Janssen Research & Development

Statistical Analysis Plan

A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide and Dexamethasone (D-VRd) vs. VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Previously Untreated Multiple Myeloma who are Eligible for High-dose Therapy

Protocol EMN17/54767414MMY3014; Phase 3

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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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	01Apr2019	Initial version, not applicable	Initial release
2.0	28Jan2023	• COVID: add the related information for protocol deviation, impact to the efficacy endpoints and safety profiles. • Add Section 5.7, for the new testing procedure, to control overall family-wise type I error for the primary and key secondary endpoints. • Add an exploratory analysis of pooled PFS (MMY3014 and MMY2004) to PFS analysis. • Modify the SAP per the latest template. • Remove the RMST from the planned analysis (would be as the potential ad hoc analysis)	1. Amendment for COVID-19 impact 2. use CR or better rate as an earlier endpoint together with the primary endpoint PFS as the base of an accelerated approval. 3. Address the concern of OS futility. 4. Justify the section order per the latest SAP template.
3.0	31Aug2023	• Define the estimand for CR+ rate. • Change the testing procedure back to the original hierarchical testing per the protocol. • Remove an exploratory analysis of pooled PFS (MMY3014 and MMY2004) to PFS analysis.	1. Per EMA feedbacks 2. Strategy change

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the planned analysis specified in the protocol EMN17/54767414MMY3014.

1.1. Objectives and Endpoints

Primary Objective

The primary objective is to determine if the addition of daratumumab subcutaneous (SC) to VRd will prolong progression-free survival (PFS), compared with VRd alone.

Secondary Objectives

The secondary objectives are:

- To determine if the addition of daratumumab SC to VRd will improve clinical outcome as measured by:
  - MRD negativity rate post-consolidation and overall MRD negativity rate achieved at any time during the study
  - ORR, rate of VGPR or better, rate of CR or better, rate of sCR at post-induction, post-transplant, post-consolidation, and overall
  - Time to response
  - Duration of response
  - Progression-free survival on the next line of therapy (PFS2)
  - Overall survival (OS)
- To assess the safety profile of daratumumab + VRd (D-VRd)
- To evaluate pharmacokinetics (PK) of daratumumab
- To determine the immunogenicity of daratumumab and rHuPH20
- To evaluate patient-reported outcomes (PROs) and medical resource utilization (MRU)
- To evaluate stem cell yield after mobilization
- To evaluate time to engraftment post-ASCT
- To evaluate the benefit/risk of stopping daratumumab upon sustained MRD-negative status

Exploratory Objectives

The exploratory objectives are:

- To evaluate durability of MRD negativity.
- To evaluate whether the loss of MRD-negative status through the monitoring of peripheral blood will be more sensitive than standard clinical evaluations to detect relapse of CR.

- To evaluate MRD negativity thresholds and durability of clinical response.
- To evaluate length of sustained MRD-negative status and durability of clinical response.

1.2. Study Design

This is a Phase 3, randomized, open-label, multicenter study evaluating subjects with newly diagnosed multiple myeloma who are deemed eligible for high-dose therapy. Approximately 690 subjects will be stratified by International Staging System (ISS) Stage I, II, or III disease (β-2 microglobulin and albumin) and cytogenetics (standard risk or high risk as defined by presence of del17p, t[4;14] or t[14;16]) and then randomized in a 1:1 ratio to Arm A (VRd) or Arm B (D-VRd).

The study will consist of 3 phases: a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will start up to 28 days before randomization. The Treatment Phase will extend from Cycle 1 Day 1 to discontinuation of all study treatment. The Treatment Phase will consist of six 28-day cycles, 4 cycles of induction, followed by ASCT, then 2 cycles of consolidation, followed by maintenance therapy until disease progression or unacceptable toxicity.

In Arm A, subjects will receive VRd for induction and consolidation, followed by lenalidomide (R) maintenance until disease progression or unacceptable toxicity. Subjects in Arm B will receive D-VRd for induction and consolidation followed by daratumumab and lenalidomide maintenance until disease progression or unacceptable toxicity. MRD-negative subjects in Arm B will stop therapy with daratumumab after sustained MRD negativity (at or below the threshold of 10^{-5}) for 12 months and after a minimum of 24 months of maintenance therapy. These subjects will continue lenalidomide maintenance therapy until disease progression or unacceptable toxicity. After stopping daratumumab therapy, subjects with sustained MRD negativity should restart therapy with daratumumab if there is a loss of MRD negativity at 10^{-4} or higher or a loss of CR without IMWG-defined disease progression. After reinitiating daratumumab, the subject will continue daratumumab and lenalidomide therapy until disease progression or unacceptable toxicity.

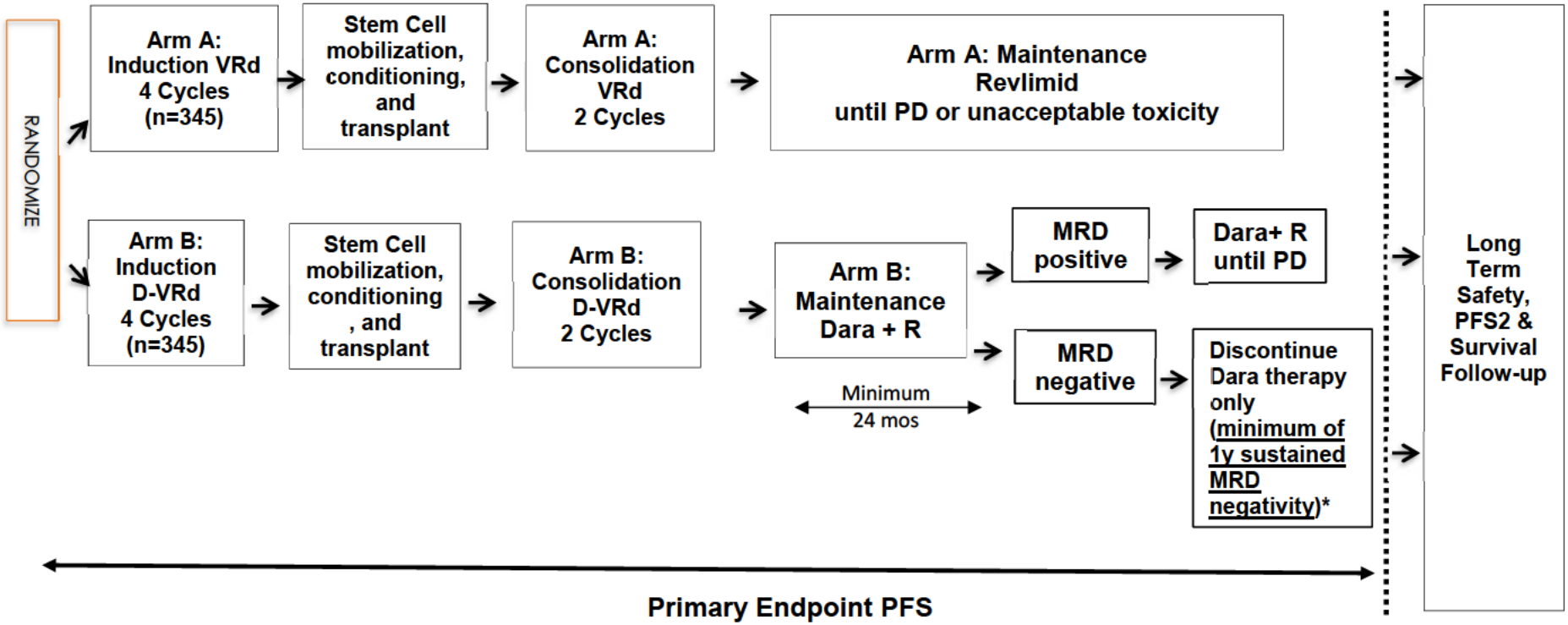
Daratumumab will be given subcutaneously (SC) at 1800 mg to subjects in Arm B once every week for Cycles 1 to 2, then every 2 weeks for Cycles 3-6. For maintenance Cycles 7+, subjects will receive daratumumab SC (1800 mg) once every 4 weeks until documented disease progression or unacceptable toxicity. Subjects in Arm B who have a post-ASCT recovery period that requires greater than 12 weeks off daratumumab will skip the consolidation treatment phase (Cycles 5-6) and proceed to maintenance therapy directly. They should restart therapy on the following schedule: daratumumab dosing every 2 weeks for 4 doses (Cycles 7-8 of maintenance therapy) then continue every 4 weeks, thereafter (for Cycles 9+). Bortezomib will be given as a SC injection (1.3 mg/ m^2) twice a week for 6 cycles. Lenalidomide will be administered PO at 25 mg on Days 1 to 21 for 6 cycles. Subjects will then start maintenance therapy (Cycle 7+), during which they will receive lenalidomide 10 mg daily PO on Days 1 to 28 (continuously) of each 28-day cycle until disease progression or unacceptable toxicity. After 3 cycles of maintenance therapy, if well tolerated, the lenalidomide dose may be increased to 15 mg daily, at the discretion of the investigator. Dexamethasone will be administered PO at 40 mg on Days 1-4 and 9-12 during Cycles 1-6.

In Arm B, upon re-initiation of daratumumab treatment during maintenance, daratumumab will be given at a dose of 1800 mg SC weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks until disease progression or unacceptable toxicity.

Subjects will enter the Follow-up Phase once they experience documented disease progression or unacceptable toxicity leading to all study treatment discontinuation or if they have not achieved a response of PR or better by C7D1. In the Follow-up Phase, subjects without disease progression must continue to have disease evaluations according to the Time and Events Schedule in the protocol and should not initiate any subsequent anti-myeloma treatment until confirmed disease progression. After disease progression is documented, follow-up will be obtained at least every 4 months ±2 weeks. Subsequent anti-myeloma treatment, disease progression data (per investigator assessment) on the first line of subsequent therapy, second primary malignancies, and survival status will be recorded.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



*Restart therapy upon relapse from CR or loss of MRD negativity status (threshold of 10^{-4} or higher)

Key: CR=complete response; Dara=daratumumab; D-VRd=daratumumab in combination with bortezomib, lenalidomide, and dexamethasone; MRD=minimal residual disease; PD=progressive disease; PFS2=progression-free survival on the next line of therapy; R=lenalidomide; VRd=bortezomib, lenalidomide, and dexamethasone.

1.3. Randomization and Blinding

Subjects will be randomized in a 1:1 ratio to either Treatment Arm A (VRd) or Treatment Arm B (D-VRd), and stratified by International Staging System stage I, II, or III (based upon central laboratory results for β-2 microglobulin and albumin) and by cytogenetics (standard risk or high risk as defined by presence of del17p, t[4;14] or t[14;16]), as centrally confirmed during screening. For stratification purposes, if cytogenetic results are not available (i.e., due to technical reasons), local cytogenetic results may be used with the approval of the medical monitor. If central and local cytogenetic results are not available, the subject will be assumed to be standard risk. The investigator will screen and if eligible randomize each subject using an interactive web response system (IWRS). Each subject will be assigned a unique subject number.

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

2. STATISTICAL HYPOTHESES

VRd induction followed by ASCT followed by VRd consolidation followed by maintenance therapy with lenalidomide alone is a standard treatment strategy in newly diagnosed patients with multiple myeloma who are deemed eligible for high-dose therapy. The new treatment strategy is to add daratumumab to the standard induction, consolidation and lenalidomide maintenance treatment phases.

With the primary efficacy endpoint PFS, the null hypothesis is that there is no difference in PFS between the two treatment strategies in subjects with previously untreated multiple myeloma who are eligible for high-dose therapy.

3. SAMPLE SIZE DETERMINATION

It is assumed that median PFS is 63 months for the VRd group, and the addition of daratumumab will decrease the risk of progression or death by 31% (HR=0.69; estimated median PFS of 91 months for D-VRd group). To achieve 85% power with a two-sided alpha of 0.05, 285 PFS events are needed. Assuming a 12-month accrual and 64-month of additional follow-up, approximately 690 subjects (345/arm) will be needed.

Long-term follow-up for survival will continue until approximately 310 deaths have been observed or 9 years have elapsed after the last subject is randomized, whichever occurs earlier. Per the protocol, this will provide approximately 70% power to detect a 25% reduction in the risk of death (HR=0.75) with a log-rank test at a 2-sided alpha of 0.05. However, a hazard ratio of 0.71 or less will provide at least 80% power. A large Phase 3 trial (CASSIOPEIA, MMY3006) comparing D-VTd versus VTd in a similar study population (N=1085), observed a HR of 0.66 from first randomization censoring the events from the crossover VTd subjects after Part 1 of the study with median follow-up of 18.8 months, such a HR would provide approximately 93.5% power for this study with 310 deaths. Note that after the significance of PFS is established, testing of OS may continue as planned until a definitive conclusion on OS is reached.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Enrolled Analysis Set	All participants who sign the ICF
Intent-to-treat (ITT) Analysis Set	Intent-to-treat (ITT) analysis set is defined as subjects who have been randomly assigned to the VRd group (Arm A) or D-VRd group (Arm B).
Per Protocol (PP) Analysis Set	Per-protocol (PP) analysis set includes all randomized subjects who don't have major protocol deviation due to not meeting all entry criteria. The per-protocol analysis set will be used for supplementary analysis of the primary endpoint PFS. If the PP analysis set comprises >95% of the ITT analysis set, no analysis by PP will be performed.
Response-evaluable Analysis Set	The response-evaluable analysis set includes all participants who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit. In addition, participants must have received at least one administration of study intervention and have adequate post-baseline disease assessments.
Safety Analysis Set	The safety analysis set includes all subjects who have received at least one dose of study treatment (partial or complete) in the study.
Subject Received Maintenance Treatment	This analysis set includes all subjects who have received at least one dose of maintenance study treatment (partial or complete) in the maintenance treatment phase, which would be used for efficacy and safety analyses. The safety analyses grouping will be based on actual treatment group.
Pharmacokinetics Analysis Set	The PK analysis set is defined as subjects assigned to Arm B who have received at least one dose of daratumumab and have at least one PK sample concentration value after the first administration of daratumumab.
Antibody Immunogenicity Analysis Set	The antibody immunogenicity analysis set is defined as subjects assigned to Arm B who receive at least one dose of daratumumab and have appropriate serum samples for detection of antibodies to daratumumab (i.e., subjects with at least 1 sample obtained after their first dose daratumumab).
rHuPH20 Immunogenicity Analysis Set	For rHuPH20, immunogenicity analysis of rHuPH20 will be performed on the rHuPH20 immunogenicity population, defined as subjects assigned to Arm B who receive at least one dose of daratumumab and have at least one serum sample for detection of antibodies to anti-rHuPH20 either pre- or post- treatment.

5. STATISTICAL ANALYSES

5.1. General Considerations

The treatment groups are,

- Arm A: VRd for induction and consolidation, followed by lenalidomide (R) maintenance
- Arm B: D-VRd for induction and consolidation followed by daratumumab and lenalidomide (D-R) maintenance.

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 the efficacy assessment of response and disease progression, a validated computerized algorithm will be utilized to determine response and disease progression for each subject. This computerized algorithm 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 and applied in several Phase 3 studies 54767414MMY3003/3004/3006/3007/3008/3012 for submission. As a sensitivity analysis, investigator assessments of response and disease progression per the IMWG response criteria will also be performed.

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

5.1.1. Visit Windows

Unless otherwise specified, data to be analyzed or listed over time will be presented by day and time point (as appropriate) that are recorded in the electronic case report form (eCRF).

Analysis time point will be based on treatment phases (induction treatment, Pre-ASCT phase, ASCT phase, consolidation treatment, and maintenance treatment) and cycles.

Induction treatment phase (Up to 4 cycles [or up to 6 cycles for subjects who started ASCT after 6 cycles of induction treatment due to COVID-19 pandemic and subjects who did not receive ASCT after 6 cycles of induction], 28-day per cycle):

For subjects who received induction treatment, from the first induction dose date to the last induction dose date, or the date of end of treatment, or subsequent antimyeloma therapy minus 1 day, whichever is earlier.

Pre-ASCT phase

For subjects who received mobilization therapy, from the day after the last dose of induction, to the day before the start date of melphalan administration, or the day before the first dose date of consolidation treatment phase, or the day before first dose of maintenance therapy (for subjects who receive mobilization therapy and did not proceed to transplant), or the date of end of treatment, or subsequent antimyeloma therapy minus 1 day, whichever is earlier.

ASCT phase

For subjects who proceed to transplant, from the start date of melphalan administration, to the day before the first dose date of consolidation treatment phase, or the day before the first date of maintenance treatment phase, or the date of end-of treatment visit, or subsequent antimyeloma therapy minus 1 day, whichever is earlier.

Consolidation treatment phase (Up to 2 cycles, 28-day per cycle):

For subjects who received consolidation treatment (cycle 5 and 6 given after ASCT), from the first dose date of consolidation treatment phase to the day before the first dose date of maintenance treatment phase, or the date of end-of-treatment visit, or subsequent antimyeloma therapy minus 1 day, whichever is earlier.

Induction/ASCT/Consolidation phase:

For subjects who received induction treatment, from the first induction dose date to the day before maintenance treatment start date, or the date of end-of-treatment visit, or subsequent antimyeloma therapy minus 1 day, whichever is earlier.

Maintenance treatment phase (28-day per cycle):

For subjects who received maintenance treatment, from the first dose date of maintenance treatment to the date of end-of-treatment (if not available, the last study treatment date plus 30 days), or subsequent antimyeloma therapy minus 1 day, whichever is earlier.

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 particular cycle in induction, consolidation, and maintenance treatment phase is respectively defined as the date of the first scheduled dose of any component of the study treatment in the induction, consolidation, and maintenance treatment phase, and the end date of a cycle (other than the last one) is the start date of the next cycle minus 1. For the last cycle, the end date is respectively defined as the end date of the induction, consolidation, and maintenance treatment phase.

5.1.2. Pooling Algorithm for Analysis Centers

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

5.1.3. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration. If the administration date is missing or the administration is not done, then the corresponding visit date should be used. If visit date is not available, then randomization date should be used.

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 Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'.

Assessments may also be presented chronologically by study day within each treatment phase, which are defined as the follows:

- Study Day in the induction treatment phase = assessment date - start date of the induction treatment + 1,
- Study Day in the consolidation treatment phase = assessment date - start date of the consolidation treatment phase + 1
- Study Day in the induction/ASCT/consolidation phase = assessment date – start date of the induction/ASCT/consolidation phase + 1

- Study Day in the maintenance treatment phase = assessment date – start date of the maintenance treatment phase + 1.

5.1.4. Baseline

Baseline measurement is defined as the closest non-missing measurement taken 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 such as SPEP, UPEP, kappa, lambda, kappa/lambda ratio, serum calcium, and albumin). If the first administration date is missing or the administration is not done, then the baseline measurement is the closest non-missing measurement taken on or prior to the corresponding visit date (if visit date is not available, then randomization date should be used).

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

The end of follow-up is the date of death from any cause for subjects who died. For those who are still alive, the end of follow-up is defined as the maximum date of the following study evaluations: labs (hematology, chemistry, serology), adverse events, vital signs, ECOG performance status, study drug administration, 12-lead ECG, pre-infusion medications, post-infusion medications, concomitant medications, subsequent anti-cancer treatment, tumor assessment, clinical events/disease response per investigator and date of last known to be alive.

Duration of follow-up (in months) equals the end of follow-up minus the randomization date plus 1, divided by 365.25/12.

5.1.6. Imputation Rules

5.1.6.1. 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 first study treatment
  - The day of first study treatment, if the month/year of the onset of AE is the same as month/year of the first study treatment and month/year of the AE resolution date is different
  - The day of first study treatment or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first study treatment and month/year of the AE resolution date are same
- If the onset date of an adverse event 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 first study treatment.
  - Month and day of the first study treatment, 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 first study treatment.
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

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

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

- If the resolution date of an adverse event 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 adverse event 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.

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

5.1.6.2. Imputation Rules for Concomitant Medication Start/End Date

In case of partially missing concomitant medication start/end dates, the following imputation rules will be applied.

- If the date is completely missing, no imputation will be performed.
- If only the day is missing, the 15th day of the month will be used.
- If both the day and month are missing, the 30th of June will be used.
- If the medication was taken prior to study start, and the imputed start date is after first study treatment date, further adjust of the imputed start date as the day prior to first dosing date; If the medication was taken after study start, and the imputed start date is prior to first dosing date, further adjust the imputed start date as first dosing date. Also, adjust the imputed medication end date so that it is on or after first dosing date.

5.1.6.3. Imputation Rules for Initial Multiple Myeloma (MM) Diagnosis Date

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

- If only the day is missing, set day=15 and pick minimum of imputed date, date of collection and date of randomization.
- If both the day and month are missing, set to January 1 and pick minimum of imputed date, date of collection and date of randomization.
- If year is missing, no imputation will be applied.

If the imputed date of original diagnosis is after the randomization date, further adjust the imputed start date as the day before the randomization date.

5.1.6.4. Imputation Rules for First Subsequent Anti-myeloma Therapy Start Date

If year or month of the first subsequent anti-myeloma therapy start date is missing or no components of the start date are present, no imputation will be performed. If only the day is missing, the following steps apply:

- If the month and year of the start date are the same as the month and year of last dosing date, the day of last dosing date +1 or the day-component of the stop date of subsequent anti-myeloma therapy is imputed, whichever is earlier.
- If the start month and year are not the same as the month and year of last dosing date, the first day of the month is imputed.

No imputation will be applied for missing or partial subsequent anti-myeloma therapy end date.

5.1.6.5. Imputation Rules for Death Date

When year and month are present, and the day is missing,

- The 15th day of the month is imputed.
- If the date of the last known alive is later than the imputed date, the date of the last known alive will be used as the imputed date instead.

When year are present, and the month and day is missing,

- The date of the last known alive will be used as the imputed date instead.

In all other cases missing or incomplete dates will not be imputed.

5.2. Participant Dispositions

The distribution of subjects by region and country will be presented for the ITT analysis set by treatment group unless otherwise noted.

Unless specified otherwise, the disposition information will be summarized for the ITT analysis set by treatment group. Number of subjects who are treated, completed and discontinued from treatment in the induction, ASCT, consolidation and maintenance treatment phases will be summarized, together with reason reported on eCRF. The reasons for trial discontinuation, including COVID-19 related reasons, will also be summarized.

Subjects who discontinue from treatment or study due to COVID-19 related reasons will be listed.

5.3. Primary Endpoint Analysis

The primary efficacy endpoint is progression-free survival (PFS) based on the computerized algorithm.

5.3.1. Definition of Endpoint

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of first disease progression (PD) according to the IMWG response criteria or death due to any cause whichever occurs earlier.

Determination of dates of PFS event and dates for censoring is summarized in Table 2 as follows.

Table 2: PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Disease progression prior to start of subsequent antimyeloma therapy	Earliest date that indicates disease progression	PFS event
Death without subsequent antimyeloma therapy and without disease progression *	Date of death	PFS event
No post-baseline disease assessment	Randomization	Censored
Disease progression or death immediately after 2 or more missing consecutive disease evaluations	Date of last disease assessment	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up, start of subsequent antimyeloma therapy, etc.)	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, or subsequent antimyeloma treatment	Censored

* Subjects who died after end of study (for example, died after consent withdrawal, and the death information was got from public information) will be censored at the date of last disease assessment prior to end of study for PFS analysis.

PFS is calculated in months as follows:

PFS (months) = (date of PD/death or censoring – date of randomization + 1) / (365.25/12).

5.3.2. Estimand

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

- Treatment: Subjects receive four cycles induction therapy. Responding subjects receive ASCT followed by two cycles of consolidation therapy. Thereafter subjects are entering maintenance therapy.
  - VRd: subjects will receive VRd for induction and consolidation, and lenalidomide (R) for maintenance.
  - D-VRd: subjects will receive D-VRd for induction and consolidation, daratumumab (D) and lenalidomide (R) for maintenance. Subjects will stop therapy with daratumumab after sustained MRD negativity (at the threshold of 10^{-5}) for 12 months and after a minimum of 24 months of maintenance therapy; and the subjects should restart therapy with daratumumab if there is a recurrence of MRD at 10^{-4} or higher or a confirmed loss of CR.
- Population: Subjects with newly diagnosed multiple myeloma who are deemed eligible for high-dose therapy (as defined by protocol eligibility criteria).

- Variable: PFS based on computerized assessment, which is defined as time from randomization to progressive disease or death whichever comes first.
- Intercurrent events (ICE):
  - Subsequent anti-myeloma therapy: the "hypothetical strategy" will be used. i.e., subjects who start subsequent anti-myeloma therapies for multiple myeloma without disease progression will be censored at the last disease assessment before the start of subsequent therapies.
  - 2 or more missing consecutive disease evaluations right after disease progression or death: the "hypothetical strategy" will be used. i.e., subjects who have disease progression or death immediately after 2 or more missing consecutive disease evaluations will be censored at the last disease assessment.
  - Death due to COVID-19 infection: the "treatment policy strategy" will be used. i.e., use time to death, regardless of COVID-19 infection or not.

Population-level summary: hazard ratio of PFS (per IMWG response criteria).

5.3.3. Analysis Methods

Analysis of PFS will be based on the ITT analysis set.

For PFS, the primary analysis will consist of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment groups. The p-value from a stratified log-rank test will be reported. The Kaplan-Meier method will be used to estimate the distribution of overall PFS for each treatment. The treatment effect, measured by hazard ratio (Arm B vs. Arm A), and its two-sided 95% confidence intervals are to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include ISS staging (I, II, III), and cytogenetic risk (standard, high). The median PFS with 95% CI will be provided. The Kaplan-Meier PFS curve will also be plotted by treatment group.

In addition, PFS rates with 95% CI will be estimated by Kaplan-Meier method at landmarks (e.g., at 12-month, and 18-month, etc.) and reported for each treatment group. The number and percentage of subjects who had a PFS event or were censored will be reported. Reasons for PFS censoring will be summarized for ITT.

PFS will also be presented by the subgroup specified in Section 5.6.7 as appropriate.

5.3.4. Sensitivity Analysis for Estimand

The following sensitivity analyses will be conducted to evaluate the robustness of the primary analysis of PFS as appropriate.

5.3.4.1. Progressive Disease Based on Investigator Assessment

A sensitivity analysis of PFS, in which progressive disease is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner as described in the Section 5.3.3. The PFS definition used in the sensitivity analysis is similar to that defined in the Section 5.3.1, except for date of progressive disease and date of censoring. The date of

progressive disease is the date of initial disease progression recorded in the Disease Progression CRF page or earliest date of confirmed progressive disease recorded in the Evaluation of Response CRF page, based on investigator assessment. Similarly, the censoring date is the latest date of disease response recorded in the Evaluation of Response CRF page, based on investigator assessment.

In addition, reasons for PFS and censoring based on investigator assessment will be summarized for ITT population.

5.3.4.2. Unstratified Analysis of PFS

A sensitivity analysis of PFS by using unstratified log-rank test and unstratified Cox's regression model will be performed in a similar manner as described in Section 5.3.3.

5.3.4.3. Not censored for Death/PD after Missing More Than One Disease Evaluation

A sensitivity analysis of PFS derived from the algorithm by not censoring for death or progression after missing consecutive evaluations will be performed in a similar manner as described in Section 5.3.3

The PFS definition used in the analysis is similar to that defined in Section 5.3.1, except for death or progression after missing more than one disease evaluation. For any PFS (death or progression) event identified by the computer algorithm, if there is more than one scheduled disease evaluation missed 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, then this event will be considered as a PFS event in the analysis.

5.3.5. Supplementary Analysis for Estimand

5.3.5.1. Censor for Treatment Discontinuation due to COVID-19

A supplementary analysis of PFS derived from the algorithm by censoring for treatment discontinuation due to COVID-19 will be performed in a similar manner as described in Section 5.3.3.

The PFS definition used in the analysis is similar to that defined in Section 5.3.1, except for treatment discontinuation due to COVID-19. Subjects who discontinue treatment due to COVID-19, start subsequent antimyeloma therapies, or with death due to COVID-19 without disease progression will be censored at the date of last disease evaluation before the treatment discontinuation date, start of subsequent therapies date, or date of death due to COVID-19, whichever is earlier.

5.3.5.2. Censor for Death due to COVID-19

A supplementary analysis of PFS derived from the algorithm by censoring for death due to COVID-19 for subjects, who have not developed a confirmed progressive disease, will be performed in a similar manner as described in Section 5.3.3.

The PFS definition used in the analysis is similar to that defined in Section 5.3.1, except for death due to COVID-19. Subjects who died due to COVID-19 without disease progression will be censored at the date of last disease evaluation before the date of death due to COVID-19.

5.3.5.3. Not Censored for Start of Subsequent Anti-Myeloma Therapies

A supplementary analysis of PFS derived from the algorithm by not censoring data due to start of subsequent anti-myeloma therapies for subjects, who have not developed a confirmed progressive disease, will be performed in a similar manner as described in Section 5.3.3.

The PFS definition used in the analysis is similar to that defined in Section 5.3.1, except for censoring data due to start of subsequent anti-myeloma therapies. Progression or death occurred after the start of subsequent anti-myeloma therapies for multiple myeloma 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.

5.3.5.4. Per-protocol Analysis of PFS

A supplementary analysis of PFS derived from the algorithm based on per-protocol population that contains less than 95% of the ITT population may be performed in a similar manner as described in Section 5.3.3.

5.3.5.5. Time-dependent Cox Regression

A supplementary analysis of PFS will be conducted based on time-dependent Cox regression model to test the treatment effect adjusting for the possible confounding from transplant. In this Cox proportional hazard model, PFS will be analyzed with treatment group, indicator for start of transplant phase, indicator for start of maintenance treatment phase, as well as their interactions with treatment group as the explanatory variables. The hazard ratios during separate phases and their corresponding 95% CI will be estimated.

5.3.6. Exploratory Analysis

5.3.6.1. Landmark Analysis of PFS

Landmark analysis may be performed to explore the add-on benefit of daratumumab in the maintenance treatment phase where subjects who do not enter into maintenance treatment phase (e.g., subjects experienced disease progression prior to start of maintenance therapy) may be excluded. In this analysis, PFS will be calculated from start of maintenance therapy to disease progression or death, whichever occurs earlier. For subjects who had withdrawal of consent to study participation, were lost to follow-up, or started subsequent antimyeloma therapy before disease progression or death occur, the PFS event dates would be censored similarly as described in Section 5.3.1.

The Kaplan-Meier method will be used to estimate the distribution of the PFS for each treatment. PFS will be analyzed by a Cox proportional hazard model with treatment group as the sole explanatory variable. The HR of Arm B relative to Arm A and the 95% CI will be reported. The

median PFS with 95% CI will be provided. The Kaplan-Meier PFS curve will also be plotted by treatment group. Note that subjects may not have balanced disease characteristics prior to start of maintenance therapy. Therefore, as an alternative landmark PFS analysis, a Cox's regression model including pre-maintenance response status and subjects' disease characteristics as explanatory factors may also be carried out, with exploratory model building/selection if the number of covariates is large.

5.3.6.2. Restricted Mean Survival Time (RMST)

The RMST may be performed as exploratory analyses: the proportional hazards assumption will be checked via graphical method as well as via formal statistical testing (i.e., Grambsch-Therneau Test). If the test of proportional hazards assumption fails at two-sided significance level of 0.2, the restricted mean survival time (RMST) method (Uno et al 2014)[4] may be performed as an exploratory analysis for the hypothesis testing, if needed.

The RMST, measured by the area under the Kaplan-Meier PFS curve up to the selected specific time point will be calculated for each treatment arm, where the selected timepoint is the smaller value of the longest PFS event time from either Arm A or Arm B. The difference in RMST and 95% CI will be reported. Additional cutoff timepoints used for RMST calculation may be used as exploratory analyses.

5.3.6.3. Inverse Probability of Censoring Weighting (IPCW)

If there is major imbalance in transplant rate between the two arms (e.g., >10%), exploratory analysis of PFS using inverse probability of censoring weighting (IPCW) may be performed to adjust for confounding from transplant. Subjects who did not receive transplant and have not progressed will be censored at the time of planned transplant, while those who received transplant will be upweighted. The weights will be estimated from covariates predictive of post-induction response and subsequent transplant such as baseline disease burden, performance status, occurrence of serious adverse event before transplant. Hazard ratio and its 95% confidence interval will be estimated based on a Cox regression analysis with IPCW (Robins and Finkelstein 2000)[3].

5.4. Secondary Endpoints Analysis

5.4.1. Key Secondary Endpoint(s)

The key secondary endpoints in this study will include:

- Overall CR or better rate
- Overall MRD negativity rate (at or below the threshold of 10^{-5})
- Overall Survival

5.4.1.1. Overall CR or Better Rate

5.4.1.1.1. Definition

Overall CR or better rate is defined as the percentage of ITT subjects who achieved CR or sCR status anytime during the study per the IMWG criteria. In addition, the specific response must be achieved prior to start of subsequent therapies.

5.4.1.1.2. Estimand

The estimand of overall CR or better rate, measurement of the overall treatment effect, is defined by the following 5 components.

- Treatment: Subjects receive four cycles induction therapy. Responding subjects receive ASCT followed by two cycles of consolidation therapy. Thereafter subjects are entering maintenance therapy.
  - VRd: subjects will receive VRd for induction and consolidation, and lenalidomide (R) for maintenance.
  - D-VRd: subjects will receive D-VRd for induction and consolidation, daratumumab (D) and lenalidomide (R) for maintenance. Subjects will stop therapy with daratumumab after sustained MRD negativity (at the threshold of 10^{-5}) for 12 months and after a minimum of 24 months of maintenance therapy; and the subjects should restart therapy with daratumumab if there is a recurrence of MRD at 10^{-4} or higher or a confirmed loss of CR.
- Population: Subjects with newly diagnosed multiple myeloma who are deemed eligible for high-dose therapy (as defined by protocol eligibility criteria).
- Variable: the variable is binary, where a successful response is given if the subjects achieve CR or better response. The detailed definition is in Section 5.4.1.1.1.
- Intercurrent events (ICE):
  - Subsequent anti-myeloma therapy or PD: the "while on treatment strategy" will be used. i.e., CR or sCR status on or after the start date of subsequent anti-myeloma therapy will not be considered in the analysis.
- Population-level summary: odds ratio of the overall CR or better rate for Arm B over Arm A.

5.4.1.1.3. Analysis Methods

The overall CR or better rate based on the computerized algorithm and corresponding exact 2-sided 95% CI from the Clopper-Person method will be calculated for each treatment group based on the ITT population. A comparison of the two treatment groups will be made using the stratified Cochran-Mantel-Haenszel test. The Mantel-Haenszel odds ratio (Arm B vs. Arm A) will be provided as the measure of treatment effect with its two-sided 95% CI and p-value reported.

The sensitivity analysis based on investigator per the IMWG response criteria will also be performed in a similar manner.

To help describe the benefit of adding daratumumab treatment during the maintenance treatment phase, a shift table will also be populated to present the change in response category from post-consolidation to post-maintenance among subjects with evaluations available at both timepoints.

5.4.1.2. Overall MRD Negativity Rate

5.4.1.2.1. Definition

Overall MRD negativity rate is defined as the proportion of ITT subjects who achieve MRD negativity (at or below the threshold of 10^{-5}) by bone marrow aspirate and achieve CR or better response at any time after the date of randomization during the study (and prior to progressive disease, subsequent therapy, or both). Subjects whose tested samples were found to be MRD positive or ambiguous, and subjects who were not tested will be considered as not achieving MRD negativity.

5.4.1.2.2. Estimand

The estimand of overall MRD negative rate, measurement of the overall treatment effect, is defined by the following 5 components.

- Treatment: Subjects receive four cycles induction therapy. Responding subjects receive ASCT followed by two cycles of consolidation therapy. Thereafter subjects are entering maintenance therapy.
  - VRd: subjects will receive VRd for induction and consolidation, and lenalidomide (R) for maintenance.
  - D-VRd: subjects will receive D-VRd for induction and consolidation, daratumumab (D) and lenalidomide (R) for maintenance. Subjects will stop therapy with daratumumab after sustained MRD negativity (at the threshold of 10^{-5}) for 12 months and after a minimum of 24 months of maintenance therapy; and the subjects should restart therapy with daratumumab if there is a recurrence of MRD at 10^{-4} or higher or a confirmed loss of CR.
- Population: Subjects with newly diagnosed multiple myeloma who are deemed eligible for high-dose therapy (as defined by protocol eligibility criteria).
- Variable: the variable is binary, where a successful response is given if the subject has negative MRD (at or below the threshold of 10^{-5}) and achieves CR or better response. The detailed definition is in Section 5.4.1.2.1.
- Intercurrent events (ICE):
  - Subsequent anti-myeloma therapy or PD: the “while on treatment strategy” will be used. i.e., MRD status on or after PD or switch to subsequent anti-myeloma therapy will not be considered in the analysis.
- Population-level summary: odds ratio of the overall MRD negativity rate for Arm B over Arm A.

5.4.1.2.3. Analysis Methods

A similar analysis as overall MRD negativity rate described in Section 5.4.1.1.3, the analysis will be performed for the ITT population.

As exploratory analyses, landmark analyses of MRD negativity rate will be performed at 12 months, 24 months, and 36 months after Cycle 1 Day 1. Subjects who did not have the MRD negativity at a given time point were considered as MRD positive in the landmark analysis. The durability of MRD negativity may also be examined and compared on the proportion of subjects remaining MRD negative at least 12 months after initial MRD negativity.

5.4.1.3. Overall Survival (OS)

5.4.1.3.1. Definition

Overall survival (OS) is measured from the date of randomization to the date of death due to any cause. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subjects who died after consent withdrawal will be considered as having an OS event. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.4.1.3.2. Analysis Methods

OS will be analyzed similarly as PFS described in Section 5.3.3. However, descriptive analysis without formal comparison will be performed at the time of the first PFS interim analysis due to the small number of events expected.

Supplementary analysis censoring death due to COVID-19 will be conducted.

5.4.2. Supportive Secondary Endpoints

5.4.2.1. Post-consolidation MRD Negativity Rate

5.4.2.1.1. Definition

The benefit of adding daratumumab up to the end of consolidation treatment phase will be primarily summarized by post-consolidation MRD negativity rate, which is defined as the proportion of subjects who achieve MRD negativity (at or below the threshold of 10^{-5}) and achieve CR or better response at the end of consolidation treatment phase.

For those missing post-consolidation MRD assessment, the last assessment obtained prior to the end of consolidation, or prior to the start of maintenance treatment (or date of end of treatment, which is earlier) for subjects who skipped or with non-applicable consolidation treatment phase, will be carried forward. Subjects without MRD assessment will be considered as having positive MRD.

5.4.2.1.2. Analysis Methods

The post-consolidation MRD negativity rate will be analyzed similar as the overall CR or better rate (Section 5.4.1.1.3) based on the ITT population.

5.4.2.2. Overall ORR, VGPR or Better Rate and sCR Rate

5.4.2.2.1. Definition

Overall ORR, VGPR or better rate and sCR rate is defined as the percentage of ITT subjects who achieved PR or better status, VGPR or better status and sCR status anytime during the study per the IMWG criteria, respectively. In addition, the specific response must be achieved prior to start of subsequent anti-myeloma therapies.

5.4.2.2.2. Analysis Methods

A similar analysis as the overall CR or better rate described in Section 5.4.1.1.3 will be performed for the ITT population based on the computerized algorithm.

A sensitivity analysis based on investigator per the IMWG response criteria will also be performed in a similar manner.

To help describe the benefit of adding daratumumab treatment during the maintenance treatment phase, a shift table will also be populated to present the change in response category from post-consolidation to post-maintenance among subjects with evaluations available at both timepoints.

5.4.2.3. ORR, VGPR or Better Rate, CR or Better Rate, and sCR Rate at Post-induction (at Post-transplant, at Post-consolidation)

5.4.2.3.1. Definition

ORR, VGPR or better rate, CR or better rate, and sCR rate at post-induction is defined as the proportions of ITT subjects who achieved PR or better, VGPR or better, CR or better, or sCR by the end date of induction treatment (defined in Section 5.1.1), per the IMWG criteria, respectively. In addition, the specific response must be achieved prior to start of subsequent anti-myeloma therapies.

Post-transplant response is defined similarly as post-induction response, with additional as,

- For subjects who skipped or with non-applicable ASCT phase, the end date would be one day prior to the start of consolidation treatment, or one day prior to the start of maintenance treatment, or date of end of treatment, which is earlier.

Post-consolidation response is defined similarly as post-induction response, with additional as,

- For subjects who skipped or with non-applicable consolidation treatment phase, the end date would be one day prior to the start of maintenance treatment, or date of end of treatment, which is earlier.

5.4.2.3.2. Analysis Methods

A similar analysis as overall CR or better rate described in Section 5.4.1.1.3 will be performed for the ITT population based on the computerized algorithm.

A sensitivity analysis based on investigator per the IMWG response criteria will also be performed in a similar manner.

5.4.2.4. Progression-free Survival on Next Line of Therapy (PFS2)

5.4.2.4.1. Definition

Progression-free survival on next line of therapy (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.

Determination of dates of PFS2 event and dates for censoring is summarized in Table 3 as follows.

Table 3: PFS2 Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
No post-baseline disease assessment	Randomization	Censored
Alive and no disease progression on study treatment	Date of last disease assessment prior to start of 1st line on next therapy (For subjects received no subsequent therapy, date of last disease assessment before last date of follow-up)	Censored
Disease progression on study treatment and progress on the 1st line of next therapy or any death	Minimum of earliest date that indicates progression on the 1st line of next therapy and date of death	PFS2 event
Other	Minimum of start date of 2nd line of next therapy minus 1 and last date of follow-up	Censored

5.4.2.4.2. Analysis Methods

Similar statistical methods will be applied as described in Section 5.3.3 for PFS analysis.

5.4.2.5. Time to Response

5.4.2.5.1. Definition

Time to response (i.e., time to first response) is defined as the time from the date of randomization to the date of first documentation of a confirmed response (PR or better) for subjects who have PR or better as their best response.

Time to CR or better is defined as the time from the date of randomization to the date of first documentation of a confirmed response of CR or better for subjects who have response of CR or better.

5.4.2.5.2. Analysis Methods

Descriptive statistics (mean, standard deviation, median, and range) will be provided to summarize time to response, time to CR and time to sCR for subjects with PR or better response, CR, and sCR, respectively, by treatment group based on the computerized algorithm.

5.4.2.6. Duration of Response

5.4.2.6.1. Definition

Duration of response is defined as the time from the date of first documentation of a confirmed response (PR or better) to the date of first documentation of a confirmed PD, according to IMWG criteria, or death due to PD, whichever occurs first, for subjects who have PR or better as their best response. Responders without PD will be censored at the last disease evaluation prior to subsequent therapy.

Duration of CR or better is defined as the time from the date of first documentation of a confirmed response of CR or better to the date of first documentation of a confirmed PD, or death due to PD, whichever occurs first, for subjects who have CR or better as their best response. CR or better responders without PD will be censored at the last disease evaluation prior to subsequent therapy.

Duration of MRD negative status is defined as the time from the date of first documentation of MRD negative status to the date of first documentation of a confirmed PD, or death due to PD, or loss of MRD negative status (threshold of 10^{-4}), whichever occurs first, for subjects who have achieved MRD negative status in the study. Subjects without PD or loss of MRD negative status (threshold of 10^{-4}) will be censored at the last disease evaluation prior to subsequent therapy or the date of last MRD negativity, whichever is later.

5.4.2.6.2. Analysis Methods

Duration of response, duration of CR or better, and duration of MRD negative status will be presented descriptively using the Kaplan-Meier estimates, respectively, for each treatment group based on the computerized algorithm.

5.5. Safety Analyses

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

5.5.1. Extent of Exposure

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

The number and percentage of subjects treated within each cycle will be summarized by treatment group for induction treatment phase, consolidation treatment phase, and maintenance treatment

phase, respectively. The total number of treatment cycles received in each treatment phase for each subject will be summarized by descriptive statistics (N, mean [STD], median, range [minimum, maximum]).

Descriptive statistics for duration of study treatment for each phase, defined as the number of days from the date of the first administration of study treatment to the date of the last administration in that phase, will be presented in months by treatment group. For duration of induction treatment phase, the duration of mobilization will be excluded. Specifically, the duration of ASCT is defined as time in between transplantation and start of consolidation treatment (or the day before the first date of maintenance treatment phase in the event ASCT was done after Cycle 6, or the date of end-of treatment visit, or subsequent antimyeloma therapy minus 1 day, whichever is earlier). In addition, the duration of study treatment for the combined induction/ASCT/ consolidation phase will be summarized in months by treatment group. Subject-month of exposure are calculated as days of duration/365.25*12.

The total number of daratumumab administrations will be summarized for subjects in Arm B. The total dose administered for daratumumab (mg), bortezomib (mg/m^2), lenalidomide (mg) and dexamethasone (mg) will be summarized by descriptive statistics for each treatment phase (for maintenance treatment phase, exposure of daratumumab and/or lenalidomide will be summarized) and for the combined induction/consolidation treatment phase. The dose intensity, which is defined as the sum of total dose administered divided by the number of treatment cycles, will be calculated for each study treatment in each treatment phase; and for daratumumab, it will be summarized by Cycles 1-2, Cycles 3-4, Cycles 5-6 (for the subjects who started ASCT after 6 cycles of induction treatment due to COVID-19 pandemic and subjects who did not receive ASCT after 6 cycles of induction) during the induction treatment phase. Accordingly, relative dose intensity (%) which is defined as the ratio of total dose received and total planned dose will be calculated. For bortezomib, lenalidomide and dexamethasone, the dose intensity and relative dose intensity will also be summarized for the combined induction/consolidation treatment phase.

Cycle delay refers to the delayed initiation of study treatment cycle starting from Cycle 2 for the induction treatment phase, Cycle 5 for the consolidation treatment phase, and Cycle 8 for the maintenance treatment phase. The number of subjects with cycle delay, treatment modification or permanent discontinuation for daratumumab, bortezomib, lenalidomide and dexamethasone, and injection abortion, interruption for daratumumab, together with the reasons reported (adverse events or other) will be summarized for each treatment arm in combined induction/consolidation treatment phase, separately. Similar summaries will be provided for daratumumab and lenalidomide for the maintenance treatment phase. Subjects who discontinued daratumumab in maintenance treatment phase due to sustained MRD negativity will be listed.

5.5.1.1. Mobilization and Harvesting

The number of subjects who underwent stem cell mobilization, and the type of mobilization medication (cyclophosphamide, G-CSF, or Plerixafor) will be summarized for each treatment arm. The number of subjects with stem cell collected, and the type of collection method (PBSC pheresis or bone marrow harvest) will be provided for each treatment group.

For subjects who underwent bone marrow harvest, the number of CD34+ cells collected (10^6/kg) from bone marrow will be summarized by descriptive statistics.

For subjects who performed PBSC apheresis, the number of days of PBSC apheresis and number of CD34+ cells collected (10^6/kg) will be summarized by descriptive statistics.

5.5.1.2. Autologous Stem Cell Transplant (ASCT)

Descriptive statistics will be provided by treatment group for:

- Number of subjects who underwent transplant, number of CD34+ cells transplanted, number of subjects with hematopoietic reconstitution.
- Time to hematological recovery (engraftment) which includes:
  - The number of days from ASCT to the initial date with ANC $\geq 0.5\times10^9$/L
  - The number of days from the ASCT to the initial date with platelet count $\geq 20\times10^9$/L

5.5.1.3. Duration of Pre-ASCT

For subjects who receive mobilization therapy, the duration of pre-ASCT is defined as the time from the day after the last dose of induction treatment before mobilization therapy to the day before the start date of melphalan administration, the day before first dose of consolidation therapy, the day before first dose of maintenance therapy, or the date of end of treatment, whichever is earlier.

For subjects who receive mobilization therapy between Cycle 4 and Cycle 5 (started prior to ASCT), the duration of pre-ASCT is defined as time from the day after the last dose of induction treatment prior to the start of mobilization therapy to the day before Cycle 5 Day 1.

5.5.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), most recent version.

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 one 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.

Any AE occurring after the initiation of study treatment, including agents used for mobilization and/or ASCT, until 30 days after the last study treatment or the day prior to start of subsequent antimyeloma therapy, whichever occurs first; or any AE occurring after initiation of

study treatment but during the non-treatment emergent period that is considered related by the investigator is considered to be treatment emergent. However, for the subjects who stopped daratumumab due to sustained MRD negativity, any events occur after the last dose of daratumumab or lenalidomide, and before the restarting date of daratumumab, would not be considered as treatment emergent. AE occurring includes onset of a new AE and worsening of a condition pre-existing at baseline. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. In addition, the follow-up AE (linked to an existing treatment-emergent AE) with onset date and time beyond 30 days after the last study agent administration but prior to the start of subsequent therapy will also be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date.

All reported treatment-emergent adverse events (TEAEs) will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. The incidence of TEAEs will be summarized overall, by treatment phase (induction/ASCT/consolidation/maintenance), by MedDRA system organ class (SOC) and preferred term, by toxicity grade, and by relationship to study treatment administration.

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.

5.5.2.1. Treatment Emergent Adverse Events

An overview of TEAEs reported through the study will be provided by treatment phase for each treatment arm. The overview will include summaries of subjects with TEAEs, TEAEs related to study treatment, TEAEs of maximum toxicity grade of 1 to 5, serious AEs, TEAEs leading to discontinuation of any study treatment, TEAEs leading to discontinuation of all study treatment, Death due to AEs (COVID-19 or not), COVID-19 TEAE, COVID-19 serious TEAE. An overview of TEAE by subgroup specified in Section 5.6.7 will be provided.

Summary tables will also be provided for:

- TEAEs by system organ class (SOC) and preferred term (PT)
- TEAEs by SOC, PT by subgroups specified in Section 5.6.7
- TEAEs by SOC, PT, and worst toxicity grade
- Most common (e.g., at least 10%) TEAEs by SOC, PT and treatment phase
- TEAEs by SOC, PT, and relationship to study treatment
- Serious TEAEs by SOC and PT
- Serious TEAEs by SOC, PT, and worst toxicity grade

- Most common (e.g., at least 2%) serious TEAEs by SOC, PT and treatment phase
- TEAEs with outcome death by SOC, PT and relationship to treatment
- TEAE of interest for COVID-19 infection by PT and toxicity grade
- Serious TEAE of interest for COVID-19 infection by PT and toxicity grade
- TEAE of interest for COVID-19 infection leading to death by PT

The following summaries of treatment modifications due to TEAEs will be provided:

- TEAEs leading to cycle delays by SOC, PT and Grade 3 or 4
- TEAEs leading to dose modification by SOC, PT and Grade 3 or 4
- TEAEs leading to daratumumab injection interrupted, aborted, site changed by SOC, PT and Grade 3 or 4
- TEAEs leading to discontinuation of all study treatments by SOC, PT and Grade 3 or 4
- TEAEs leading to discontinuation of any study treatment by SOC, PT and Grade 3 or 4

5.5.2.2. TEAEs of Clinical Interest

- Incidence of following treatment-emergent adverse events of clinical interest will be summarized for each treatment group.
- Infusion-related reactions (IRRs) associated with daratumumab by SOC, PT and Grade 3 or 4
- Injection site reactions (ISRs) related to daratumumab by SOC, PT and Grade 3 or 4
- Cytopenia by PT and grade 3 or 4
- Hemorrhage by SOC, PT and Grade 3 or 4. Hemorrhage is defined by Standardized MedDRA Queries (SMQ) with the first subcategory SMQ of hemorrhage terms (exclude laboratory terms).
- Toxicity Grade 3 or 4 treatment-emergent infections and infestations by PT and relationship to treatment. Infections and infestations refer to adverse events with SOC of infections and infestations.
- COVID-19 by PT and worst toxicity grade
- Hepatitis B virus reactivation by PT. Hepatitis B virus reactions refer to adverse events with PT of hepatitis viral, acute hepatitis B, hepatitis B, hepatitis B reactivation, chronic hepatitis B, hepatitis B DNA assay positive, and hepatitis B DNA increased.
- Opportunistic infections by PT and treatment phase, toxicity grade 3 or 4 treatment-emergent opportunistic infections by PT and treatment phase
- Viral infections by PT and treatment phase, toxicity grade 3 or 4 treatment-emergent viral infections by PT and treatment phase
- Interference blood typing by preferred term and grade 3 or 4
- Peripheral neuropathies (PNs) by MedDRA high level term, and PT. Peripheral neuropathies (PNs) refer to adverse events with high level term (HLT) of peripheral neuropathies NEC

A listing of subjects who reported new 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.) and other information whenever a new malignancy is observed.

5.5.3. Additional Safety Assessments

5.5.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be summarized for the subjects included in the safety analysis set.

Hematology parameters include:

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

During induction and consolidation treatment phases, chemistry parameters include:

- sodium
- potassium
- creatinine
- creatinine clearance
- total bilirubin, direct bilirubin
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- alkaline phosphatase
- urea
- glucose
- total protein
- lactic acid dehydrogenase (LDH)
- uric acid

During maintenance treatment phase, chemistry parameters include:

- total bilirubin, direct bilirubin
- aspartate aminotransferase (AST)
- alanine aminotransferase (ALT)
- creatinine
- urea

Descriptive statistics will be presented for all chemistry, hematology laboratory tests at scheduled time points. Change from baseline to above scheduled time points will be summarized for chemistry, hematology tests and displayed by treatment group.

In addition, shifts summaries from baseline value to the worst toxicity grade during treatment in chemistry and hematology test will be generated. The laboratory toxicity grades would be derived based on the NCI-CTCAE. Plots for selected laboratory tests change over time may be provided.

5.5.3.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, weight, pulse, blood pressure (systolic and diastolic) will be summarized at each assessment time point. Changes from baseline over time will be summarized for the treatment period. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

5.5.3.3. Electrocardiogram

A 12-lead ECG will be performed at Screening and at EOT; and as clinically indicated. Frequencies of overall interpretation of ECG results (normal, abnormal and clinically significant, abnormal and not clinically significant) over time will be provided. A listing of subjects who experienced clinically significant abnormal ECG in either baseline or post-baseline will be produced.

5.5.3.4. Other Safety Parameters

5.5.3.4.1. ECOG Performance Score

Frequencies of ECOG performance status (0, 1, 2, >2) over time will be summarized at the scheduled time point. Shift from baseline to worst score during treatment will be provided.

5.6. Other Analyses

5.6.1. Pharmacokinetics

PK analyses will be performed on the PK-evaluable population. The pharmacokinetic parameters are defined as

- C_{min} – Minimum observed concentration
- C_{max} – Maximum observed concentration

The two parameters will be determined based on the assigned collection timepoints. If there are sufficient data, population PK analysis of serum concentration-time data of daratumumab may be performed and may include data from other clinical studies. If performed, details will be provided in a population PK analysis plan and results of the analysis will be presented in a separate report.

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. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics (N, mean, STD, median, range, coefficient variation and geometric mean) will be used to summarize daratumumab serum concentrations at each sampling time point for Arm B. Predose concentrations are considered C_{min} and post-dose concentrations are defined as C_{max}. Plot of mean (±SD) daratumumab serum peak and trough concentrations over time will be provided.

5.6.2. Immune Response

Immunogenicity analyses will be performed on the immunogenicity analysis set. The incidence of anti-daratumumab antibodies will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of anti-daratumumab antibodies (at least 1 sample collected after the start of daratumumab administration). The prevalence and incidence of anti-rHuPH20 antibodies will be summarized for all subjects who receive a dose of daratumumab and have at least 1 sample for detection of anti-rHuPH20 antibodies. In addition, subjects who are positive for anti-daratumumab or anti-rHuPH20 antibodies will be listed. A listing of sample level anti-daratumumab and anti-rHuPH20 antibodies with the concurrent daratumumab concentration will be provided.

5.6.3. Pharmacokinetic/Pharmacodynamic Relationships

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

5.6.4. Biomarkers

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information. Results of biomarker analyses may be presented in a separate report.

Blood and bone marrow samples will be drawn from all subjects in both treatment groups to better understand the mechanism of action and mechanism of resistance of daratumumab, and will be summarized as applicable.

Descriptive statistics for values and changes from baseline at each scheduled visit for specific subsets of immune cells such as cytotoxic T cells, regulatory T cells, and activated NK cells may be provided by treatment group. Plots for these biomarkers over time may be provided as well.

5.6.4.1. Minimal Residual Disease (MRD)

Bone marrow aspirates will be collected at screening for all subjects and at post-consolidation in subjects with VGPR or better for MRD assessment. Additional bone marrow aspirates will be collected at time of suspected CR or better and for subjects who achieve CR, have not progressed, and remain on the study; additional bone marrow aspirate will be obtained at 12, 18, 24, 30 and 36 months post Cycle 1 Day 1 (±1 month) and yearly thereafter (±1 month). If feasible, a bone marrow aspirate may be collected from subjects at disease progression to evaluate mechanisms of daratumumab resistance.

Bone marrow aspirates will be analyzed by NGS. If this methodology is unavailable, or determined to be scientifically inferior, then alternative methods for MRD assessment may be used.

5.6.5. Details on MRD Negativity Rate Analyses are Described in Section

5.6.5.1. Medical Resource Utilization

Medical resource utilization (excluding protocol-mandated procedures, tests, and encounters) will be descriptively summarized by treatment group. Frequencies of medical encounter, type of medical encounter, reasons for the medical encounter, and durations of medical encounters will be calculated and tabulated.

5.6.6. Patient-reported Outcomes (PRO)

5.6.6.1. Definition

Subjects health-related quality of life (HRQoL), symptoms, functional status and well-being will be assessed using 3 PRO measures, the EORTC-QLQ-C30, EORTC QLQ-MY20, and the EQ-5D-5L. They will be scored based on the instrument developer guidelines and 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, 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 verbal rating 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)[5]. A higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

The EORTC 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 (Cocks 2007)[6].

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 (but allows for values less than 0 by UK scoring algorithm).

5.6.6.2. Analysis Methods

Analysis of PRO data will be performed on the ITT analysis set. For subjects with multiple records at the same visit, the closest one to the visit date will be selected as the scheduled assessment. Compliance rates for completion of EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D-5L at

each time point will be generated based on the actual number of PRO assessments received over the number of expected.

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

Key PRO endpoints

- EORTC QLQ-C30 global health status, physical functioning, fatigue, and pain scales
- EORTC QLQ-MY20 Disease Symptoms scale
- EQ-5D-5L VAS, and utility score

Summary descriptive statistics will be calculated for the EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D-5L baseline values (screening visit) by treatment arm and for the total study population. The descriptive statistics and change from baseline at each time point will be summarized 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. ITT 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 week, treatment-by-time interaction, and stratification factors as fixed effects. Line plots of the change from baseline with standard error over time by treatment group will be displayed. 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 meaningful important difference (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 D-VRd relative to VRd 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

For the EORTC QLQ-C30, these include:

- 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
- For QLQ-MY20, these include side effects of treatment, future perspective, and body image.

The descriptive statistics and change from baseline at each time point will be summarized descriptively by treatment group. The mixed effect model analysis, as described for the key PRO endpoints, may be performed as appropriate.

5.6.7. Definition of Subgroups

The following pre-specified subgroup analyses are to be performed for the efficacy and/or safety endpoints. Additional subgroup analyses may be planned if deemed necessary.

Table 4: Definition of Subgroups

Subgroup	Definition	Analysis Type
Age	• <65 • ≥65	Efficacy
	• <50 • =50-<65 • ≥65	Safety
Sex	• Male • Female	Efficacy, Safety
Race	• White • Other	Efficacy, Safety
International Staging System (ISS)	• I • II • III	Efficacy
Cytogenetic risk	• High risk • Standard risk • Indeterminate	Efficacy
Baseline hepatic function	• Normal • Impaired[a]	Safety
Type of MM[b]	• IgG • Non-IgG	Efficacy
Baseline renal function (CrCl)[c]	• <60 mL/min/1.73m^2 • 60 to <90 mL/min/1.73m^2 • ≥90 mL/min mL/min/1.73m^2	Safety
Baseline body weight (kg)	• ≤ 65 kg • >65 to ≤ 85 kg • > 85kg	Safety
Baseline ECOG performance score	• 0 • ≥1	Efficacy

a Includes mild, moderate, and severe. Mild (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN); moderate (1.5×ULN < total bilirubin ≤ 3×ULN); and severe (total bilirubin > 3×ULN).
b based on subjects with measurable disease in serum.
c based on Modified Diet in Renal Disease (MDRD) Formula.

5.7. Interim Analyses

The study design includes 2 interim analyses and a final analysis for PFS, the first interim analysis will be performed when approximately 143 PFS events have occurred (corresponds to 50% of the total planned PFS events), the second interim analysis for PFS will be performed when approximately 185 PFS events have occurred (corresponds to 65% of the total planned PFS). If the superiority of D-VRd over VRd alone with respect to PFS could be established at the first or second interim analysis, the interim PFS analysis would serve as the primary PFS analysis, which otherwise is to occur when approximately 285 PFS events had been observed.

A hierarchical testing proposed by Tang and Geller (1999)[7] will be used for the primary superiority hypothesis and 3 key secondary superiority hypotheses. Table 5 summarizes the hypotheses and specifies alpha-spending functions if a group sequential testing is planned for a particular hypothesis.

Table 5: Summary of Primary and Key Secondary Hypotheses

Label	Description	Type	Group sequential testing	Effect size assumption[a]	n[b]
H1	Dara on PFS	primary	Hwang-Shih-DeCani, parameter = -2.5	0.69	285
H2	Dara on CR/sCR	secondary	No group sequential testing	0.15	709
H3	Dara on MRD	secondary	No group sequential testing	0.15	709
H4	Dara on OS	secondary	Lan-DeMets Pocock approximation c	0.75	310

a. Expressed as rate difference in proportions for binary endpoints and hazard ratio (HR) for the time-to-event endpoints.
b. Refer to the subjects' number for the binary endpoints and events number for the time-to-event endpoints.
c. A Lan-DeMets spending function to approximate Pocock design will be used to determine the OS stopping boundary.

The overall Type I family-wise error rate across the testing of all 4 hypotheses, overall (interim and final) analyses, is strongly controlled to 5% (two-sided).

The primary hypothesis is to be tested at the 0.05 significance level (overall). The exact significance level for superiority at the first and second PFS interim analyses is to be determined by the observed number of events per the Hwang-Shih-DeCani alpha spending function with gamma parameter = -2.5. Assuming that 143 and 185 PFS events, respectively, are observed at the first and second PFS interim analyses, the two-sided alpha to be spent in the two interim analyses will be 0.0112 and 0.0126, and it will be 0.0414 for the final analysis. If the observed two-sided p-value is smaller than 0.0112, 0.0126 or 0.0414 at the corresponding interim or final analysis, the superiority of D-VRd over VRd with respect to PFS will be established.

Only if the primary endpoint of PFS is statistically significant, the following key secondary endpoints would be sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing the hierarchical testing approach that strongly controls Type I error rate. The key secondary endpoints will be tested in the following order:

1. Overall CR or better rate
2. Overall MRD negativity rate (threshold of 10^{-5})
3. Overall Survival

- For Overall CR or better rate and MRD negativity rate (10^{-5}) will only be tested at the interim or final PFS analysis when PFS is statistically significant.
- For OS, descriptive analysis will be performed at the time of the first PFS interim analyses, expecting few OS events. In case PFS significance is established prior to the second interim or final PFS analysis, OS analysis will continue to be performed at approximately same time as if the second interim and final PFS analysis would occur (185, 285 PFS events). Expecting a long gap between the final PFS and final OS analysis, additional looks may be added to provide periodically OS updates until a definitive conclusion on OS is reached.

For each hypothesis, Table 6 gives the local significance alpha levels and powers at different information fractions. If for a given hypothesis group sequential testing is planned, the table reports a nominal p-value boundary derived from the given alpha-spending function. This boundary will be compared to the observed p-values calculated for the test statistics at the corresponding analyses. The timing of analyses is expressed in terms of statistical information fractions, i.e., current analysis information relative to the total plan information for that hypothesis test.

Table 6: Efficacy p-value Boundaries

Analysis	Information fraction	Nominal p-value	Hurdle delta[b]	Power
H1: PFS				
1	0.502	0.011	0.654	0.38
2	0.649	0.013	0.693	0.54
3	1.000	0.041	0.785	0.87
H2: CR/sCR				
1	1.000	0.050	0.065	>0.99
H3: MRD rate				
1	1.000	0.050	0.072	0.99
H4: OS[a]				
1	0.600	0.0354	0.734	0.44
2	1.000	0.0257	0.776	0.66

OS[a]: descriptive analysis will be performed for OS at the time of the first PFS interim analyses and without alpha spending; additionally, a nominal 2-sided alpha of 0.0001 will be spent at the second PFS interim analysis; the boundary will be determined by the spending function using the remaining alpha at the PFS final analysis and OS final analysis.
Hurdle delta[b]: which is an approximate value and not for the testing purpose.

5.7.1. Futility Analysis of OS

All subjects in the ITT population were randomized between 19 January 2019 and 03 January 2020. Given that the study was fully enrolled and ongoing at the peak of the COVID-19 pandemic prior to the availability of vaccine and/or treatment, and multiple myeloma subjects with advance aged are at high risk of developing serious COVID-19 infection and resulting in death, no formal OS futility analysis will be conducted for this trial since it would be difficult to accurately assess COVID-19 impact on the OS, especially if there is any imbalance between the two arms. Instead, sensitivity OS analyses such as censoring the COVID-19 death shall be conducted at the planned analyses, together with the routine IDMC's cumulative safety data review (especially for

COVID-19 cases, and exposure impacted by the pandemic) every 6 months before the primary PFS analysis. In the event that the observed OS HR is greater than 1, it would be more appropriate to put it in the context of safety profile and benefit-risk assessment.

5.7.2. Review Board

5.7.2.1. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC), consisting of 2 clinicians and 1 statistician who are independent experts not otherwise participating in the study, will be established to review safety results after approximately 100 subjects have completed the induction treatment phase (i.e., Cycle 1 through Cycle 4) plus stem cell mobilization and again after approximately 100 subjects have completed the consolidation treatment phase (i.e., Cycle 5 and Cycle 6). In addition, the IDMC will review cumulative safety data on a regular basis before the primary PFS analysis and will also review efficacy and safety results at the 2 planned PFS interim analyses. After each of these reviews, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of 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
D-VRd	daratumumab in combination with bortezomib, lenalidomide, and dexamethasone
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
HR	hazard ratio
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IMWG	International Myeloma Working Group
IRR	infusion-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
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
VRd	bortezomib, lenalidomide, and dexamethasone

6.2. Appendix 3 Demographics and Baseline Characteristics

Unless specified otherwise, all demographic and baseline characteristics variables will be summarized for the ITT analysis set by treatment group. No statistical comparison between the treatment groups is planned.

A list of subjects who did not meet study inclusion/exclusion criteria will be provided. This listing will include treatment group, subject ID, category of study selection criteria not met and specific criteria not met.

Table 7 and Table 8 respectively present a list of the demographic variables and baseline disease characteristics that will be summarized by treatment group and overall. A listing of subject demographic and baseline characteristics will be provided as well.

Table 7: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [STD], median and range [minimum and maximum]).
Weight (kg)	
BSA (m2)	
Height (cm)	
Categorical Variables	
Age (<50 years, ≥50 and <65 years, ≥65 years)	N, frequency distribution with the number and percentage of subjects in each category.
Weight (≤65kg, >65kg and ≤85kg, >85kg)	
Sex (male, female)	
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple[a])	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported)	
Baseline ECOG (0, 1, 2, 3)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

Table 8: Baseline Disease Characteristics

Parameters	**Summary Type**
Continuous Variables:	
Time from MM diagnosis to randomization (months)	Descriptive statistics (N, mean, standard deviation [STD], median and range [minimum and maximum]).
Categorical Variables	
Type of multiple myeloma (IgG, IgA, IgM, IgD, IgE, light chain only [kappa, lambda, FLC-kappa and FLC-lambda], biclonal, negative immunofixation)	N, frequency distribution with the number and percentage of subjects in each category.
Type of measurable disease (serum measurable [IgG, IgA and Other], urine measurable only, serum FLC measurable)	
ISS staging at screening by central laboratory assessment (I, II, III)	
Number of lytic bone lesions (None, 1-3, 4-10, more than 10)	
Presence of diffuse myeloma-related osteopenia (Yes, No)	
Number of extramedullary plasmacytomas (0, ≥1)	
Bone marrow % plasma cells (<10, 10 – 30, >30)	
Cytogenetic risk (standard-risk, high-risk, indeterminate),	

Selected hematology and chemistry laboratory analytes at baseline will be summarized for each treatment group:

- Hematology: hemoglobin, neutrophils, lymphocytes, platelet, white blood cell
- Chemistry: potassium, creatinine, creatinine clearance, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactic acid dehydrogenase, uric acid

In addition, the selected hematology and chemistry laboratory analytes at pre-maintenance will be summarized by treatment group for subjects who enter into the maintenance treatment phase:

- Hematology: hemoglobin, neutrophils, lymphocytes, platelet, white blood cell
- Chemistry: total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, creatinine clearance.

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

A summary of stratification factors (ISS staging and cytogenetic risks) used in the randomization based on IWRS will be provided by treatment group for ITT population.

6.3. Appendix 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 (including COVID-19 related deviations) will be summarized by category for ITT analysis set.

- Entered but did not satisfy inclusion/exclusion criteria.
- Received a disallowed concomitant treatment.
- Received wrong treatment or incorrect dose.
- Developed withdrawal criteria but not withdrawn.
- Other
- A listing of all major protocol deviations including subject ID, type of deviation, and reasons for deviation will be provided. Similar listing may be presented for all COVID-19 related minor protocol deviations. Minor protocol deviations related to COVID-19 will be listed.

6.4. Appendix 5 Prior and Concomitant Medications

With the study population of newly diagnosed subjects with multiple myeloma, prior systemic use of corticosteroids is limited to a short course of emergency use to treat multiple myeloma symptoms. A listing of all prior systemic use of corticosteroids, if any, will be provided for the ITT population.

Summaries of concomitant medications will be presented by therapeutic class, pharmacologic class and preferred term for each treatment group of safety analysis set. Pre-infusion medications and post-infusion medications will be summarized similarly for each treatment group.

In addition, concomitant medication for COVID-19 infection will be summarized and listed.

6.5. Appendix 6 Subsequent Antimyeloma Therapy

The total number of subjects who received subsequent anti-myeloma therapy will be reported for safety analysis set by treatment group. A summary of subsequent anti-myeloma therapy will be presented by therapeutic class, pharmacologic class and drug name.

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