studies without daratumumab.

1.4. Sample Size Justification

For the D-VMP cohort, 60 subjects will be required to test the null hypothesis that the ORR is at most 70%, against the alternative hypothesis that the ORR is at least 90% with a 1-sided alpha of 0.05 and at least 98% power (Table 1). Similarly, for the D-Rd cohort, the corresponding power is >90% to test the null hypothesis that the ORR is at most 75%, against the alternative hypothesis that the ORR is at least 90% (Table 1). For the D-VRd cohort, 60 subjects will achieve a power of at least 93% to test the null hypothesis that the response rate of VGPR or better is at most 50%, against the alternative hypothesis that the ORR is at least 70% with a 1-sided alpha of 0.05 (Table 1). For the D-Kd cohort, the corresponding power is >80% to test the null hypothesis that the ORR is at most 65%, against the alternative hypothesis that the ORR is at least 80%. (Table 1).

Table 1: Hypothesis and Power Table

Cohort	N	H_0	H_1	Power
D-VRd	60	VGPR or better rate ≤50%	VGPR or better rate ≥70%	>93%
D-VMP	60	ORR ≤70%	ORR ≥90%	>98%
D-Rd	60	ORR ≤75%	ORR ≥90%	>90%
D-Kd	60	ORR ≤65%	ORR ≥80%	>80%

1.5. Randomization and Blinding

This is a non-randomized open-label study, no randomization and blinding procedures will be performed for this study. Each subject will be assigned into the treatment cohort for which he or she is eligible and will receive a unique subject number.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

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 cycle is defined as the first scheduled dose date of the study treatment for that particular cycle, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or the minimum of last dose date plus 30 days or subsequent anticancer therapy minus 1 day, if the end of treatment visit date is not available.

In general, if data (e.g., laboratory and vital sign etc.) are collected by cycle, the nominal cycle will be used to summarize data. However, due to possible cycle delays, assessment performed in the same cycle may not be well aligned in time scale for different subjects. To address this, by-week windowing rules may be applied in the overtime data summary by study week.

2.2. Pooling Algorithm for Analysis Centers

Data from all study centers will be pooled for analyses.

2.3. Study Treatment and Study Drug

For subjects who receive D-VRd treatment, study treatment refers to bortezomib, dexamethasone, lenalidomide, and daratumumab SC.

For subjects who receive D-VMP treatment, study treatment refers to bortezomib, melphalan, prednisone, and daratumumab SC.

For subjects who receive D-Rd treatment, study treatment refers to lenalidomide, dexamethasone, and daratumumab SC.

For subjects who receive D-Kd treatment, study treatment refers to carfilzomib, dexamethasone, and daratumumab SC.

Study drug refers to daratumumab SC for all the subjects treated in 4 treatment cohorts.

2.4. Study Treatment Dosing Date

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

For subjects who receive D-VRd treatment, the first study treatment dosing date is defined as the earliest date of non-zero dose of the following administration: bortezomib, lenalidomide, dexamethasone or daratumumab SC. The last study treatment dosing date is defined as the latest date of non-zero dose of the following administration: bortezomib, lenalidomide, dexamethasone or daratumumab SC.

For subjects who receive D-VMP treatment, the first study treatment dosing date is defined as the earliest date of non-zero dose of the following administration: bortezomib, melphalan, prednisone or daratumumab SC. The last study treatment dosing date is defined as the latest date of non-zero dose of the following administration: bortezomib, melphalan, prednisone or daratumumab SC.

For subjects who receive D-Rd treatment, the first study treatment dosing date is defined as the earliest date of non-zero dose of the following administration: lenalidomide, dexamethasone or daratumumab SC. The last study treatment dosing date is defined as the latest date of non-zero dose of the following administration: lenalidomide, dexamethasone or daratumumab SC.

For subjects who receive D-Kd treatment, the first study treatment dosing date is defined as the earliest date of non-zero dose of the following administration: carfilzomib, dexamethasone or daratumumab SC. The last study treatment dosing date is defined as the latest date of non-zero dose of the following administration: carfilzomib, dexamethasone or daratumumab SC.

2.5. Analysis Sets

The analysis sets for the study are:

- All treated analysis set: defined as all subjects who receive at least 1 dose of study treatment. This analysis set will be used for analyses of disposition, demographic and baseline disease characteristics, treatment exposure, safety and efficacy. All subjects in all treated analysis set will be analyzed according to the treatment that they actually received.
- Pharmacokinetics (PK) analysis set: defined as subjects who received at least 1 dose administration of daratumumab SC and have at least 1 PK sample concentration value after the first dose. All PK parameters will be analyzed based on the PK analysis set.
- Immunogenicity-evaluable analysis set is defined as all subjects who receive at least 1 dose administration of daratumumab SC and have at least 1 immunogenicity sample for detection of anti-daratumumab antibodies after the first dose.
- Immunogenicity-evaluable analysis set for rHuPH20 is defined as all subjects who receive at least one dose of daratumumab SC and have appropriate plasma samples for detection of antibodies to rHuPH20 (at least 1 sample after the start of the first dose of daratumumab SC).

2.6. Definition of Subgroups

In general, subgroup analyses on the pre-specified subgroups in Table 2 will be performed for the primary efficacy endpoints of ORR and VGPR or better rate, major secondary endpoint of rate of infusion-related reactions (IRRs), and safety endpoints treatment-emergent adverse event (TEAE). Additional exploratory subgroup analyses may be performed for selected efficacy and/or safety endpoints.

Table 2: Subgroup Analyses for Efficacy and Safety Endpoints

Subgroup	Definition	Analysis Type
Sex	Male, Female	E, S
Race	White, Other	S
Weight	≤ 65 kg, 66 to 85 kg, and >85 kg	S
Baseline renal function (Glomerular filtration rate [GFR] [mL/min/1.73m^2])	S: ≤60, >60 (mL/min/1.73m^2)	S
Baseline hepatic function	Normal, Impaired[a]	S
ISS staging	I, II, and III	E
Type of myeloma	IgG, non-IgG	E
Cytogenetic risk	High risk, Standard risk	E
ECOG performance score	0, ≥1	E

E: efficacy (ORR and VGPR or better rate); S: safety (IRR, TEAE)

[a:] Includes mild, moderate and severe.

2.7. Baseline Definition

The baseline value is defined as the last non-missing measurement taken on or prior to the first dose administration of study treatment (including time if time is available).

2.8. Imputation Rules for Missing Dates

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

2.8.1. Adverse Event Start and End Date

Adverse Event Start Date

If the onset date of an adverse event is completely or partially missing, 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 dosing date, the day of first dosing 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, the first day of the month is imputed.
- When only a year of the onset date is 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 dosing date, the day and month of AE end date are imputed;
    - Otherwise, the day and month of the first dosing date 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 first dosing date is imputed as the onset date.

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

Adverse Event End Date

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

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.

After the imputation, if the imputed date is later than the date of death (if available) after imputation, the date of death will be used as the imputed date.

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

2.8.2. Prior and Concomitant Medication/Therapy Start and End Date

For prior or concomitant medications/therapy, if the start or end date is completely missing, no imputation will be performed. If the start or end date is partially missing, the following imputation rules will be used.

- 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/therapy was taken prior to study start, and the imputed start date is after first dosing date, further adjust the imputed start date as the day prior to first dosing date; if the medication/therapy 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/therapy end date so that it is on or after first dosing date.

2.8.3. Multiple Myeloma Diagnosis Date

If the diagnosis date of multiple myeloma (MM) is completely missing, no imputation will be applied. If the diagnosis date is partially missing, the following imputation rules will be applied:

- If only the day of the diagnosis date is missing:
  - If the month and year of the diagnosis date are the same as the month and year of the start date of the first line of prior MM therapy, and day of the start date of the first line of prior MM therapy is available, impute day of the diagnosis date with the day of the start date of the first line of prior MM therapy;
  - Otherwise, impute day of diagnosis date with 15;
- If both month and day of the diagnosis date are missing:

- If the year of the diagnosis date is the same as the year of the start date of the first line of prior MM therapy, and the month of the start date of the first line of prior MM therapy is available:
  - if both month and day of the start date of the first line of prior MM therapy are available, impute diagnosis month and day with the month and day of the start date of the first line of prior MM therapy;
  - if only the month of the start date of the first line of prior MM therapy is available, impute the month of diagnosis date with the month of the start date of the first line of prior MM therapy and the day of the diagnosis date with 15;
- Otherwise, impute the month and day of the diagnosis date with June 30.

2.8.4. Subsequent Anti-cancer Therapy Start Date

If the start date of subsequent anti-cancer therapy is completely missing or the month is missing, no imputation will be performed. If only the day of subsequent therapy start date is missing, the following imputation rules will be applied:

- If the month and year of the start date are the same as the month and year of the last dosing date, the day of last dosing date or the day-component of the stop date of subsequent anti-cancer therapy will be imputed, whichever is earlier.
- If the month and year of the start date are not the same as the month and year of last dosing date, the first day of the month will be imputed.

2.9. Unique Lab Value

In general, in instances when there are multiple records at a given visit date for lab parameters associated with disease assessment, the following rules will be applied to select the unique lab value for analysis: a.) multiple records from both central and local lab, central lab value always takes precedence over local lab value; b) multiple records from central lab, select the latest value as the unique lab value; c.) multiple records from local lab, select the latest lab value as the unique lab value.

2.10. Other General Definitions

2.10.1. Measurable Disease of Multiple Myeloma at Baseline and Measurable Type

Measurable disease at baseline is defined by any of the following:

- Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

If a subject meets the criteria for serum M-protein, the measurable disease type is serum; otherwise, if a subject meets the criteria for urine M-protein, the measurable disease type is urine; otherwise if a subject meets the criteria for FLC, the measurable disease type is FLC. If a

subject meets both of the criteria for serum M-protein and urine M-protein, then the measurable disease type is "serum and urine".

2.10.2. Type of Multiple Myeloma

Type of myeloma for a subject is determined by serum heavy chain or serum FLC or urinary FLC. Serum heavy chain refers to serum immunoglobulin of IgG, IgA, IgM, IgD, or IgE. Serum and urine FLC refers to kappa or lambda type.

A subject will be classified as IgG type of myeloma if any reported result contains serum heavy chain 'IgG' regardless of FLC reported, similarly for IgA, IgM, IgD and IgE type. A subject will be classified as the light chain type of myeloma if any reported result is either 'Lambda light chains' or 'Kappa light chains' but without heavy chain reported. A subject will be reported as 'biclonal' if the distinct test results contain different heavy chain values or different FLC values. A subject will be classified as "Negative immunofixation" if the reported result is "Not Detected" and with no serum heavy chain, serum light chain and urine light chain reported.

2.10.3. International Staging System (ISS)

ISS staging is based on the combination of serum β2-microglobulin (B2MG) and serum albumin (ALB) at baseline.

- Stage I: β2-microglobulin<3.5 mg/L and serum albumin≥ 35 g/L
- Stage III: β2-microglobulin ≥ 5.5 mg/L
- Stage II: Neither stage I nor stage III
  - (β2-microglobulin<3.5 mg/L but serum albumin< 35 g/L, or β2-microglobulin
  - ≥3.5 mg/L to 5.5 mg/L irrespective of the serum albumin level)

2.10.4. Hepatic Function

Hepatic impairment is classified into 4 levels per NCI organ dysfunction criteria, using baseline total bilirubin and Aspartate Aminotransferase (AST):

- Normal: total bilirubin ≤ ULN and AST ≤ ULN
- Mild: (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN)
- Moderate: 1.5×ULN < total bilirubin ≤ 3×ULN
- Severe: total bilirubin > 3×ULN

2.10.5. Relapsed Disease

For D-Rd cohort, relapsed disease is defined as an initial response to previous treatment, followed by progressive disease (PD) by IMWG criteria >60 days after cessation of treatment.

2.10.6. Refractory Disease

For D-Rd cohort, refractory disease is defined as <25% reduction in M-protein or confirmed PD by IMWG criteria during previous treatment or ≤60 days after cessation of treatment.

2.10.7. High Risk/Standard Risk Cytogenetics

The high risk and standard risk cytogenetics are defined as follows:

- High risk: subjects that are positive for any of del17p, t(14;16), t(4;14) by FISH/Karyotype
- Standard risk: subjects that are negative for del17p, t(14;16), t(4;14) by FISH/Karyotype

2.10.8. Years since Initial Multiple Myeloma Diagnosis

This is calculated as date of first dosing – date of initial MM diagnosis + 1, divided by 365.25.

2.10.9. End of Follow-up and Duration of Follow-up

The end of follow-up is defined as the maximum date of the following study evaluations: labs (hematology, chemistry, immunology), adverse events, vital signs, ECOG performance status, bone marrow cytogenetics, lytic bone lesions, extra-medullary plasmacytomas, study treatment administration, ECG, pre-infusion medications, post-infusion medications, concomitant medications, subsequent therapy, medical encounters, clinical events/disease response per investigator and date of last known to be alive. For subjects who died, the end of follow-up is the date of death.

Duration of follow-up (in months) = the date of end of follow-up - the date of first dose + 1, divided by 365.25/12.

2.11. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, which is defined as from the date of first dose to the date of the event, the Kaplan-Meier method will be used for descriptive summaries. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus 1 day will be used.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analysis is planned for this study.

A SET consisting of the participating investigators, the sponsor's medical monitor, the sponsor's clinical pharmacologist (if PK data are being evaluated), the sponsor's statistician the sponsor's safety officer, and the sponsor's study manager will evaluate safety data after at least 6 toxicity-evaluable subjects complete Cycle 1 in each cohort. The details will be provided in a separate SET charter.

4. SUBJECT AND TREATMENT INFORMATION

Analyses of subject disposition, demographic and baseline disease characteristics, and extent of exposure will be conducted on all treated analysis set.

4.1. Demographics and Baseline Characteristics

The following subject demographics will be summarized using descriptive statistics:

- Age (continuous)
- Age category (< 65 years, 65 to < 75 years, and ≥ 75 years)
- Sex (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Weight (kg)
- Baseline ECOG performance status (0, 1, 2)

The following baseline disease characteristics will be summarized using descriptive statistics:

- Type of myeloma (IgA, IgD, IgE, IgG, IgM, light chain, biclonal, or negative immunofixation)
- Type of measurable disease (serum and urine, serum, urine, FLC)
- ISS staging (I, II, III)
- standard-risk and high-risk cytogenetic abnormalities (del17p, t(4;14), t(14;16))
- Time since initial diagnosis (years)
- Number of lytic bone lesions (None, 1-3, 4-10, more than 10)
- Presence of diffuse myeloma-related osteopenia (Yes, No)
- Presence of extramedullary plasmacytomas (Yes, No)
- Bone marrow % plasma cells (<10, 10 – 30, > 30)

In addition, a descriptive summary of selected hematology and chemistry laboratory analytes at baseline will be provided for each treatment cohort and overall. The baseline toxicity grade of selected laboratory analyte in hematology and chemistry panel will be summarized by treatment cohort using frequency.

4.2. Disposition Information

The number of subjects who are treated, ongoing, and discontinued treatment with reasons of discontinuation reported on eCRF will be summarized. The number of subjects who discontinued from study with the reported reasons will also be presented. The number of subjects who discontinued treatment by cycle with the reported reasons will also be provided.

Subject enrollment will also be summarized by country and site for all treated analysis set.

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

4.3. Extent of Exposure

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

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

Duration of study treatment, defined as the number of days from the date of the first administration of study treatment to the date of the last administration of study treatment, will be summarized.

The number of daratumumab administrations (continuous and categorical variables) will be summarized for each treatment cohort.

For subjects treated with D-VRd, the total dose administered for daratumumab (mg), lenalidomide (mg), bortezomib (mg/m^2), and dexamethasone (mg) will be summarized overall, by cycle, by high-intensity (Cycles 1-3) and low-intensity (Cycles 4) for daratumumab.

For subjects treated with D-VMP, the total dose administered for daratumumab (mg), bortezomib (mg/m^2), melphalan (mg/m^2), prednisone (mg/m^2), and dexamethasone (mg) will be summarized overall, by cycle, by high-intensity (Cycle 1) and low-intensity (Cycles 2-9) for bortezomib, and by Cycle 1, Cycles 2-9 and Cycles 10+ for daratumumab and dexamethasone.

For subjects treated with D-Rd, the total dose administered for daratumumab (mg), lenalidomide (mg), and dexamethasone (mg) will be summarized overall, by cycle, by high-intensity (Cycles 1-2) and low-intensity (Cycles 3-6 and Cycles 7+) for daratumumab.

For subjects treated with D-Kd, the total dose administered for daratumumab (mg), carfilzomib (mg/m^2), and dexamethasone (mg) will be summarized overall, by cycle, by high-intensity (Cycles 1-2) and low-intensity (Cycles 3-6 and Cycles 7+) for daratumumab.

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. Additionally, the daratumumab dose intensity will be summarized by cycles with high-intensity and low-intensity for each treatment cohort (i.e., Cycles 1-3 and Cycles 4 for D-VRd; Cycle 1, Cycles 2-9 and Cycles 10+ for D-VMP; Cycles 1-2, Cycles 3-6 and Cycles 7+ for D-Rd and D-Kd). In addition, for the D-VMP treatment cohort, the bortezomib dose intensity will be summarized by cycles with high-intensity and low-intensity (i.e., Cycle 1 and Cycles 2-9).

The relative dose intensity (%), which is defined as the ratio of total dose actually received and total planned dose, will be calculated for each study treatment and summarized using descriptive statistics for each treatment cohort.

The number of subjects with cycle delays or dose modifications (dose delays, dose skipping, or dose reduction) including reasons (AE or other) for cycle delays or dose modifications, will be reported. In addition, a summary of study treatment dose modifications by cycle will be provided.

4.4. Medical History

General medical history will be summarized by body system organ class and preferred term for each treatment cohort.

4.5. Prior Therapies

4.5.1. Prior Multiple Myeloma Therapies

D-Rd and D-Kd Cohort:

For the subjects enrolled in D-Rd and D-Kd treatment cohort with relapsed or refractory MM, the number and percentage of subjects who had prior exposure to multiple myeloma therapies (systemic therapy, ASCT, radiotherapy, cancer-related surgery) will be summarized. Specifically, for prior systemic therapies, the number of prior lines of therapy will be summarized descriptively and summarized by the following categories: 1, 2, 3 and > 3(for D-Rd); 1 and >1 (for D-Kd)

The summary of prior systemic therapies will be presented by therapy class and therapy. The therapy classes include proteasome inhibitors (PI), immunomodulatory drugs (IMiD), steroids, alkylating agents and anthracyclines.

- PI therapy class includes: bortezomib, carfilzomib (D-Rd only), oprozomib, ixazomib, and marizomib;
- IMiD therapy class includes: lenalidomide, pomalidomide, and thalidomide;
- Steroids therapy class includes: dexamethasone and prednisone, among others.

Further update of the above lists will be specified in the Data Presentation Specifications (DPS). The number of subjects who had prior exposure to multiple therapy classes (e.g., PI + IMiD) or multiple therapies (e.g., bortezomib + lenalidomide) may be provided, if the number of subjects who exposed to those therapy class or therapies is sufficient.

Additionally, the prior systemic therapy will be summarized by therapeutic class, pharmacologic class and preferred term.

D-VMP Cohort:

With the study population of newly diagnosed subjects with multiple myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant (ASCT), prior

systemic use of corticosteroids is limited to a short course of emergency use to treat multiple myeloma symptoms. If any, a listing of all prior systemic use of corticosteroids will be provided.

D-VRd Cohort:

With the study population of newly diagnosed subjects with multiple myeloma who are eligible for transplant, a listing of prior systemic use of corticosteroids will be provided. A listing of prior radiotherapies may also be provided.

4.5.2. Refractory Status to Prior Systemic Therapy

For the subjects enrolled in D-Rd and D-Kd treatment cohorts with relapsed or refractory MM, the refractory status to prior systemic therapy will be summarized. Refractory status (yes, no) to a particular prior systemic therapy class (i.e., PI/IMiD) or prior systemic therapy (e.g., bortezomib or thalidomide) will be based on refractory status to each line of therapy, or each specific therapy collected on prior systemic therapy CRF page. For each subject, refractory to each therapy class/therapy refers to refractory to his/her most recent therapy-containing line.

The number and percentage of subjects' refractory status to the most recent PI or IMiD therapy class will be summarized by the following 4 categories: none (neither PI-refractory nor IMiD-refractory), PI only (PI-refractory but not IMiD-refractory), IMiD only (IMiD-refractory only but not PI-refractory), both PI and IMiD. Refractory to specific prior therapy, such as bortezomib, carfilzomib (D-Rd only), ixazomib, lenalidomide, pomalidomide, or thalidomide and the relevant combinations of the aforementioned therapies will be provided separately.

The incidence of subjects who are refractory to their last line of therapy will be reported.

4.6. Prior and Concomitant Medications

Medications administered prior to the first dose date of study treatment will be considered as prior medications. Concomitant medications are defined as those medications taken on or after the first dose date through 30 days after the last dose date.

Prior and concomitant medications will be summarized on all treated analysis set by therapeutic class, pharmacologic class, and preferred term. Similar summaries will be provided for subjects who received growth factor support, systemic steroids, and prophylactic antiviral medication as concomitant medication use during the study, respectively.

Pre-infusion medications and post-infusion medications will also be summarized, respectively. Pre-infusion medications will be grouped by analgesics, antihistamines, corticosteroids (intermediate acting, long acting), and other. The incidence of pre-infusion medications will be presented by the aforementioned groups and preferred terms. The similar summary will be provided for post-infusion medications.

4.7. Subsequent Anti-cancer Therapies

The total number of subjects who received subsequent anti-cancer therapy for multiple myeloma will be reported for all treated analysis set in each treatment cohort. A summary of subsequent anti-cancer therapy will be presented by therapeutic class, pharmacologic class and preferred term.

4.8. Protocol Deviations

Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized for all treated analysis set by the following categories of deviation for each treatment cohort:

- Entered but did not satisfy criteria
- Developed withdrawal criteria but not withdrawn
- Received wrong treatment or incorrect dose
- Received a disallowed concomitant treatment
- Other

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

5. EFFICACY

A validated computerized algorithm, which is based on the IMWG response criteria (Durie 2006, Rajkumar 2011)[1,2] and has been used and validated by an independent review committee in study MMY2002, also used in MMY3003, MMY3004, MMY3006, MMY3007, MMY3008, and MMY3012 will be used to determine response and disease progression for each subject. Unless specified otherwise, relapse from CR by positive immunofixation or trace amount (defined as less than 0.5 g/dl) of M protein is not considered to be progressive disease in the IMWG response criteria.

The primary efficacy analyses will be based on the computerized algorithm assessments. The primary analysis will occur at least 6 months after approximately the sixtieth subject is enrolled in the last treatment cohort (D-VRd, D-VMP, or D-Rd). The primary efficacy analysis for D-Kd cohort will occur at least 6 months after approximately the sixtieth subject is enrolled in the D-Kd cohort. Analyses for the primary endpoint and selected major secondary efficacy endpoints based on investigator assessments using the IMWG response criteria will also be performed as sensitivity analyses.

No formal comparisons between treatment cohorts will be performed.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical hypothesis tests will be based on one-sided test at significance level of alpha=0.05. All interval estimations will be reported using 2-sided 90% confidence interval (CI).

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

5.2. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is ORR for the D-VMP, D-Rd and D-Kd cohorts and VGPR or better response rate for the D-VRd cohort.

5.2.1. Definition

The ORR, which is the primary efficacy endpoint for the D-VMP, D-Rd and D-Kd cohorts, is defined as the proportion of subjects who achieve a response of PR or better according to IMWG response criteria, including the subjects with either complete response (including stringent complete response [sCR]) or partial response (including VGPR), during or after the study treatment but prior to the start of subsequent anti-cancer therapy.

The VGPR or better response rate, which is the primary efficacy endpoint for the D-VRd cohort, is defined as the proportion of subjects who achieve a response of VGPR or better (VGPR, CR or sCR) according to IMWG response criteria, during or after the study treatment but prior to the start of subsequent anti-cancer therapy.

5.2.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 4 components:

- Population:
  - D-VRd cohort: subjects with newly diagnosed MM who are transplant eligible;
  - D-VMP cohort: subjects with newly diagnosed MM who are ineligible for transplant;
  - D-Rd cohort: subjects with relapsed or refractory MM.
  - D-Kd cohort: subjects in first relapse or refractory MM after initial treatment with a lenalidomide-containing regimen.

- Variable: overall response for D-VMP, D-Rd and D-Kd cohorts and VGPR or better response D-VRd cohort;
- Intercurrent event: Treatment discontinuation is considered as an intercurrent event for overall response and treatment policy strategy will be implemented, i.e., analysis of overall response ignores treatment discontinuation.

- Population-level summary: overall response rate for D-VMP, D-Rd and D-Kd cohorts and VGPR or better response rate for D-VRd cohort.

5.2.3. Analysis Methods

The primary analysis of ORR for D-VMP, D-Rd and D-Kd cohorts and the primary analysis of VGPR or better response rate for D-VRd cohort will be performed on all treated analysis set. The number and percentage of subjects in the following response categories will be tabulated for each treatment cohort: sCR, CR, VGPR, PR, stable disease (SD), progressive disease (PD), and not evaluable (NE). The overall response (including sCR + CR + VGPR + PR), VGPR or better (sCR + CR + VGPR), and CR or better (sCR + CR) will also be summarized. For each of the above categories, two-sided 90% Clopper-Pearson exact CI will also be presented

Sensitivity analyses of ORR for D-VMP, D-Rd and D-Kd cohorts and a sensitivity analysis of VGPR or better response rate for D-VRd cohort, in which disease response is based on investigator assessment according to the IMWG response criteria, will also be performed in a similar manner.

No formal comparisons between treatment cohorts will be performed.

5.3. Major Secondary Endpoints

The major secondary efficacy endpoints include VGPR or better response rate (for D-VMP, D-Rd and D-Kd cohorts), ORR (for D-VRd cohort), CR or better response rate, duration of response (DOR), and MRD negativity rate (for D-VMP, D-Rd, and D-Kd cohorts).

5.3.1. VGPR or Better Rate (D-VMP, D-Rd and D-Kd cohorts)

5.3.1.1. Definition

The secondary endpoint of VGPR or better rate for D-VMP, D-Rd and D-Kd cohorts is defined as the same as specified in Section 5.2.1.

5.3.1.2. Analysis Methods

The secondary analysis of VGPR or better response rate for D-VMP, D-Rd and D-Kd cohorts will be performed on all treated analysis set. The VGPR or better response rate and corresponding two-sided 90% Clopper-Pearson exact CI will be provided.

5.3.2. ORR (D-VRd cohort)

5.3.2.1. Definition

The secondary endpoint of ORR for D-VRd cohort is defined as the same as specified in Section 5.2.1.

5.3.2.2. Analysis Methods

The secondary analysis of ORR for D-VRd cohort will be performed on all treated analysis set. The ORR and corresponding two-sided 90% Clopper-Pearson exact CI will be provided.

5.3.3. CR or Better Rate

5.3.3.1. Definition

CR or better response rate is defined as the proportion of subjects with a response of a CR or better (CR or sCR) according to IMWG response criteria, during or after the study treatment but prior to the start of subsequent anti-cancer therapy.

5.3.3.2. Analysis Methods

CR or better response rate will be calculated on all treated analysis set for each treatment cohort. The corresponding two-sided 90% Clopper-Pearson exact CI will be provided.

5.3.4. Duration of Response

5.3.4.1. Definition

Duration of response is calculated from the date of initial documentation of a response (PR or better for D-VMP, D-Rd and D-Kd cohorts) to the date of first documented evidence of progressive disease as defined according to IMWG criteria or death due to PD, whichever occurs first, for the subjects who had achieved a response (PR or better for D-VMP, D-Rd and D-Kd cohorts).

Subjects who start subsequent anti-cancer therapies without PD will be censored at the date of the last disease assessment prior to the start of subsequent anti-cancer therapies. Subjects who have not progressed or subjects who die due to causes other than disease progression will be censored at the last disease assessment date.

5.3.4.2. Analysis Methods

At the time of the primary analysis, data for DOR may not be mature and may be analyzed later.

Analysis of DOR will be based on subjects who achieved a response (PR or better for D-VMP, D-Rd and D-Kd cohorts.). Median DOR with 90% CI will be estimated based on the Kaplan-Meier method for each treatment cohort. The Kaplan-Meier curve for DOR will be plotted.

5.3.5. MRD Negativity Rate

5.3.5.1. Definition

MRD negativity rate is defined as the proportion of subjects who are considered MRD negative after MRD testing by bone marrow aspirate at any timepoint after first dose and before disease progression or starting subsequent therapy. MRD positive subjects include subjects of which all tested samples were found to be MRD positive or ambiguous. Subjects with missing or unevaluable MRD status or not evaluated will be considered as MRD positive.

5.3.5.2. Analysis Methods

At the time of the primary analysis, data for MRD negative data may not be mature and may be analyzed later.

The MRD negativity rate will be calculated for D-VMP, D-Rd and D-Kd cohorts based on all treated analysis set. The corresponding two-sided 90% Clopper-Pearson exact CI will be provided.
For this study, threshold value of 10^{-5} will be used for the primary MRD negativity analysis. Additional supportive analyses will be performed using different thresholds (i.e. $<10^{-6}$ and $<10^{-4}$).

5.4. Other Efficacy Variable(s)

Other efficacy endpoints include the proportion of subjects with best M-protein response for subjects with measurable disease in serum or urine, and the proportion of subjects with maximal reduction of ≥90% and ≥50% from baseline in the difference between involved and uninvolved serum FLC (dFLC) for subjects with measurable disease of FLC only.

For the treatment cohorts of D-VMP, D-Rd and D-Kd, other efficacy endpoints may also include progression-free survival (PFS) and overall survival (OS).

5.4.1. Progression-free Survival (D-VMP, D-Rd and D-Kd cohorts)

5.4.1.1. Definition

At the time of the primary analysis, data for PFS may not be mature and may be analyzed later.

PFS for D-VMP, D-Rd and D-Kd cohorts is defined as the duration from the date of the first study treatment administration to either progressive disease, according to the IMWG response criteria, or death due to any cause, whichever occurs first. Subjects who start subsequent anti-cancer therapies for multiple myeloma without disease progression will be censored at the last disease assessment before the start of subsequent therapies. Subjects who withdrew consent from the study before disease progression will be censored at the last disease assessment before withdrawal of consent to study. Subjects who are lost to follow-up will be censored at the last disease assessment before the subjects were lost to follow-up. Subjects who have not progressed and are still alive at the clinical cut-off 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 the first study treatment administration.

Determination of dates of PFS event and dates for censoring is summarized in Table 3 as follows.

Table 3: PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
No postbaseline disease assessment	Date of the first study treatment administration	Censored
Disease progression prior to start of subsequent anti-cancer therapy	Earliest date that indicates disease progression	PFS event
Death prior to start of subsequent anti-cancer therapy	Date of death	PFS event
Other, such as: o Withdrawal of consent to study participation, o Lost to follow-up o Start of subsequent anti-cancer therapy prior to disease progression or death	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, or start of subsequent anti-cancer therapy	Censored

5.4.1.2. Analysis Methods

Analysis of PFS will be performed on all treated analysis set for the treatment cohorts of D-VMP, D-Rd and D-Kd. The Kaplan-Meier method will be used to estimate the distribution of overall PFS. The median PFS with 90% CI will be provided. The Kaplan-Meier curve for PFS will also be plotted.

5.4.2. Overall Survival (D-VMP, D-Rd and D-Kd cohorts)

5.4.2.1. Definition

At the time of the primary analysis, data for overall survival may not be mature and may be analyzed later. Descriptive summaries overall survival data may be provided for exploratory purposes.

Overall survival for D-VMP, D-Rd and D-Kd cohorts is defined as the duration from the date of the first study treatment administration to the date of the subject's death due to any cause. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subject who is still alive at the clinical cut-off date for the analysis will be censored at the date of last known to be alive. The date of last known to be alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.4.2.2. Analysis Methods

OS will be analyzed using similar statistical methods as described in Section 5.4.2.2 for PFS analysis.

5.5. Subgroup Analysis for Efficacy Endpoints

For assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, subgroup analyses of the primary efficacy endpoints of ORR (D-VMP, D-Rd and D-Kd cohorts) and VGPR or better rate (D-VRd cohort) based on pre-specified subgroups defined in Section 2.6 will be conducted.

Additional exploratory subgroup analyses may be performed for selected efficacy and/or safety endpoints.

6. SAFETY

Analysis of safety data will be provided on all treated analysis set. All subjects will be analyzed according to the actual treatment they received.

The safety assessments to be evaluated include AEs, deaths, clinical laboratory tests (hematology, chemistry), vital signs, electrocardiogram (ECG) and ECOG performance scores.

6.1. Adverse Events

AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. For AE reporting, the verbatim term used in the CRF by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

The relationships to study treatment will be recorded as not related, doubtful, possible, probable, or very likely on eCRF for all the AEs. Adverse events will be categorized and summarized according to their highest relationship to study treatment. An adverse event is considered as related to study treatment if the relationship is recorded as possible, probable or very likely.

Treatment-emergent adverse events (TEAEs) are defined as any AE with onset date and time on or after that of the first dose through 30 days after the last dose of study treatment, or the day prior to start of subsequent therapy, whichever is earlier; or the follow-up AE (linked to an existing TEAE) with onset date and time beyond 30 days after the last dose of study treatment but prior to the start of subsequent therapy; or any AE that is considered related to (very likely, probably, or possibly related) study treatment 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 treatment-related by the investigator. AEs with missing or partial onset date and time will be considered as treatment-emergent unless the onset date and time of an AE can be determined as earlier than that of the first dose, or later than 30 days after last dose of study treatment.

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. For summarizing new onset events, all event records of the same preferred term from the same subject are to be linked by the onset date and the end date. If an event is followed by another event of the same preferred term with an onset date (or date/time)

the same as or 1 day (or 1 minute if applicable) after the end date (or date/time) of the previous record and any features of the adverse event (i.e.: toxicity grades/seriousness/action taken) are different between these two records, these 2 records should be linked together and considered as 1 event. A Grade 5 event will be linked to previous event of the same preferred term if the onset date of Grade 5 record is the same or one day after the end date of previous record.

6.1.1. Overview of TEAEs

An overview of TEAEs reported through the study will be provided for each treatment cohort. Overall summary of TEAE will include the subjects with TEAEs, serious TEAEs, TEAEs related to study treatment, TEAEs of maximum toxicity grade of 1 to 5, TEAEs leading to treatment discontinuation, TEAEs leading to dose modifications, and TEAEs with fatal outcome.

A similar overview of TEAEs will be presented by treatment cycle.

6.1.2. All TEAEs

The following summaries will be provided for all TEAEs:

- TEAEs by system organ class (SOC) and preferred term (PT)
- Most common (e.g., ≥10%) TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum toxicity grade

6.1.3. Toxicity Grade 3 or 4 TEAEs

The following grade 3 or 4 TEAEs will be summarized:

- Grade 3 or 4 TEAEs by SOC and PT
- Most commonly reported (e.g., ≥5%) grade 3 or 4 TEAE by SOC and PT

A similar summary of grade 3 or 4 TEAEs will be presented by SOC, PT and by treatment cycle.

In addition, a listing of grade 3 or 4 TEAEs will also be provided.

6.1.4. Treatment-related TEAEs

The following TEAEs will be summarized by relationship to study treatment:

- TEAEs by SOC, PT, and relationship
- Grade 3 or 4 TEAEs by SOC, PT and relationship

6.1.5. Serious TEAEs

The incidence of serious TEAEs will be summarized as below:

- Serious TEAEs by SOC and PT
- Serious TEAEs by SOC, PT and relationship to study treatment
- Most commonly reported (e.g., ≥2%) serious TEAEs by SOC and PT

A similar summary of serious TEAEs will be presented by SOC, PT and treatment cycle.

In addition, a listing of serious TEAEs will be provided.

6.1.6. TEAEs Leading to Treatment Discontinuation

The TEAEs leading to permanent treatment discontinuation will be summarized by SOC, PT and grade 3/4 for those subjects indicated as having discontinued study treatment due to an adverse event on the eCRF "End of Treatment" page.

A listing for subjects who discontinued study treatment due to AE will be provided.

6.1.7. TEAEs Leading to Dose Modifications

Incidence of TEAEs leading to treatment cycle delays or dose modifications will be summarized by SOC, PT and grade 3/4 for each treatment cohort.

6.1.8. TEAEs with Fatal Outcome

The TEAEs with fatal outcome will be summarized by PT and relationship to study treatment for each treatment cohort. A listing of TEAEs with fatal outcome will also be provided.

6.2. Deaths

The number of subjects who died during the study and the primary causes of death will be summarized for all treated analysis set. In addition, the similar summaries will be presented for all deaths within 30 days of last dose of study treatment and deaths within 60 days of first dose of study treatment, respectively.

A listing of subjects who died during the study will be provided.

6.3. Adverse Events of Clinical Interest

6.3.1. Infusion-related Reactions

6.3.1.1. Rate of Infusion-related Reactions

For the major secondary endpoint of rate of IRRs, the proportion of subjects who have an IRR along with its two-sided 90% Clopper-Pearson exact CI will be calculated for each treatment cohort on all treated analysis set.

6.3.1.2. Summary of Infusion-related Reactions

The incidence of infusion-related reactions (IRRs), as recorded on eCRF, will be presented by SOC, PT, and toxicity grade 3/4. In addition, the total number of subjects with IRR in more than 1 infusion will be presented. The timing of IRR will also be evaluated through a summary of IRR by event onset time.

A listing of infusion-related reactions will be provided.

6.3.2. Injection-site Reactions

The incidence of injection-site reactions, as recorded on eCRF, will be summarized by SOC, PT, and toxicity grade 3/4. A listing of injection-site reactions will be provided.

6.3.3. Infections and Infestations

Infections and infestations refer to the adverse events with SOC of infections and infestations. The grade 3 or 4 treatment-emergent infections and infestations will be summarized by preferred term and relationship to treatment. Treatment-emergent infections and infestations may also be summarized by preferred term and treatment cycles.

6.3.4. 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 system organ class and preferred term. The summaries will be presented by all grades and maximum toxicity grade for each treatment cohort.

6.3.5. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) events refer to the adverse events defined by narrow SMQ of tumor lysis syndrome (e.g., haemorrhagic tumour necrosis, tumour lysis syndrome, or tumour necrosis). A listing of subjects who reported any treatment-emergent TLSs during the study will be provided.

6.3.6. Second Primary Malignancies

The second primary malignancies during the study will be summarized by cancer type and preferred term. A listing of subjects who reported second primary malignancies during the study will also be provided. This listing will include diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and pathology diagnosis (biopsy, aspirate etc.) information whenever a second primary malignancy is observed. In addition, cumulative study treatment exposure, the treatment for second primary malignancy and the outcome information will also be presented in the listing.

6.3.7. Cardiac-related Treatment-emergent Adverse Events of Interest (D-Kd cohort only)

A summary of subjects with 1 or more treatment-emergent cardiac events of interest by standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ) and preferred term will be summarized for D-Kd cohort. A listing of D-Kd subjects with cardiac disorders will be provided.

6.3.8. Adverse Events by Subgroups

The subgroup analysis for the following TEAEs will be performed based on the subgroups specified in Section 2.6:

- Overview of TEAEs
- Summary of all TEAEs
- Grade 3 or 4 TEAEs
- Serious TEAEs

The subgroup analysis for the rate of IRRs will be performed by weight categories specified in section 2.6.

6.4. Clinical Laboratory Tests

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

- Hematology Panel:
  - hemoglobin
  - white blood cell (WBC) count, absolute neutrophil count, and absolute lymphocyte count
  - platelet count

- Serum Chemistry Panel:
  - AST
  - ALT
  - total bilirubin
  - glucose
  - creatinine
  - sodium
  - alkaline phosphatase
  - uric acid
  - blood urea nitrogen (BUN) or urea
  - calcium and albumin-adjusted calcium
  - lactic acid dehydrogenase (LDH)
  - potassium

Descriptive statistics for values and changes from baseline at each scheduled visit for hematology and chemistry laboratory parameters will be provided. Line plot of mean with standard error for each laboratory analyte over time will be displayed for hemoglobin, neutrophils, lymphocytes, platelets, WBC, AST, ALT, creatinine, and creatinine clearance/GFR.

In addition, the worst toxicity grade in hematology and chemistry during the treatment will be summarized by toxicity grade. Shifts tables from baseline to the worst toxicity grade during treatment will be generated.

A listing of subjects with any laboratory results outside the reference ranges will be provided.

6.5. Vital Signs and Physical Examination Findings

Descriptive statistics will be provided for values and changes from baseline over time for vital signs (pulse, temperature, systolic and diastolic blood pressure) at each scheduled visit and timepoint. Similar analysis may be performed for weight at Day 1 of each treatment cycle.

Clinically significant physical examination findings occurred at post-baseline were collected as AEs, and therefore will not be summarized.

6.6. Electrocardiogram

The ECG data will be collected at Screening, visits as clinically indicated during treatment, and End-of-Treatment visit.

The number and percentage of subjects with normal and abnormal either clinically significant or not clinically significant ECG results will be summarized for each treatment cohort.

A listing of subjects who experienced clinically significant abnormal ECGs in either baseline or post-baseline will be produced.

Both the summary and the listing of left ventricular ejection fraction (LVEF) will be provided (D-Kd cohort only).

6.7. ECOG Performance Status

ECOG performance status, which evaluates the effect of the disease status on the activities of daily living, will be assessed at Screening, Day 1 of each treatment cycle and end-of-treatment visit. The shift summaries of ECOG performance status from baseline to each scheduled visit, including Day 1 of each treatment cycle and end-of-treatment visit, will be provided for each treatment cohort. The shift summary from baseline to the worst performance score during treatment will also be presented.

6.8. Stem Cell Collection (D-VRd cohort only)

Descriptive statistics of number of stem cells collected, number of days of autologous stem cell collection, drugs used for autologous stem cell mobilization, and requirement special stem cell mobilizing agent (e.g. mozobil) will be summarized for D-VRd cohort.

7. PHARMACOKINETICS/IMMUNOGENICITY/PHARMACODYNAMICS

Unless specified otherwise, descriptive statistics will be used to summarize pharmacokinetics and pharmacodynamics data. In addition, coefficient variation and geometric mean will be provided in the pharmacokinetic concentration summary.

7.1. Pharmacokinetics

All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

The pharmacokinetic parameters are defined as:

- C_{min}: Minimum observed concentration, defined as the concentration observed immediately before the drug administration;
- C_{max}: Maximum observed concentration, defined as the concentration observed after the end of drug administration.

The C_{min} and C_{max} will be determined based on the assigned collection timepoints. Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point specified in protocol on the pharmacokinetics analysis set. Plot of mean (±SD) daratumumab serum peak and trough concentrations over time by cohort will be provided. If sufficient data are available, other pharmacokinetic parameters may be calculated and analyzed.

If there are sufficient data, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed effects modeling and may include data from other clinical studies. If performed, details will be provided in a population pharmacokinetic analysis plan and results of the analysis will be presented in a separate report.

7.2. Immunogenicity

The incidence of anti-daratumumab antibodies along with the titer and incidence of neutralizing antibodies will be summarized for all subjects who receive a dose of daratumumab and have at least 1 sample for detection of anti-daratumumab antibodies after the first dose (daratumumab immunogenicity-evaluable analysis set).

The prevalence and incidence of anti-rHuPH20 antibodies along with the titer will be summarized for all subjects who receive a dose of daratumumab and have at least 1 sample for detection of anti-rHuPH20 antibodies after the first dose (rHuPH20 immunogenicity-evaluable analysis set).

A listing of anti-daratumumab antibody sample and subject status with concurrent daratumumab concentration will be provided. A listing of anti-rHuPH20 antibody sample and subject status will also be provided.

7.3. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

8. BIOMARKER

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Samples for biomarker evaluations will be collected as specified in the protocol Time and Events Schedule. Baseline bone marrow aspirate samples are required, if feasible. In addition to planned bone marrow aspirate assessment, whole blood samples will be collected from subjects as outlined in the Time and Events Schedule for processing to plasma and peripheral blood mononuclear cells (PBMCs). Results of biomarker analyses may be presented in a separate report.

8.1. Minimal Residual Disease (MRD)

Bone marrow aspirate will be collected for MRD analysis, in the D-VMP, D-Rd and D-Kd cohorts only, when bone marrow samples are obtained at screening, confirmation of CR/sCR, and subsequent timepoints after the first dose as outlined in the protocol Time and Events Schedule.

Minimal residual disease (MRD) negativity rate is defined as the proportion of subjects who are considered MRD negative after MRD testing at any timepoint after first dose and before disease progression or starting subsequent therapy by bone marrow aspirate. MRD positive subjects include subjects of which all tested samples were found to be MRD positive or ambiguous. Subjects with missing or unevaluable MRD status or not evaluated will be considered as MRD positive.

The MRD negativity rate will be calculated for treatment cohorts D-VMP, D-Rd and D-Kd on the pharmacokinetics analysis set. The corresponding two-sided 90% exact CI will be provided. Reasons for missing or unevaluable MRD status will be tabulated by treatment group.

In addition, MRD negativity rate will be summarized at each post-baseline sampling timepoints. The percentage of subjects with MRD negative by different thresholds (i.e. $<10^{-6}$, $<10^{-5}$, and $<10^{-4}$) at each sampling timepoints will also be reported, based on bone marrow aspirate.

9. MEDICAL RESOURCE UTILIZATION

Medical resource utilization data associated with medical encounters due to IRRs, primarily hospitalizations, outpatient visits and emergency room visits, will be collected on eCRF by the investigator and study-site personnel for all subjects throughout the study.

Medical resource utilization will be descriptively summarized for each treatment cohort. Frequencies of hospitalization, outpatient visits, type of hospitalization or outpatient visit, reasons for hospitalization or outpatient visit, durations of hospitalization or outpatient visit, types of adverse events if involved, blood product transfusions will be tabulated. The treatment-emergent adverse events leading to the hospitalization/outpatient visits and leading to on-study transfusions will also be summarized.

REFERENCES

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