Official Title of Study:

Study of Daratumumab (JNJ-54767414 (HuMax® CD38) in Combination with Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTD) in the First Line Treatment of Transplant Eligible Subjects with Newly Diagnosed Multiple Myeloma.

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Janssen Research & Development

Statistical Analysis Plan (Part 2)

A Phase 3 Study of Daratumumab (JNJ-54767414 (HuMax® CD38) in Combination with Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTd) in the First Line Treatment of Transplant Eligible Subjects with Newly Diagnosed Multiple Myeloma

Protocol 54767414MMY3006; Phase 3

JNJ54767414 (daratumumab)

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ABBREVIATIONS

AE	Adverse event
ALB	Albumin
ALKY	Alkylating agent
ASCT	Autologous stem cell transplant
B2MG	Beta2 microglobulin
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete response
DOR	Duration of response
DPS	Data presentation specifications
ECOG	European cooperative oncology group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQol Five Dimension Questionnaire
eCRF	Electronic case report form
GHS	Global health status
FLC	Free light chain
HEMAR	Health Economics/Market Access/Reimbursement
HRQoL	Health-related quality of life
ICH	International Conference on Harmonization
IMiD	Immunomodulatory drug
IMWG	International multiple myeloma working group
IRR	Infusion related reaction
ISS	International staging system
ITT	Intent-to-Treat
IWRS	Interactive web response system
LLN	Lower limit normal
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRD	Minimal residual disease
NCI CTC	National cancer institute common terminology criteria
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PI	Proteasome inhibitor
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sCR	Stringent complete response
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
TTP	Time to disease progression
TTR	Time to response
ULN	Upper limit normal
VAS	Visual analog scale
VGPR	Very good partial response
VTd	VELCADE (bortezomib) + thalidomide + dexamethasone

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of the analysis set(s), derived variables and statistical methods for the primary analyses pertaining to Part 2 specified in the protocol 54767414MMY3006.

Part 2 is defined as the study where subjects with at least a partial response by IMWG criteria after induction/ASCT/consolidation (Part1) are randomized to enter the Maintenance Phase:

- **Arm A:** Observation only until documented disease progression (or a maximum of 2 years)
- **Arm B:** Daratumumab monotherapy until documented disease progression (limited to 2 years maximum treatment duration)

1.1. Trial Objectives

Primary Objective

The primary objective in Part 2 is to determine if the use of daratumumab as single agent in maintenance compared to observation only will increase progression-free survival (PFS) when used after autologous stem cell transplant and consolidation therapy.

Secondary Objectives

Major secondary efficacy objectives in Part 2 of the trial are:

- Time to progression (TTP) from second randomization
- Complete response (CR) or better rate
- Stringent complete response (sCR) rate
- Rate of improved response
- Minimal residual disease (MRD) negative CR or better rate
- Minimal residual disease (MRD) negative rate
- Rate of MRD negative CR or better conversion rate
- Rate of MRD negative conversion
- Progression-free survival after next line of therapy (PFS2) from second randomization
- Overall survival (OS) from second randomization

Other secondary objectives are:

- To evaluate health-related quality of life (HRQoL) and health economic/resource utilization
- To assess immunogenicity of daratumumab
- To assess safety and tolerability of daratumumab

Exploratory Objectives

The exploratory objective of the study is to evaluate daratumumab's impact on response and resistance to treatment.

1.2. Trial Design

This is a randomized, open-label, active control, parallel group, multicenter, Phase 3 study in subjects with previously untreated multiple myeloma. Out of 1080 subjects randomized in Part 1 (Induction Phase) of the trial, approximately 800 subjects (400/arm) were supposed to be randomized in Part 2 (Maintenance Phase). The actual accrual into the Induction phase was 1085 subjects and is 886 subjects in the Maintenance phase.

The Treatment Phase in Part 2 is described below and will extend from the second randomization after completion of consolidation treatment and determination of response (partial response [PR] or better) at approximately Day 100 after autologous stem cell transplant (ASCT) until the documented progressive disease (PD) or 2 years of maintenance therapy/observation, whichever occurs first. The Follow-up Phase will extend from treatment discontinuation or completion of observation period, until death, loss to follow-up, withdrawal of consent, or study end, whichever occurs first.

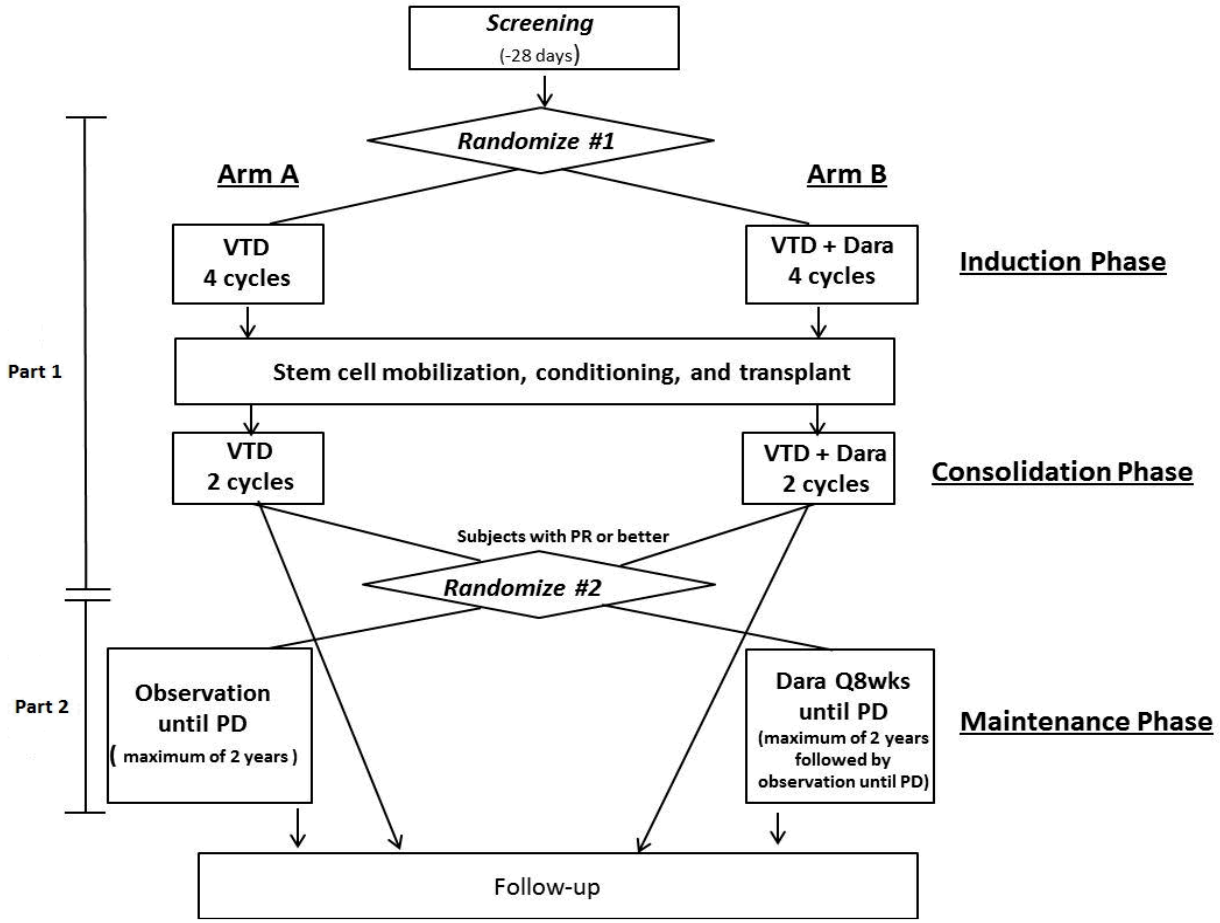
Part 2: Maintenance Phase (1:1 Second randomization of subjects achieving at least a PR after consolidation)

After completion of consolidation and determination of response at approximately Day 100 after ASCT, subjects with at least a PR will be randomized to Arm A and Arm B in 1:1 manner. Subjects will then enter the Maintenance Phase. Subjects who have not achieved at least a PR after the completion of consolidation treatment and therefore are not second randomized to Part2 will enter the Follow-up Phase for Part 1 and will be followed until disease progression or death, even if they receive subsequent treatment.

- **Arm A:** Observation only until documented disease progression **Arm B:** Daratumumab monotherapy (16 mg/kg once every 8 weeks) until documented disease progression (limited to 2 years maximum treatment duration).

A schematic overview of the study is provided in Figure 1 below.

Figure 1: Schematic Overview of the Study



Response will be assessed approximately 100 days after ASCT and eligibility for the second randomization will be determined. Subjects will be stratified at the second randomization by type of induction treatment (VTd or VTd + daratumumab) and by depth of response to induction / ASCT / consolidation therapy (as determined by MRD status and post-consolidation response, see table 1).

Assessment of tumor response and disease progression will be conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD will be conducted using next-generation sequencing and next generation flow cytometry on bone marrow aspirate from the subjects who achieve at least VGPR in maintenance phase.

Safety evaluations will include adverse event monitoring, physical examinations, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status.

The primary analysis for Part 2, i.e. PFS, will be performed when approximately 390 PFS events have been observed among subjects randomized to Maintenance phase after the second randomization. In addition, an interim analysis is planned for Part 2 after approximately 273 (70%) PFS events are observed in the population of subjects who are second randomized to Maintenance phase. After the

interim analysis, IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

A final data cutoff will occur at the end of study, when approximately 350 subjects have died, or approximately 5 years after the last subject is randomized in Part 2 to the Maintenance phase, whichever comes first. Investigators will be informed when the cutoffs are to occur.

1.3. Statistical Hypotheses for Trial Objectives

The statistical hypothesis in Part 2 of the trial is that daratumumab maintenance after ASCT prolongs PFS compared with observation.

1.4. Sample Size Justification

For Part 2 (maintenance phase), it is assumed that median PFS from the second randomization is 45 months for observation, and daratumumab maintenance will decrease the risk of progression or death by 25% (HR=0.75; estimated median PFS of 60 months for daratumumab maintenance). To achieve 80% power with a significance level of 0.05, 390 PFS events are needed.

1.5. Randomization and Blinding

Permuted block randomization will be implemented in this study.

At the second randomization, subjects will be stratified by type of induction treatment and by depth of response to induction/consolidation therapy (as determined by MRD status and post-consolidation response). The stratification factors for the second randomization are presented in Table 1. This is an open-label study. Subjects and sites will not be blinded to treatment assignment.

Table 1: Part 2 (Maintenance Phase) Stratification Factors

Randomized to VTd arm in the induction/ASCT/consolidation phase				
MRD* Status	**IMWG Response**			
	sCR	CR	VGPR	PR
Negative	Stratum 1	Stratum 1	Stratum 1	NA**
Positive	Stratum 2	Stratum 3	Stratum 3	Stratum 4
Randomized to VTd+dara arm in the induction/ASCT/consolidation phase				
MRD* Status	**IMWG Response**			
	sCR	CR	VGPR	PR
Negative	Stratum 5	Stratum 5	Stratum 5	NA**
Positive	Stratum 6	Stratum 7	Stratum 7	Stratum 8

CR=complete response; IMWG=International Myeloma Working Group; MRD=minimum residual disease; PR=partial response; sCR=stringent complete response; VGPR=very good partial response
* MRD by Flow at 10^{-4} as a stratification factor recorded in the CRF.
** Six subjects were observed to be MRD negative with IMWG response of PR at Day 100 post-ASCT. These subjects were mapped to Stratum 4 or Stratum 8 due to the lack of specific stratum defined in the protocol for such subjects.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Analysis time points for Part 2 will be based on treatment phase (maintenance) and administrations instead of visits.

Maintenance phase (8 weeks per administration):

The start date of the maintenance phase is the 2nd randomization date, and the end date of the maintenance phase is the start date of the follow-up phase - 1 day (if not available, use the maximum date defined in section 2.6.).

Pre-maintenance baseline value:

For subjects who are randomized in the maintenance phase, the last non-missing observation on or before the date of second randomization or Week 1 visit date, whichever is later.

End of treatment (EOT):

a. For subjects treated with Daratumumab maintenance treatment, within 30 days after the last dose of Daratumumab treatment has been discontinued or completed.
b. For subjects assigned to observation maintenance arm, within 30 days after the last observation visit or as soon as possible before the start of subsequent therapy.

Follow-up phase:

The follow-up phase will begin once a subject discontinues treatment with study medications, except for subjects randomized to Arm A (observation) in the maintenance phase. These subjects will enter the follow-up phase after end of treatment visit date in the maintenance phase, disease progression, start of new anticancer therapy, or end of maintenance phase due to any reasons, whichever is earliest.

Relative day:

Assessments will be presented chronologically by administration day, study day, which are defined as the follows:

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

2.2. Pooling Algorithm for Analysis Centers

Data from all study centers will be pooled for analyses.

2.3. Analysis Sets

The following analysis sets are defined.

ITT

- **Maintenance-specific Intent-to-treat (ITT-m) analysis set**: includes all subjects randomized in the second randomization. Analyses for Part 2 maintenance comparison of demographics, baseline characteristics, baseline lab, and primary and secondary efficacy endpoints will be primarily analyzed based on this population.

Safety

- **Maintenance-specific Safety (Safety-m) analysis set:** includes all subjects randomized to Arm B (daratumumab) in the second randomization and have received at least 1 administration of daratumumab and all subjects randomized to Arm A (observation) in the second randomization. This population will be used for all safety analyses for Part 2.

Immune response-evaluable

- **Maintenance-specific immune response-evaluable analysis set:** includes all subjects who received at least 1 administration of daratumumab in either Part 1 or Part 2 (maintenance phase) and had at least 1 immunogenicity sample obtained during Part 2 after the first administration.

Pharmacokinetic (PK)

- **Maintenance-specific PK-evaluable analysis set:** includes all subjects who received at least 1 administration of daratumumab either in Part 1 or Part 2 (maintenance phase) and had at least 1 pharmacokinetic sample obtained during Part 2 after the first administration.

2.4. Definition of Subgroups

Subgroup analysis will be performed for the subgroups specified in **Table 2**.

Table 2: Subgroup Analyses for Efficacy and Safety Endpoints

Subgroup	Definition	Analysis Type
Sex	Male, Female	E, S
Age	<50, 50-60, >60	E, S
Site	IFM, Hovon	E, S
ISS staging	I, II, and III	E
Cytogenetics	high risk vs. standard risk	E
Pre-maintenance baseline renal function (CrCl)	E: >90 mL/min; ≤90 mL/min; S: ≤90, >90 mL/min	E, S
Pre-maintenance baseline renal function (CrCl) with adjustment for overweight subjects (BMI>30kg/m^2)	≤90, >90 mL/min	S
Type of MM	IgG, Non-IgG	E
Pre-maintenance baseline ECOG performance score	0, ≥1	E
Induction/ASCT/Consolidation treatment group	VTd, DVTd	E
MRD (Stratification factor)	MRD positive, MRD negative	E
Response (Stratification factor)	VGPR or better vs PR	E

E: efficacy (PFS, Overall CR or better rate, Overall MRD negative rate); S: TEAE
Note: Age will be calculated based on the second randomization date and date of birth of the subject.
Subgroups that are not specified as pre-maintenance baseline will be based on the pre-induction baseline results.

2.5. Imputation of Missing Data

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

2.5.1. Adverse Event Start and End Date

Adverse Event Start Date

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

- When month and year are presented and the day is missing:
    - If the onset month and year are the same as the month and year of second randomization date, the day of second randomization date or the day-component of the AE end date (possibly imputed) is imputed, whichever is earlier;
    - If the onset month and year are not the same as the month and year of second randomization date, the first day of the month is imputed.
- When only a year of the onset date is present:
    - If the onset year is the same as the year of second randomization date:
        - If AE end date is available and is prior to second randomization date, the day and month of AE end date are imputed;
        - Otherwise, the day and month of second randomization date are imputed.
    - If the onset year is different from the year of second randomization date, the 1st of January is imputed.
- If the onset date is completely missing, the second randomization date is imputed as the onset date.

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

Adverse Event End Date

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

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

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

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

2.5.2. Concomitant Medication/Therapy Start and End Date

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

- If only the day is missing, the 15th day of the month will be used.
- If both the day and month are missing, the 30th of June will be used.

If the medication/therapy was taken after second randomization, and the imputed start date is prior to second randomization date, further adjust the imputed start date as second randomization date. Also adjust the imputed medication/therapy end date so that it is on or after second randomization date.

2.5.3. Subsequent Anti-cancer Therapy Start Date

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

- If the month and year of the start date are the same as the month and year of the last dosing date (for observational arm, end of treatment date in disposition or 2 years after second randomization if end of treatment date in disposition is not available), the day of last dosing date or the day-component of the stop date of subsequent anti-cancer therapy will be imputed, whichever is earlier.
- If the month and year of the start date are not the same as the month and year of last dosing date (for observational arm, end of treatment date in disposition or 2 years after second randomization if end of treatment date in disposition is not available), the first day of the month will be imputed.

2.6. Other General Definitions

2.6.1. Treatment Arms

Treatment arms for Part 2 maintenance phase are: Observation vs. Daratumumab. Induction-maintenance arms are: VTd-Observation, VTd-Daratumumab, DVTd-Observation, DVTd-Daratumumab.

2.6.2. International Staging System (ISS) Staging

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

- Stage I: B2MG <3.5 mg/L and ALB ≥3.5 g/dL (≥35 g/L)
- Stage III: B2MG ≥5.5 mg/L
- Stage II: neither I nor III

2.6.3. Month and Year

One year equals to 365.25 days. One month equals to 365.25/12 days.

2.6.4. Maximum Date

Maximum date is same as overall survival date.

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

The end of follow-up is defined as the maximum date.

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

2.6.6. Relationship of Adverse Events to Study Medication

For each adverse event, its relationship to study medication is determined by investigator and recorded on the eCRF. An adverse event is considered as related to study medication if the relationship is possible, probable or very likely.

2.6.7. General Analysis Specifications

Categorical variables are to be summarized using frequency counts and percentages. Continuous variables are to be summarized by the following descriptive statistics: mean, standard deviation, median and range (minimum and maximum).

3. INTERIM ANALYSIS

The primary objective of Part 2 of the study is to evaluate the 2 maintenance arms with response for PFS, which will be performed when approximately 390 PFS events have been observed in the population of subjects who are second randomized in the maintenance phase.

An interim analysis is planned for Part 2 of the study after 273 (70%) PFS events are observed in the population of subjects who are second randomized. The significance level at this interim analysis will be determined based on the observed number of PFS events at the time of the analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If 273 PFS events are observed, the alpha to be spent in this interim analysis will be 0.0147 (2-sided) and will be 0.0455 (2-sided) for the final analyses.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Demographics: age (continuous), age category (< 50 years, 50-60, and > 60 years), sex (male, female), height (cm), weight (kg) and ECOG performance status (0, >=1) at the pre-maintenance baseline will be summarized by induction-maintenance arms for ITT-m subjects.

Baseline disease characteristics such as, type of myeloma (heavy chain, light chain, biclonal), type of measurable disease, free light chain (ratio K/L, dFLC), ISS staging (I, II, III), cytogenetics profile, time since initial diagnosis (months), serum M-protein, urine M-protein, number of lytic bone lesions (None, 1-3, 4-6, more than 7), plasmacytoma (Yes, No) presence of diffuse myeloma-related osteopenia (Yes, No), presence of evaluable bone marrow assessment (Yes, No), bone marrow % plasma cells (<10, 10 – ≤ 30, > 30), bone marrow cellularity (hypocellular, normocellular, moderately cellular, severely acellular, indeterminate) at the baseline of the first randomization will be summarized by induction-maintenance treatment arms for the ITT-m subjects.

A summary for depth of response, including MRD status assessed by NGS method at pre-maintenance baseline will be summarized by induction-maintenance treatment arms.

A summary of hematology and chemistry laboratory values at pre-maintenance baseline will be provided.

General medical history will be summarized by body system and condition status as reported on eCRF for ITT-m subjects by maintenance treatment arms.

4.2. Disposition Information

For Part 2, the number of subjects who completed, discontinued the maintenance treatment phase will be summarized for ITT-m analysis set by maintenance arms. The number of subjects that are randomized to daratumumab maintenance arm but were not treated along with the reasons will be presented. Subjects who discontinued the study along with the reasons reported for the discontinuation on the eCRF will also be summarized.

4.3. Treatment Compliance

Refer to Section 4.4.

4.4. Extent of Exposure

Extent of exposure to daratumumab during the maintenance phase will be summarized and presented by the induction-maintenance treatment arms based on the maintenance-specific safety analysis set for the subjects that are randomized to Arm B (daratumumab).

The number of daratumumab administrations (continuous and categorical variables) will be summarized. For subjects randomized to daratumumab maintenance arm, duration of study treatment during the maintenance phase will be calculated as the number of days from the date of the first administration of daratumumab during the maintenance phase to the date of the last administration of daratumumab. For subjects randomized to the observation maintenance arm, duration of study treatment will be calculated as the number of days from the date of second randomization to the end of treatment date. Duration of study treatment will be summarized descriptively.

The total dose administered for daratumumab (mg/kg) will be summarized by descriptive statistics. The dose intensity, which is defined as the sum of total dose administered divided by the number of treatment administrations, will be calculated for daratumumab and summarized by descriptive statistics. Relative dose intensity (%) is the ratio of total dose received and total planned dose, where total planned dose will be calculated as the planned dose level times the number of administrations. Descriptive summary statistics will be presented for relative dose intensity.

4.5. Protocol Deviations

The incidence of major protocol deviation during the maintenance phase of the study, together with the corresponding deviation terms will be summarized by maintenance treatment arms for the ITT-m subjects. A listing of all major protocol deviations during the maintenance phase will be provided. In case COVID-19 pandemic leads to major protocol deviations those will be flagged as such.

4.6. Concomitant Medications

Concomitant medications collected on the CRF page during the maintenance phase of the study will be summarized by therapeutic class, pharmacologic class, and drug name for each maintenance treatment arm. A similar summary will be provided for subjects randomized to Arm B (daratumumab) who received growth factor support, pre-infusion medication and post-infusion medication, respectively. Additionally, prophylactic antiviral medication use will be tabulated.

4.7. Subsequent Anticancer Therapies in Part 2

Subsequent anticancer therapies during the maintenance phase will be tabulated by therapeutic class, pharmacologic class, and drug name within each maintenance treatment arm for the ITT-m subjects.

5. EFFICACY

A validated computerized algorithm, which is based on the IMWG response criteria (Durie 2006, Rajkumar 2011), which has been used and validated by an independent review committee in study MMY2002, will be utilized to determine response and disease progression for each subject. As a sensitivity analysis, investigator assessments of response and disease progression per the IMWG response criteria will also be performed.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical hypothesis tests and 95% confidence interval presented will be 2-sided. The primary hypothesis will be tested at the 0.05 significance level (overall). The main purpose for Part 2 of the study is to evaluate the 2 maintenance arms with response for PFS, which will be performed when approximately 390 PFS events have been observed in the population of subjects who are second randomized in the maintenance phase.

In Part 2, if the testing for the primary endpoint of PFS post-completion of maintenance therapy is statistically significant, the following key secondary endpoints in Part 2 as given in the order below will be sequentially tested. Each endpoint will be tested with an overall two-sided alpha of 0.05 by utilizing a hierarchical testing approach as proposed by (Tang and Geller, 1999) that strongly controls Type I error rate. The key secondary endpoints are ordered as follows:

1) TTP from second randomization
2) Overall CR or better rate
3) Overall MRD negative CR or better rate
4) OS from second randomization

An interim analysis will be performed after 273 (70%) PFS events are observed in the ITT-m subjects. The significance level at this interim analysis will be determined based on the observed number of PFS events at the time of the analysis, using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. If 273 PFS events are observed, the alpha to be spent in this interim analysis will be 0.0147 (2-sided) and will be 0.0455 (2-sided) for the final analyses.

For OS, a modified linear alpha spending function will be used to determine the efficacy boundary. The alpha to be spent for OS at the time of interim efficacy analysis (i.e, 273 PFS events, which is 70% of the total planned PFS events) is 0.0002 (2-sided). The final analysis of OS will occur when approximately 350 deaths have been recorded, or approximately 5 years after the last subject is second randomized to the Maintenance phase, whichever comes first.

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values, except for missing MRD assessment results as such results will be considered as positive.

5.2. Primary Efficacy Endpoint in Part 2

The primary efficacy endpoint is the PFS.

5.2.1. Definition

PFS is defined as the duration from the date of second randomization to progressive disease, according to the validated computerized algorithm based on the IMWG criteria, or death, whichever occurs first.

Determination of dates of PFS event from 2nd randomization and dates for censoring is summarized in Table 3 as follows.

Table 3: PFS from 2nd Randomization Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
No post-second randomization disease assessment	Second randomization	Censored
Disease progression	Earliest date that indicates disease progression	PFS event
Death in the absence of PD	Date of death	PFS event
Other (e.g., withdrawal of consent to study participation, lost to follow-up, etc.)	Date of last disease assessment prior to Other	Censored

5.2.2. Analysis Methods

The primary comparison of the 2 randomized maintenance treatments (daratumumab maintenance and observation) will be made with respect to PFS from the second randomization using a stratified log-rank test in the ITT-m population. The Kaplan-Meier method will be used to estimate the distribution of PFS from the second randomization for each arm. The treatment effect (hazard ratio) and its 2-sided 95% confidence intervals will be estimated using a stratified Cox regression model with maintenance treatment as the sole explanatory variable. The stratification factors used in the analysis include type of induction treatment and depth of response to induction/consolidation therapy (Please refer to Table 1 for the stratification factors used for second randomization).

In addition, the interaction between induction/consolidation and maintenance will be tested at a 2-sided significance level of 0.05 by a stratified Cox regression model that includes the interaction term between maintenance treatment and induction/consolidation treatment. The stratification factor will only include the depth of response.

The comparison of the 2 randomized maintenance treatments will also be made with respect to PFS from the second randomization using a stratified log-rank test in the ITT-m analysis set separately by the induction treatment received (VTd or DVTd) by the subjects. The stratification factor will include the depth of response. The Kaplan-Meier method will be used to estimate the distribution of PFS from

the second randomization for each of the maintenance treatment arm and Kaplan-Meier plots will be created separately by the induction treatment received.

5.2.3. Sensitivity and Supplementary Analysis

A sensitivity analysis of PFS from 2nd randomization based on investigator assessment of progressive disease as per the IMWG response criteria will be performed in a similar manner as described in Section 5.2.2.

Another sensitivity analysis of PFS from 2nd randomization based on investigator assessment of PD as per the IMWG response criteria will be performed separately for each of the induction treatment received by the subjects.

Additionally, a sensitivity analysis of PFS from 2nd randomization by censoring data due to start of subsequent anticancer therapy will be performed in a similar manner as described in Section 5.2.2.

Further, a sensitivity analysis of PFS derived from the algorithm by censoring for death or progression after missing more than one evaluation will be performed in a similar manner as described in Section 5.2.2.

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 5.2.2.

A sensitivity analysis using unstratified log-rank test and unstratified Cox regression model will also be performed.

5.3. Major Secondary Endpoints in Part 2

5.3.1. Time to Progression from 2nd Randomization

5.3.1.1. Definition

TTP from 2nd randomization is defined as the duration from the date of second randomization to confirmed progressive disease, according to the validated computerized algorithm based on the IMWG response criteria, or death due to progressive disease, whichever occurs first.

The censoring rules for TTP from second randomization will be similar to the ones applied for PFS from second randomization (please refer to Table 3), except that death not due to PD will be censored instead of considering that as an event for TTP.

5.3.1.2. Analysis Methods

TTP from 2nd randomization will be analyzed in a similar manner as PFS from 2nd randomization described in Section 5.2.2 based on the ITT-m population.

Competing risk analysis will be performed for TTP as a sensitivity analysis by treating deaths not due to PD as competing events. The treatment effect (hazard ratio) and its 2-sided 95% confidence intervals will be estimated using a proportional sub-distribution hazards model with maintenance treatment as the sole explanatory variable. The stratification factors used in the analysis include type of induction treatment and depth of response to induction/consolidation therapy (Please refer to Table 1 for the stratification factors used for second randomization).

5.3.2. Overall CR or better rate

5.3.2.1. Definition

All patients came to maintenance phase had PR or better at post-consolidation by investigator. Overall CR or better rate is defined as the percentage of ITT-m subjects who have achieved CR or better from post-consolidation onward per validated computerized algorithm based on the IMWG criteria. The response of CR or better must be achieved on or prior to the start of subsequent therapies.

Overall VGPR or better rate is defined as the percentage of ITT-m subjects who achieved the best response of VGPR or better from post-consolidation onward. The VGPR better status is assessed using the computerized algorithm based on the IMWG response criteria and must be achieved on or prior to start of subsequent therapies.

Further, additional analyses of overall CR or better rate at 1 year and 2 years will be conducted. Overall CR or better rate at 1 year (or 2 years) defines as the percentage of ITT-m subjects who achieved the best response of CR or better from post-consolidation onward to 1 year (or 2 years) after second randomization. The CR or better status is assessed using the computerized algorithm based on the IMWG response criteria and must be achieved on study treatment or on observation and on or prior to start of subsequent therapies with no progressive disease within 1 year (or 2 years) after second randomization.

5.3.2.2. Analysis Methods

The comparison of the 2 randomized maintenance arms (observation vs. daratumumab) will be made with respect to CR or better rate using the stratified Cochran-Mantel-Haenszel (CMH) chi-square test in the ITT-m analysis set. A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval and the p-value from the CMH test will be reported. Stratification factors used in the analysis include the stratification factors used for the second randomization (Please refer to Table 1 for the stratification factors).

CR or better rate at 1 year and 2 years will be analyzed in a similar manner to the analysis of overall CR or better rate as described above

5.3.3. Overall MRD negative rate

An assessment of MRD will be conducted using next generation flow cytometry (NGF) and next generation sequencing (NGS) on bone marrow aspirates for all subjects who achieve at least VGPR in maintenance phase. NGS will be performed on subjects with available sample with the clonoSEQ

MRD assay to detect malignant plasma cells and will be considered as the primary method of MRD assessment. The clonoSEQ assay and Euroflow based multiparametric flow cytometry assay both have a sensitivity of 1 cancer cell in the background of 100,000 white blood cells ($<10^{-5}$) or greater and will both be utilized in this study to assess MRD.

5.3.3.1. Definition

Overall MRD negative rate is defined as the proportion of subjects who have achieved negative MRD status from post-consolidation onward. The MRD negativity must be achieved on or prior to the start of subsequent therapies. For analysis purpose, subjects in the ITT-m population without MRD assessment will be considered as having positive MRD.

Additionally, analyses of overall MRD negativity rate at 1 year and 2 years will be performed. It is defined as the proportion of subjects who have achieved negative MRD status from post-consolidation onward to 1 year (or 2 years) after second randomization. The MRD negativity must be achieved on study treatment or on observation and on or prior to the start of subsequent therapies and the last MRD assessment within 1 year (or 2 years) after second randomization has to be negative. For analysis purpose, subjects in the ITT-m population without MRD assessment will be considered as having positive MRD

5.3.3.2. Analysis Methods

The MRD negative rate by using threshold of $< 10^{-5}$ will be analyzed like the analysis of CR or better rate as described in Section 5.3.2.2. MRD by flow is used as the primary analysis, while MRD by next generation sequencing (NGS) is used as the sensitivity analysis.

Overall MRD negativity rate at 1 year and 2 years will be analyzed in a similar manner to the analysis of overall MRD negativity rate as described above.

A sensitivity analysis of MRD negative rate by using threshold of $<10^{-6}$will be performed in a similar manner as described above.

5.3.4. MRD Negative CR or Better Rate

5.3.4.1. Definition

MRD negative CR or better rate is defined as the proportion of subjects who achieved negative MRD (at 10^{-5} threshold value) and CR or better response per validated computerized algorithm based on the IMWG criteria from post-consolidation onward. The MRD negativity and CR or better response must be achieved on or prior to the start of subsequent therapies. For analysis purpose, subjects in the ITT-m population without MRD assessment will be considered as having positive MRD.

Further MRD negative CR or better rate at 1 year (or 2 years) defines as the proportion of subjects who achieved negative MRD (at 10^{-5} threshold value) and CR or better response per validated computerized algorithm based on the IMWG criteria from post-consolidation onward to 1 year (or 2 years) after second randomization. The MRD negativity and CR or better response must be achieved

on study treatment or on observation and on or prior to the start of subsequent therapies and patient should not have progression disease within 1 year (or 2 years) after second randomization. The last MRD assessment within 1 year (or 2 years) after second randomization has to be negative. For analysis purpose, subjects in the ITT-m population without MRD assessment will be considered as having positive MRD.

5.3.4.2. Analysis Methods

The comparison of the MRD negative CR or better rate between the 2 randomized maintenance arms (observation vs. daratumumab) will be made using the stratified CMH chi-square test in the ITT-m analysis set. A Mantel-Haenszel odds ratio, along with its 2-sided 95% confidence interval and the p-value from the CMH test will be reported. Stratification factors used in the analysis include the stratification factors used for the second randomization (Please refer to Table 1 for the stratification factors).

MRD negative CR or better rate at 1 year and 2 years will be analyzed in a similar manner to the analysis of MRD negative CR or better rate as described above.

5.3.5. Progression-free Survival after next line of therapy (PFS2) from 2nd Randomization

5.3.5.1. Definition

Progression-free survival on next line of therapy (PFS2) from 2nd randomization is defined as:

- The time from second randomization to the 2nd progression or death, whichever comes first. The 2nd disease progression will be based on investigator judgment.
- Any deaths are considered as PFS2 events.
- Subjects, who are alive and with no disease progression, will be censored at the last disease assessment.
- Subjects without any post-second randomization follow-up will be censored at the date of second randomization.
- Otherwise, subject will be censored at the minimum of last disease assessment and last date of follow-up.

Determination of dates of PFS2 from 2nd randomization event and dates for censoring is summarized in Table 4 as follows.

Table 4: PFS2 from 2nd Randomization Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
No post-second randomization disease assessment	Second randomization	Censored
Alive and no disease progression	Date of last disease assessment	Censored
Two disease progressions from two different lines of treatments or death	Minimum of earliest date that indicates the 2nd progression and date of death	PFS2 event
Other	Minimum of last disease assessment and last date of follow-up	Censored

5.3.5.2. Analysis Methods

PFS2 from 2nd randomization will be analyzed for the ITT-m population. The analysis like PFS from 2nd randomization described in Section 5.2.2 will be performed. If the number of PFS2 events is less than 80, non-stratified analyses will be used.

5.3.6. Overall Survival (OS) from 2nd Randomization

5.3.6.1. Definition

Overall survival from 2nd randomization is measured from the date of second 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 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 among the selected data domains within the clinical database.

5.3.6.2. Analysis Methods

OS from 2nd randomization will be analyzed for the ITT-m population. The analysis like PFS from 2nd randomization described in Section 5.2.2 will be performed. If the number of deaths is less than 80, non-stratified analyses will be used.

5.4. Other Secondary Endpoints in Part 2

5.4.1. Rate of Improved Response During Maintenance

5.4.1.1. Definition

Rate of improved response during maintenance is defined as the proportion of subjects who have achieved a better category of response as per the validated computerized algorithm based on IMWG criteria during maintenance compared to the response status at the end of consolidation (up to the second randomization). This will be evaluated among the group of subjects who achieved the response of PR, VGPR, and CR at the second randomization. The response has to be assessed on or before the start of the subsequent therapy.

5.4.1.2. Analysis Methods

The rate of improved response will be analyzed for ITT-m subjects in a similar manner to the analysis of CR or better rate as described in Section 5.3.2.2. Improvement in responses by one, two, and three categories with further clarification on the specific response improvements will also be presented in the summary.

5.4.2. Rate of MRD Negative Conversion During Maintenance

5.4.2.1. Definition

The rate of MRD negative conversion during maintenance is defined as the percentage of subjects who achieved de novo MRD negative status during maintenance among subjects with MRD positive measurement at Day 100 post-ASCT. Subjects with missing MRD measurement at day 100 post-ASCT will not be included

5.4.2.2. Analysis Methods

The rate of MRD negative conversion during maintenance will be analyzed in a similar manner to the analysis of CR or better rate as described in Section 5.3.2.2.

5.4.3. Rate of MRD Negative CR or Better Conversion During Maintenance

5.4.3.1. Definition

The rate of MRD negative CR or better conversion during maintenance is defined as the percentage of subjects who achieved de novo MRD negative and CR or better status during maintenance among subjects with post-consolidation response status worse than CR or a positive MRD measurement at Day 100 post-ASCT. Subjects with missing MRD measurement at day 100 post-ASCT will not be included

5.4.3.2. Analysis Methods

The rate of MRD negative CR or better conversion during maintenance will be analyzed in a similar manner to the analysis of CR or better rate as described in Section 5.3.2.2.

5.5. Time to Subsequent Antimyeloma Treatment

5.5.1.1. Definition

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

5.5.1.2. Analysis Methods

The Kaplan-Meier method will be used to estimate the distribution of time to subsequent antimyeloma treatment for the ITT-m population. Median time to subsequent antimyeloma treatment with 95% CI will be tabulated. In addition, a Kaplan-Meier curve for time to subsequent antimyeloma treatment will be plotted. The hazards ratio and its 95% CI will be obtained through a stratified Cox's regression model with maintenance treatment as the sole explanatory variable. Treatment comparison will be made via a stratified log-rank test. The stratification factors used in the analysis include type of induction treatment and depth of response to induction/consolidation therapy (Please refer to Table 1 for the stratification factors used for second randomization).

5.6. Subgroup Analysis of Efficacy Endpoints in Part 2

For assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, a subgroup analysis of the primary and secondary endpoints of PFS, overall CR or better rate, and overall MRD negative rate on pre-specified subgroups defined in Section 2.4 will be conducted. Subgroup analyses will be performed if data warrants such investigation.

Forest plots of subgroup analysis of the given endpoints will be generated.

6. SAFETY

Key safety analyses will be summarized by the induction-maintenance treatment arms (VTd-Observation, VTd-Daratumumab, DVTd-Observation, and DVTd-Daratumumab) and total columns for observation and Dara maintenance for subjects in maintenance-specific safety analysis set in Part 2.

6.1. Adverse Events in Part 2

Unless otherwise specified, treatment-emergent adverse events are defined as follows:

Arm A (observation): Any AE with onset date and time on or after the date of second randomization through the day prior to start of subsequent therapy or end of observation date +30 days in the maintenance phase, whichever is earlier. Adverse events start before second randomization and ongoing at second randomization with an improvement or no change in toxicity will not be considered as a treatment-emergent adverse event in part 2.

Arm B (daratumumab): Any AE with onset date and time on or after the date of second randomization through 30 days after the last study agent administration; or the day prior to start of subsequent therapy, whichever is earlier; or any AE that is considered Dara related on or after second randomization. Adverse events start before second randomization and ongoing at second randomization with an improvement or no change in toxicity will not be considered as a treatment-emergent adverse event in part 2.

AEs will be monitored throughout the study. All AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria

for Adverse Events (NCI-CTCAE), most recent version. For AE reporting, the verbatim term used in the eCRF by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Unless otherwise specified, at each level of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded.

Treatment-emergent adverse events will be summarized for induction-maintenance treatment arms in Part 2. An overview of TEAEs reported through the maintenance phase will be provided for each treatment arm. The overview will include summaries of subjects with TEAEs, with TEAEs related to study treatment, with TEAEs of maximum toxicity grade of 1 to 5, SAEs, TEAEs leading to discontinuation of study treatment (Arm B only).

TEAEs leading to discontinuation of study treatment are summarized for subjects having discontinued the study treatment due to adverse event(s) on the end of treatment CRF page. A summary of number of subjects who discontinued study treatment because of 1 or more TEAEs by MedDRA system-organ class and preferred term will be provided.

6.1.1. Treatment Emergent Adverse Events

The following summaries will be provided for all TEAEs:

- An overview of TEAE
- An overview of TEAE by subgroups specified in Section 2.4

In addition, the following summaries will be generated:

- TEAEs by system organ class (SOC) and preferred term (PT)
- Most common (at least 10%) TEAEs by SOC, PT
- TEAEs by SOC, PT by subgroups specified in Section 2.4
- TEAEs by SOC, PT, and relationship to study drug (Arm B only)
- TEAEs by SOC, PT, and worst grade
-
- Serious TEAEs by SOC and PT
- Most common (at least 0.6%) serious TEAEs by SOC, PT
- Serious TEAEs by SOC, PT by subgroups specified in Section 2.4
-
- Grade 3/4 TEAEs by SOC and PT
- Most common (at least 1%) Grade 3/4 TEAEs by SOC, PT
- Grade 3/4 TEAEs by SOC, PT by subgroups specified in Section 2.4

The following summaries of treatment modifications (only in Arm B) due to TEAEs will be provided:

- Administration delay due to TEAE by PT and grade 3/4.
- Infusion skipping due to TEAE by PT and grade 3/4.
- Infusion interruption due to TEAE by PT and grade 3/4.

In addition, the following summaries will be generated:

- Treatment discontinuation (Arm B only) due to TEAEs by PT and grade ≥ 3.
- TEAEs with outcome of death by PT and relationship to study medication

6.1.2. Adverse Events of Clinical Interest

The adverse events of clinical interest would focus on below items (detail would be defined on the DPS or below sections),

- Infusion related reactions (IRR)
- Infections
    - Infections and Infestations
    - Opportunistic infections
- Hemorrhage events
- Interferences for blood typing
- Neutropenia events
- Thrombocytopenia events
- Second primary malignancies (SPM)

6.1.2.1 Infusion-Related Reactions

Subjects with any IRR associated with daratumumab administration will be summarized by MedDRA system-organ class and preferred term. The summaries will be presented by all grades, Grade 3, 4, and 5. In addition, the total number of subjects with IRR in more than 1 infusion will be reported. Additionally, the timing of IRR associated with daratumumab administration will be evaluated through a summary of IRR by event onset time. IRRs leading to infusion modifications during infusion will be summarized by system-organ class and preferred term. The summaries will be presented by induction treatment arms for the subjects treated with daratumumab maintenance. A summary of infusion related reaction at first Daratumumab maintenance infusion by infusion volume will also be provided.

A listing of subjects with Grade 3 or higher treatment-emergent infusion-related reactions associated with daratumumab administration will be provided. In addition, subjects with treatment-emergent infusion-related reactions resulting in discontinuation of daratumumab will be listed.

6.1.2.2 Infections

6.1.2.2.1 Infections/Infestations

Infections and infestations refer to adverse events with SOC of infections and infestations. A summary of number of subjects with 1 or more toxicity Grade 3 or 4 treatment-emergent infections and infestations by MedDRA preferred term and relationship to treatment will be provided. Additional summary analyses may include by onset time (i.e., ≤ 6 months vs. 6-≤ 12 months vs. 12+ months from the date of second randomization).

6.1.2.2.2 Opportunistic Infections

Opportunistic Infections refer to adverse events with PT which would be defined on the DPS. The summaries will be presented by for grades and Grade 3 or 4 for each induction-maintenance treatment arm.

6.1.2.3 Neutropenia

Neutropenia refers to adverse events with PT which would be defined on the DPS. The summaries will be presented for all grades and Grade 3 or 4 for each induction-maintenance treatment arm.

6.1.2.4 Thrombocytopenia

Thrombocytopenia refers to adverse events with PT which would be defined on the DPS. The summaries will be presented for all grades and Grade 3 or 4 for each induction-maintenance treatment arm.

6.1.2.5 Hemorrhage

Hemorrhage will be defined by Standardized MedDRA Queries (SMQ) with the first subcategory SMQ of hemorrhage terms (exclude laboratory terms). The summaries will be presented for all grades and Grade 3 or 4 for each induction-maintenance treatment arm.

6.1.2.6 Peripheral neuropathies

Peripheral neuropathies (PNs) refer to adverse events with high level term (HLT) of peripheral neuropathies NEC. Incidences of PNs will be summarized by MedDRA high level term and preferred term. The summaries will be presented for all grades and grade 3 or 4 for each induction-maintenance treatment arm.

6.1.2.7 Second Primary Malignancy

SPM data is collected from both the AE form and the SPM form. A listing of second primary malignancy (SPM) will be provided. Second primary malignancies will be clinically reviewed and

categorized as cutaneous/non-invasive, non-cutaneous/invasive or hematologic malignancies, which will be summarized accordingly.

6.2. Deaths in Part 2

The total number of subjects who died during the maintenance phase will be tabulated by induction-maintenance treatment arm. The number of subjects who died within 30 days of end of treatment (Arm A) or within 30 days of last dose of study maintenance treatment (Arm B) will be summarized for the Part 2 maintenance-specific safety subjects. The primary cause of death collected on eCRF page will also be summarized. If the primary cause of death reported is AE, the number of subjects who died due to at least one reasonably study drug related AE will be further reported.

A listing of subjects who died after second randomization during maintenance phase will be provided.

6.3. Vital Signs

Vital signs including temperature (°C), systolic and diastolic blood pressure (mmHg) and pulse (beats per minute [bpm]) values will be descriptively summarized (mean, standard deviation, median, minimum and maximum) at each scheduled time point by induction-maintenance treatment arms using maintenance-specific safety set.

6.4. Clinical Laboratory Tests

Treatment-emergent worst toxicity grade (NCI-CTAE version 4.03) during maintenance treatment phase, defined as the worst toxicity grade observed for any laboratory parameter assessed on or after the second randomization, will be tabulated for applicable laboratory parameters for maintenance-specific safety subjects for Part 2. Descriptive statistics for values and changes from pre-maintenance baseline for these laboratory parameters will be provided. In addition, shifts from pre-maintenance baseline toxicity grade to worst toxicity grade during maintenance treatment phase will be generated.

6.5. Other Safety Parameters

6.5.1. ECOG Performance Status

Frequencies of ECOG performance status (0, >=1) over time during the maintenance treatment phase will be summarized for maintenance-specific safety subjects for Part 2. In addition, shift from pre-maintenance baseline to worst score during maintenance treatment phase will be provided.

7. PHARMACOKINETICS/IMMUNOGENICITY/PHARMACODYNAMICS

Samples to assess the generation of antibodies to daratumumab (immunogenicity) and concentration of daratumumab will be obtained from subjects according to the Time and Events Schedule in the protocol.

7.1.1. Sampling Timepoints

For subjects receiving daratumumab treatment, the daratumumab immunogenicity and concentration data for Part 2 analysis will be collected at the pre-dose of Week 1 and Week 52 of maintenance

treatment, and 8 weeks post last dose of Daratumumab and will be summarized using descriptive statistics.

7.1.2. Analysis Methods

The incidence of anti-daratumumab antibodies will be summarized by daratumumab induction/consolidation and maintenance treatments among immune response-evaluable analysis set in the maintenance subjects.

Concentration of daratumumab in serum will be summarized by daratumumab induction/ consolidation and maintenance treatments using pharmacokinetic-evaluable analysis set in the maintenance subjects. The summary will be descriptive including the mean, SD, coefficient of variation, median, range and geometric mean, at each assessment visit during the maintenance phase.

8. BIOMARKER

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 samples will be drawn from all subjects to better understand the mechanism of action and mechanism of resistance of daratumumab and summarized as applicable.

8.1. Minimal Residual Disease (MRD)

An assessment of MRD will be conducted using NGS and multiparametric flow cytometry on bone marrow aspirates for all subjects who achieve at least VGPR in maintenance phase.

8.1.1. Sampling Timepoints

In Part 2, bone marrow aspirates will be analyzed by EuroFlow based multiparametric flow cytometry assay and NGS for MRD on Week 25, 52 and 105.

8.1.2. Analysis Methods

Details on MRD negativity rate analyses are described in Section 5.3.3.2.

9. PATIENT REPORTED OUTCOMES (PRO)

It is anticipated that daratumumab will provide benefits in terms of symptom reduction, improved functioning, and improved utilities. To measure functional status, well-being, and symptoms, the EORTC QLQ-C30 and the EQ-5D-5L instruments will be used. Both questionnaires will be completed at the timepoints outlined in the Time and Events Schedule given in the protocol before any other study procedures scheduled for the same day.

9.1.1. PRO Instruments

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical, role, emotional, cognitive, and social), 1 Global Health Status (GHS) scale, 3 symptom scales (fatigue, nausea/vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The instrument contains 28 items using a Likert scale with 4 response options: “Not at All,” “A Little,” “Quite a Bit,” and “Very Much” (scored 1 to 4). Two additional items use response options (1 to 7): 1 = Very Poor, to 7 = Excellent. All scale and item scores will be linearly transformed to be in the range from 0 to 100 according to the algorithm in EORTC QLQ-C30 scoring manual, version 3.0 (Fayers et al, 2001). A higher score represents a higher ("better") HRQoL, higher (“better”) level of functioning, or a higher ("worse") level of symptoms.

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 dimensions are used to compute a single utility score ranging from 0 to 1 representing the general health status of the individual (but scoring by the UK algorithm allows for value less than 0).

The PRO includes the following:

- Summary Scores
    - EORTC-QLQ-C30 functional scales (physical, role, emotional, cognitive, social), global health status (GHS) scale, symptom scales (pain, fatigue, nausea/vomiting)
    - EQ-5D-5L utility score
- Single Item Scores
    - EORTC QLQ-C30 single symptom items
    - EQ-5D-5L visual analog scale (VAS)

9.1.2. Analysis Methods

Compliance rates for completion of EORTC QLQ-C30 and EQ-5D-5L at each time point during the maintenance phase will be generated based on the actual number of subjects received PRO assessments over the number of expected.

EORTC QLQ-C30 domain scores (functional scales, GHS, symptom scales), and single symptom items will be descriptively summarized at each time point for ITT-m analysis set by maintenance treatment arms. Descriptive statistics will also be provided for change from pre-maintenance baseline in GHS score by the MRD negativity status.

EQ-5D-5L utility score and VAS will be descriptively summarized at each time point for ITT-m analysis set by maintenance treatment arms.

A repeated measures mixed effects model analysis will be conducted estimating change from baseline (pre-maintenance) at each time point between two maintenance arms. ITT-m subjects who have a baseline value, last PRO assessment before second randomization, and at least one value from the maintenance phase 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 month, treatment-by-time interaction, and stratification factors as fixed effects.

A distribution-based method will be used to define improvement/worsening in scores, i.e., half SD away from the mean score at baseline (pre-maintenance) combining both treatment groups. Time to improvement will be summarized by using descriptive statistics such as mean, standard deviation (SD), median and range. Time to worsening will be estimated using Kaplan-Meier methods. The hazard ratio for Daratumumab relative to observation group and its associated 95% confidence interval (CI) will be calculated based on the stratified Cox proportional hazards model by the stratification factor at second 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 pre-maintenance baseline assessment or post pre-maintenance baseline assessment will be censored at date of second randomization.

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ATTACHMENT 1: PD AND RESPONSE ALGORITHM

PD and Response Algorithm
54767414MMY3006

The issues addressed by the program are:

1. Whether or not the disease progressed and date* of progression
2. The date* of censoring for subjects whose disease never progressed
3. Reason(s) for PD
4. The date* and category of best and first response
5. Duration of response

* Day post-randomization for randomized subjects.

1 Determination of PD and Relapse from CR

1.1 IMWG Criteria

1.1.1 Progressive Disease

PD is to be used for calculation of time to disease progression and progression-free survival for all subjects including those experiencing CR.

PD is defined as satisfying any one of the criteria listed below. These are identical to the IMWG criteria as described in the protocol. Further explanations (noted in superscript) pertaining to particular PD criteria are provided in Section 1.2, Clarifications and Modifications.

a. Increase (1.2.2) of ≥25% in the level of serum M-protein and absolute increase (1.2.2) must be ≥0.5 g/dL (5 g/L) (1.2.3; 1.2.4).

b. Increase (1.2.2, 1.2.18) of ≥25% in the 24-hour urinary light chain excretion (urine M-protein) and absolute increase (1.2.2) must be ≥200 mg/24 hours (1.2.3).

c. Only in subjects without measurable serum and urine M-protein levels: increase (1.2.2) of ≥25% in the difference between involved and uninvolved FLC levels (1.2.20) and absolute increase (1.2.2) must be >10 mg/dL (1.2.3).

d. Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels: increase (1.2.2) of ≥25% in the level of bone marrow plasma cells percentage and absolute increase (1.2.2) must be ≥10% (1.2.3).

e. Definite increase (1.2.8) in the size of existing bone lesions (1.2.9) or soft tissue plasmacytomas (1.2.9; 1.2.10).

f. Definite development of new bone lesions (1.2.11) or soft tissue plasmacytomas (1.2.12, 1.2.13).

g. Development of hypercalcemia [1.2.14; 1.2.15; 1.2.16] (corrected serum calcium >2.875 mmol/L or >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder.

1.1.2 Relapse from CR

Relapse from CR is to be used for calculation of disease-free survival for subjects experiencing CR.

Relapse from CR is defined as satisfying any one of the criteria listed below (a, b, or c). These are identical to the IMWG criteria as described in the protocols. Further explanations (noted in superscript) pertaining to particular relapse from CR criteria are provided in Section 1.2, Clarifications and Modifications.

a. Reappearance of serum or urinary M-protein by immunofixation or electrophoresis [1.2.3; 1.2.7].

b. Development of ≥5% plasma cells in the bone marrow.

c. Appearance of any other sign of progression (i.e., new plasmacytomas, lytic bone lesion if the lesion is marked 'relationship with the disease', or hypercalcemia) [1.2.11; 1.2.12; 1.2.13; 1.2.14; 1.2.15].

1.2 Clarifications and Modifications

In order to allow these rules to be applied consistently and to be programmed, the Sponsor has added certain clarifications and modifications for using the IMWG criteria.

1.2.1 Measurable disease is defined in the protocol by at least one of the following measurement: (1) serum M-protein ≥ 1g/dL (≥ 10 g/L) or ≥ 0.5 g/dL (≥ 5 g/L) for subjects with IgA, IgD, IgE or IgM multiple myeloma; (2) urine M-protein ≥ 200 mg/24h; (3) serum FLC assay: involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal.

1.2.2 The reference point for calculating increase and % of increase for M-protein, FLC and bone marrow plasma cells will be the lowest response value and the "lowest response value" does not need to be a confirmed value.

1.2.3 Requires 2 consecutive (i.e., no intermediate values that do not meet the definition of PD) assessments made at any time before the institution of any new therapy (i.e., subsequent anti-cancer therapy). If a subject has an unconfirmed PD followed by death due to PD within 30 days of unconfirmed PD, or PD (the same parameter as of initial observed PD) observed within 4 weeks after start of subsequent anti-cancer therapy, the unconfirmed PD will be considered as PD.

1.2.4 If nadir serum M-protein is ≥ 50g/L (≥5 g/dL), M-protein increases of ≥ 10g/L (1g/dL) is sufficient for progressive disease. It does not require meeting "increase of ≥ 25% in the level of serum M-protein".

1.2.5 Any 2 consecutive increase of serum M-protein ≥5 g/L (≥0.5 g/dL) is consistent with progressive disease, assuming that increase of ≥25% is met or not applicable, even if the serum M-protein level is below measurable disease threshold.

1.2.6 The baseline value for assessing disease progression is the last pretreatment measurement (it applies to SPEP, UPEP, FLC, plasmacytomas and bone lesions except as noticed in Section 1.2.10). For example, if there is a screening value and a Cycle 1 Day 1 value (prior to start of treatment) for M-protein, the program ignores the screening value and uses Cycle 1 Day 1 as the reference point for assessing PD for the first post-treatment results.

1.2.7 The program disregards serum M-protein and urine paraprotein measurements prior to Day 5 after dosing. These tests are considered too soon after dosing to be regarded as legitimate on-treatment values.

1.2.8 The program computes the date of progression as the earliest date of any of the tests listed in Section 1.1.1 (a, b, e, f or g for subjects with measurable serum or/and urine M-protein; or a, b, c, e, f or g for subjects without measurable serum and urine M-protein) that indicate PD. Similarity, the program computes the date of relapse from CR as the earliest date of any of the tests listed in Section 1.1.2 (a, b, or c) that indicate relapse from CR.

1.2.9 For PD due to bone lesions, the algorithm will rely on information collected on the eCRF regarding skeletal survey (i.e., increase in the size of lytic bone lesions or increase in the total number of lytic bone lesions if the lesion is marked 'relationship with the disease') and other radiology reports. At any time, study sites may report progressive disease based on an increase in the size or number of lytic bone lesions if the lesion is marked 'relationship with the disease'. The algorithm accepts this determination as definitive.

1.2.10 Plasmacytomas/bone lesions that are first reported during the first week on study are treated as baseline plasmacytomas/bone lesions. The rationale for this rule is that plasmacytomas/bone lesions take time to develop, so anything reported within 1 week of first dose almost certainly existed before the start of study drug. In the case that no pre-treatment value for plasmacytomas/bone lesion is available, the first post-treatment value is used as baseline.

1.2.11 For plasmacytomas, the Sponsor has defined "definite increase in size" as an increase of over 50% in the sum of the products of the two longest perpendicular diameters when available, using the smallest previous product as the reference point.

1.2.12 New post-baseline bone lesions are evidence of PD. If no baseline bone lesions are available, then any subsequent data that report a bone lesion will be considered as development of new bone lesions.

1.2.13 New post-baseline plasmacytomas are evidence of PD, even if the measurements are not available. If no baseline plasmacytoma data are available, then any subsequent data that

report a plasmacytoma will be considered as a "new" plasmacytoma and will be considered as evidence of PD.

1.2.14 Hypercalcemia will be based on corrected calcium values as long as they are available (i.e., corrected calcium values are collected or serum calcium and albumin are collected). If corrected calcium values are not available, free-ionized calcium values will be used if they are available. Hypercalcemia based on free-ionized calcium will be defined as >1.5 mmol/L.

1.2.15 For subjects who have hypercalcemia at baseline, the program will never assess PD due to "development of hypercalcemia". A subject is considered to have hypercalcemia at baseline if he or she meets one of the following criteria:

a. For subjects with corrected calcium values, any corrected calcium value >ULN which occurs on or before Day 4 (relative to first dose).

Note: if subject had central and local assessments done on the same day, the central record takes precedence.

b. For subjects without corrected calcium values in all visits, but with free-ionized calcium values on or before Day 4, any free-ionized calcium value >ULN which occurs on or before Day 4 (relative to first dose).

1.2.16 For subjects with normal calcium at baseline, if the first PD criteria met is a post-baseline hypercalcemic value, then the following programming algorithm will be applied:

a. The program will first search for evidence of progression in other parameters within the following 112 days. If PD is determined in other parameters within the following 112 days, then the subject is assessed as PD. The date of PD is the date of the initial hypercalcemic value and hypercalcemia is indicated as the reason or one of the reasons for PD.

b. If PD is not determined in other parameters within 112 days, the program will search for the next available corrected calcium/free-ionized calcium value. If the second value also meets the criteria for hypercalcemia, the subject is assessed as PD. The date of PD is the date of the initial hypercalcemic value and hypercalcemia is indicated as the reason or one of the reasons for PD.

c. If there is no more follow-up calcium value, then the subject is assessed as PD.

d. Any PD identified through a), b) or c) will be flagged and reviewed by clinical to ensure that hypercalcemia can be attributed solely to the plasma cell proliferative disorder. Hypercalcemia due to other reasons will not be considered as PD in the algorithm.

1.2.17 Descriptive (or non-numeric) results from bone marrow aspirate or bone marrow biopsy will be given a numeric interpretation based on the following conventions:

a. Percentage plasma cells reported as a range on the CRF page will be assigned the mean value (i.e., lower range plus upper range divide by 2) that will be analyzed by the

programming algorithm (e.g., an amount reported as 10-15% would be interpreted as 12.5%).

b. Percent plasma cells reported as <x% will be interpreted as (x-1)% and percent plasma cells reported as >x% will be interpreted as x%.

c. Other conventions include:

Reported as:	Interpreted as:
"Not significantly present"	4%
"Sheets of plasma cells not seen"	4%

1.2.18 Imputation of UPEP and SPEP values: If the serum immunofixation result is "Not Detected" and the SPEP value is missing or not done, then SPEP value is treated as 0. If the urine immunofixation is "Not Detected" and the UPEP is missing or not done, then UPEP value is treated as 0.

1.2.19 a. Spurious UPEP values are not used in the determination. Determination of a spurious value is as follows: If at least 4 values exist in the neighborhood (+/- 178 days) of the value of interest, the mean and standard deviation of the values is computed (not including the value of interest in the calculation). The value of interest is compared to the mean +/- 3 standard deviations. If the value < mean-3*standard deviation or the value > mean+3*standard deviation then the value is considered spurious. The last two values available for a particular subject are never considered as spurious. The baseline value for a subject is also never considered as spurious.

b. If the first PD criteria met is two consecutive UPEP values and subject has started subsequent anticancer therapy, this subject is assessed as PD and date of PD is the date of first UPEP assessment. Otherwise, if the first PD criteria met is two consecutive UPEP values and subject has not started subsequent anticancer therapy, then the following programming algorithm will be applied:

1) The program will first search for evidence of progression in other parameters within the following 178 days. If PD is determined in other parameters within the following 178 days, then the subject is assessed as PD. The date of PD is the date of the initial UPEP value.

2) If PD is not determined in other parameters within 178 days and no more UPEP values are available, then the subject is assessed as PD due to UPEP.

3) Otherwise, the third UPEP value is considered. If the third value meets the criteria for PD, the subject is assessed as PD due to UPEP. If the third value does not meet the criteria for PD, but other parameters indicate PD within the next 178 days, the subject is assessed as PD due to UPEP at the time of the initial UPEP value.

4) Otherwise, the fourth UPEP value is considered. If the fourth value meets the criteria for PD, the subject is assessed as PD due to UPEP. If the fourth value does not meet the criteria for PD, the subject is not assessed as PD due to UPEP. If no fourth UPEP value is available, the subject is not assessed as PD.

1.2.20 Difference between involved and uninvolved FLC level is defined as absolute value of kappa FLC level minus lambda FLC level in the serum.

1.2.21 Development of plasma cell leukemia is considered as disease progression. The date of PD is the date of event onset.

2 Determination of Date of Censoring and Reason for PD

The date of last post-baseline efficacy measure is used as the censoring date for all subjects without progressive disease. Subjects that have no post-baseline efficacy data are censored at the date of randomization for randomized subjects.

The reason(s) for PD is defined as the initial reason(s) that caused the program to indicate PD as well as any other criteria that were met by the time of confirmation of PD. Indicator variables for each reason (SPEP, UPEP, FLC, bone marrow, bone lesion [increase in number, increase in size], extramedullary plasmacytoma [new extramedullary plasmacytoma, increase in size], hypercalcemia and plasma cell leukemia) are created.

3 Determination of Response Category and Duration of Response

3.1 IMWG Criteria

According to IMWG criteria, response categories include complete response (CR), stringent complete response (sCR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD) (defined in Section 1). Although minimal response (MR) is not officially a response category in the IMWG criteria, consensus recommendations state that for subjects with relapsed and /or refractory myeloma, MR should be reported separately in clinical trials. Categories of sCR, CR, VGPR, PR, and SD are determined using the IMWG criteria and MR adopted from the EBMT criteria for subjects with relapsed refractory myeloma as outlined below.

Further explanations (noted in superscript) pertaining to particular response criteria are provided in Section 3.2, Clarifications and Modifications. The definition for duration of response is also covered in Section 3.2.18.

3.1.1 Definition of CR

Requires all of the following:

a. Negative immunofixation of serum and urine (3.2.4; 3.2.5; 3.2.6; 3.2.19).

b. Disappearance of any soft tissue plasmacytomas.

c. <5% plasma cells in the bone marrow (3.2.7).

3.1.2 Definition of sCR

Requires all of the following:

a. CR as defined above.

b. Normal FLC ratio (3.2.5, 3.2.8).

c. Absence of clonal bone marrow plasma cell (PCs)(3.2.21) by 2- to 4-color flow cytometry.

3.1.3 Definition of VGPR

Requires any of the following:

a. Serum and urine M-component detectable by immunofixation but not on electrophoresis (3.2.5; 3.2.11;3.2.12), or

b. ≥90% reduction (3.2.10) in serum M-protein plus urine M-protein <100 mg/24 hours (3.2.5; 3.2.11)

c. If the serum and urine M-protein are not measurable, a reduction (3.2.10) of >90% in the difference between involved and uninvolved FLC levels (3.2.5; 3.2.13) is required.

d. In addition to the above criteria, if present at baseline, ≥50% reduction (3.2.10) in the size of soft tissue plasmacytomas is also required.

3.1.4 Definition of PR

Requires all of the following:

a. ≥50% reduction (3.2.10) of serum M-protein (3.2.5) and reduction (3.2.10) in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours (3.2.5).

b. If the serum and urine M-protein are not measurable, a reduction (3.2.10) of ≥50% in the difference between involved and uninvolved FLC levels (3.2.5; 3.2.13) is required.

c. In addition to the above criteria, if present at baseline, ≥50% reduction (3.2.10) in the size of soft tissue plasmacytomas is also required.

3.1.5 Definition of SD

Not meeting the criteria for sCR, CR, VGPR, PR, or PD.

3.2 Clarifications and Modifications

As was the case with PD, developing a program to assess response requires adding certain clarifications, minor modifications and additions to the IMWG criteria.

3.2.1 Only subjects with measurable disease at baseline are eligible for assessment of response (i.e., considered in the response-evaluable population). Measurable disease is defined in Section 1.2.1; only legitimated on treatment serum M-protein and urine paraprotein measurements are used for assessment of response. The legitimated on treatment measurements is defined in Section 1.2.6.

3.2.2 CR, sCR, VGPR, PR, MR and SD response categories require no known evidence of progressive or new bone lesions if radiographic studies were performed. Once the program has determined PD for a subject, no subsequent response assessments are performed. For example, a subject who progresses at week 6 cannot have a first response or best response that starts after week 6.

3.2.3 Subjects with measurable disease (defined in Section 1.2.1) in serum (SPEP) and urine (UPEP) need to be followed by both SPEP and UPEP for response assessment and categorization; Except for assessment of CR or better, subjects with measurable disease restricted to the SPEP will need to be followed only by SPEP (i.e., urine M-protein need not show a reduction, but the available urine M-protein values must not meet the criteria for PD); correspondingly, subjects with measurable disease restricted to the UPEP will need to be followed only UPEP (i.e., serum M-protein need not show a reduction, but the available serum M-protein values must not meet the criteria for PD). For example, a subject who has baseline values of 0.1 g/dL of IgG M-protein and 300 mg/24 hrs. of urine paraprotein and who subsequently maintains values of 0.1 g/dL and 120 mg/24 hrs. will be regarded as achieving a PR; Subjects with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay.

3.2.4 To be considered CR, both serum and urine immunofixation must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine; subjects with negative UPEP values pretreatment still require UPEP testing to confirm CR.

3.2.5 Requires 2 consecutive (i.e., no intermediate values that do not meet the definition of response) assessments made at any time before the institution of any new therapy (i.e., subsequent anti-cancer therapy).

3.2.6 For coding CR in subjects in whom the only measurable disease is by serum FLC levels: it requires a normal FLC ratio (Kappa/Lambda) in addition to CR criteria. However, a normal FLC ratio is not required if the involved FLC level decrease to below detectable level (Kappa<0.5 mg/L; or lambda<0.6 mg/L). The default reference range of 0.26 to 1.65 will be used to determine normal FLC ratio, if the reference range from central/local laboratory is not available.

3.2.7 If all criteria for confirmed CR were met, except that bone marrow aspirate and biopsy were not performed, and baseline bone marrow evaluation showed <5% plasma cells, then the algorithm accepts this as a CR. If both bone marrow aspirate and bone marrow biopsy were performed at baseline, then both values must have <5% plasma cells for the rule to be applied. For subjects without measurable disease at baseline or subjects whose baseline bone marrow plasma cells percentage is >5%, bone marrow confirmation is required for CR response.

3.2.8 Normal FLC ratio is required for all subjects regardless of whether disease at baseline was measurable on serum, urine, both or neither. However, a normal FLC ratio is not required if the involved FLC level decrease to below detectable level (Kappa<0.5 mg/L; or lambda<0.6 mg/L). The default reference range of 0.26 to 1.65 will be used to determine normal FLC ratio (Kappa/Lambda), if the reference range from central/local laboratory is not available.

3.2.9 Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

3.2.10 Reductions are based on changes from baseline.

3.2.11 VGPR categories require serum and urine studies regardless of whether disease **at** baseline was measurable on serum, urine, both or neither. For coding VGPR in subjects in whom the only measurable disease is by SPEP, it is not required that UPEP value must meet VGPR criteria, but UPEP test must be performed and not meeting PD criteria whenever SPEP meet VGPR criteria; correspondingly, for coding VGPR in subjects with measurable disease restricted to the UPEP, it is not required that SPEP value must meet VGPR criteria, but SPEP test must be performed and not meeting PD criteria whenever UPEP meet VGPR criteria.

3.2.12 Serum and urine M-protein via SPEP and UPEP must be reported as 0, not detected, or below level of quantification and positive serum or urine immunofixation.

3.2.13 Difference between involved and uninvolved FLC level is defined as absolute value of kappa FLC level minus lambda FLC level in the serum.

3.2.14 Skeletal survey is not required for assessment of response unless clinically indicated. However, if skeletal survey is performed, there should be no indication of disease progression before confirmation of response.

3.2.15 The date of first/best response is the earliest date that all available and required response criteria are met. The date of serum immunofixation response is the initial date of response, not the date of confirmation. The date of urine immunofixation response is the initial date of response, not the date of confirmation. The latest date of response (date at which all criteria were met) among all the relevant response criteria will also be stored in the analysis dataset.

3.2.16 Duration of response (DOR) applies to subjects achieving at least PR by IMWG criteria and is measured from start of achieving PR (first observation of PR before confirmation) to the time of disease progression, with deaths owing to causes other than progression not counted but censored. DOR is derived as (date of PD or date of censoring – date of first response + 1).

3.2.18 Occasionally, the results of the urine immunofixation and UPEP may conflict. If the urine IFE is negative and the UPEP has any value less than 200 mg/24 hrs., the UPEP is disregarded and the urine results are treated as satisfying the requirement for a CR. Similarly, if serum IFE becomes and remains negative, appearance of low level of paraprotein (≤0.5 g/dL or 5 g/L) in SPEP will be disregarded.

3.2.19 A DIRA result of NEGATIVE is treated as equivalent to a negative immunofixation of serum (SIFE) if it is associated with (IGG, Kappa). If SIFE is not done at the visit of DIRA result of NEGATIVE, then the baseline SIFE needs to be (IGG, Kappa) to be treated as

equivalent to a negative SIFE. If there is no repeat of the DIRA test, we consider a single DIRA test as equivalent of two consecutive immunofixation of serum tests if that indicates a CR.

3.2.20 Subjects with at least one post-baseline disease assessment corresponding to the type of measurable disease at baseline and also not falling into any response category or progressive disease are assigned as response category- stable disease (SD).

3.2.21 Refers to <10-3 residual clonal plasma cells.

4 REFERENCES

1. BGM Durie *et al*. International uniform response criteria for multiple myeloma. *Leukemia 2006*
2. Rajkumar *et al*. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood 2011*