# Statistical Analysis Plan

# Protocol OP-103

## A Randomized, Controlled, Open-Label, Phase 3 Study of Melflufen/Dexamethasone Compared with Pomalidomide/Dexamethasone for Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Lenalidomide

**Investigational Agent:** Melphalan flufenamide (referred to as melflufen)

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## DOCUMENT HISTORY

| Version | Prepared/Modified by | Description of Changes |
|---|---|---|
| 21 Jun 2016<br>Version 0.1 | [redacted] | Initial version |
| 06 Jun 2018<br>Version 0.2 | [redacted] | Updated version for SPA review |
| 26 Nov 2018<br>Version 0.3 | [redacted] | Updated version following SPA review |
| Updated Draft<br>15 May 2020<br>Version 0.4 | [redacted] | • General restructuring of document.<br>• Clarification of analytical definitions.<br>• Updates to account for COVID-19 including protocol amendment |
| 09 Dec 2020<br>Version 1.0 | [redacted] | • Clarification of PK analysis set and analyses<br>• Clarification of Data Cutoff under Data management.<br>• CNS bleeding, SPM and MDS added as AESIs |
| 17 March 2021<br>Version 2.0 | [redacted] | • Update definition of AESIs<br>• Clarify definition of baseline, HRQoL visits, and MRD<br>• Add imputation for unknown death dates<br>• Add AE event counts<br>• Add time to grade 3 or 4 ANC and separately platelet count<br>• Update changes from planned analyses |

| Version | Prepared/Modified by | Description of Changes |
|---|---|---|
| 29 April 2021<br>Version 3.0 | [redacted] | • Incorporate FDA feedback<br>o Update primary endpoint analysis to be based on stratified log-rank test<br>o Move DOR from key secondary endpoint to other secondary endpoint, clarify that analyses are for exploratory, descriptive purposes only<br>o Clarify efficacy subgroup and DOCB analyses are exploratory<br>o Correct typographical errors |
| 20 September 2021<br>Version 4.0 | [redacted] | • Add time from prior autologous stem cell transplant to randomization subgroup analysis for PFS, ORR, and OS<br>• Add time from prior autologous stem cell transplant to randomization subgroup analysis for TEAEs<br>• Add imputation rules related to the development of the time from prior autologous stem cell transplant to randomization subgroup<br>• Add analytical definition for subsequent therapies<br>• Add subject disposition and demographics presented by prior autologous stem cell transplant subgroup<br>• Update safety and tolerability endpoint to include pomalidomide for “Time to dose modification for melflufen” |

## LIST OF ABBREVIATIONS

| Abbreviation or Term | Definition |
|---|---|
| ADaM | Analysis Data Model |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT (SGPT) | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ASCT | autologous stem cell transplantation |
| AST (SGOT) | aspartate aminotransferase |
| ATC | Anatomical/Therapeutic/Chemical |
| BSA | body surface area |
| C1D1 | Cycle 1 Day 1 |
| CBR | clinical benefit rate |
| CDISC | Clinical Data Interchange Standards Consortium |
| CM | concomitant medication |
| CR | complete response |
| CrCl | creatinine clearance |
| CRF | case report form |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| dFLC | difference in serum free light chains |
| DMC | Data Monitoring Committee |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EMD | extramedullary disease |
| FDA | Food and Drug Administration |
| FISH | fluorescent in situ hybridization |
| HRQoL | Health related quality of life |
| IMiD | immunomodulatory drug |

| Abbreviation or Term | Definition |
|---|---|
| IMWG-URC | International Myeloma Working Group-Uniform Response Criteria |
| IRC | independent review committee |
| ISS | international staging system |
| kg | kilogram(s) |
| K-M | Kaplan-Meier |
| LDH | lactase dehydrogenase |
| mAb | monoclonal antibodies |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram(s) |
| min | minute |
| M-protein | monoclonal protein spike |
| MM | multiple myeloma |
| MR | minimal response |
| NCI | National Cancer Institute |
| NDA | new drug application |
| NE | not evaluable |
| ORR | overall response rate |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression free survival |
| PI | proteasome inhibitor |
| PR | partial response |
| PT | preferred term |
| QoL | quality of life |
| QT | Interval of time from the start of the Q wave to the end of the T wave |
| QTcF | Fridericia's formula for the interval of time from the start of the Q wave to the end of the T wave, corrected for heart rate |
| RR | interval of time between QRS complexes |
| RRMM | relapsed and refractory multiple myeloma |
| SAE | serious adverse event |

| Abbreviation or Term | Definition |
|---|---|
| SAP | statistical analysis plan |
| sCR | stringent complete response |
| SD | standard deviation; stable disease (depending on context) |
| SDG | (WHO DD) Standardized Drug Groupings |
| SDTM | Study Data Tabulation Model |
| sFLC | serum free light chain |
| SMQ | standardized MedDRA query |
| SOC | system organ class |
| SPEP | serum protein electrophoresis |
| TEAE | treatment emergent adverse event |
| TTP | time to progression |
| TTR | time to response |
| ULN | upper limit of normal range |
| UPEP | urine protein electrophoresis |
| VGPR | very good partial response |
| WBC | white blood cell count |
| WHO | World Health Organization |
| WHO DD | World Health Organization Drug Dictionary |

## TABLE OF CONTENTS

# 1 INTRODUCTION

This statistical analysis plan (SAP) was prepared in accordance with version 5 of Protocol OP-103, datedMarch 24, 2020, and was generated prior to locking the study database. This document outlines the main safety and efficacy analyses to be performed for the clinical study report (CSR).

Any changes that are made to the planned analyses after the SAP is finalized, along with an explanation as to when and why they occurred, will be noted in the CSR. Any changes made to the planned analyses that are in the protocol are summarized in Section 10.4 of this document.

# 2 OVERVIEW OF STUDY DESIGN

This is a randomized, controlled, open-label, Phase 3 multicenter study which will enroll patients with relapsed refractory multiple myeloma (RRMM) following 2-4 lines of prior therapy, who are refractory to both last line of therapy and to lenalidomide (≥ 10 mg) administered within 18 months prior to randomization as demonstrated by disease progression on or within 60 days of completion of the last dose of lenalidomide.

Patients will be randomized to either one of two treatment arms. Randomization will be stratified by:

- Age (≥ 75 years of age versus < 75 years of age)
- Number of lines of prior therapy (2 versus 3-4 prior lines)
- International staging system (ISS) Score (1 versus ≥ 2)

**Arm A:**

Melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.

**Arm B:**

Pomalidomide 4 mg daily on Days 1 to 21 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.

**For Both Arms:**

Patients ≥ 75 years of age will have a reduced dose of dexamethasone of 20 mg on Days 1, 8, 15 and 22.

Oral dexamethasone may be substituted with intravenous dexamethasone at the investigator's discretion (USA only). In the event of a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

Patients may receive treatment until there is documented disease progression, unacceptable toxicity or the patient/treating physician determines it is not in the patient's best interest to continue.

Dose modifications and delays in therapy may be implemented based on patient tolerability as detailed in the protocol section 7.8.

A schedule of events for the study is outlined in the protocol section 8.1.

An Independent Review Committee (IRC) will assess all tumor responses and PD assessments during the study. The IRC members will be blinded to all treatment data and perform their reviews in closed-meeting sessions. All activities and processes surrounding the IRC will be outlined in the IRC Charter.

The Sponsor may be unblinded to individual subject data during the study but will not have access to the unblinded summaries and listings used by the Data Monitoring Committee (DMC) for their review.

All activities and processes surrounding data access will be outlined in a Data Access Plan.

# 3 STUDY OBJECTIVES AND ENDPOINTS

## 3.1 Primary Objective

To compare the PFS of melflufen plus dexamethasone (**Arm A**) versus pomalidomide plus dexamethasone (**Arm B**) as assessed by the IRC according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC). [Rajkumar 2011]

### *3.1.1 Primary Endpoint*

PFS is defined as time (months) from date of randomization to the earlier of confirmed disease progression or death due to any cause. Progression dates will be assessed by the IRC using the IMWG-URC. The conventions for censoring of PFS are described in Table 3.

## 3.2 Key Secondary Objectives

- To assess and compare the overall response rate (ORR), i.e., proportion of patients with ≥ PR (stringent complete response [sCR], complete

response [CR], very good partial response [VGPR] and partial response [PR]) as best response in Arm A versus Arm B

- To assess and compare overall survival (OS) in Arm A versus Arm B
- To assess and compare the safety and tolerability in Arm A and Arm B

All tumor response and progression-dependent objectives are as assessed by the Independent Review Committee (IRC) according to the IMWG-URC.

### *3.2.1 Key Secondary Efficacy Endpoints*

Unless stated otherwise, response and progression status will be assessed by the IRC using the IMWG-URC.

ORR: defined as a best confirmed response of sCR, CR, VGPR, or PR using local laboratory evaluation.

OS: defined as time (months) from date of randomization to death due to any cause. Patients still alive at end of study, or lost to follow up, will be censored at last day known alive.

### *3.2.2 Safety and Tolerability Endpoints*

- Frequency and grade of treatment emergent adverse events (TEAEs)
- Frequency and grade of TEAEs of special interest
- Frequency of TEAEs leading to dose modifications
- Frequency of melflufen dose modifications based on study drug exposure
- Treatment duration of melflufen and pomalidomide
- Time to dose modification for melflufen and pomalidomide

## 3.3 Other Secondary Objectives

- To assess and compare duration of response (DOR) in patients with ≥ PR (sCR, CR, VGPR, PR) as best response in Arm A versus Arm B
- To assess and compare clinical benefit rate (CBR) (i.e. proportion of patients with ≥ MR) as best response in Arm A versus Arm B
- To assess and compare time to response (TTR) in patients with an PR or better in Arm A versus Arm B
- To assess and compare time to progression (TTP) in Arm A versus Arm B

- To assess and compare the duration of clinical benefit (i.e., ≥ MR) in Arm A versus Arm B
- To assess and compare best response during the study in Arm A versus Arm B.
- To assess and compare investigator assessment of primary and secondary endpoints in Arm A versus Arm B

All tumor response and progression-dependent objectives are as assessed by the Independent Review Committee (IRC) according to the IMWG-URC.

### *3.3.1 Other Secondary Endpoints*

Unless stated otherwise, response and progression status will be assessed by the IRC using the IMWG-URC.

- DOR: defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression, or to death due to any cause. DOR is defined only for patients with a confirmed PR or better.
- CBR, i.e. ≥ MR: is the rate of response evaluable patients that achieve a confirmed MR or better.
- TTR: is defined as the time from the date of randomization to the date of the first documented confirmed response in a patient that has responded with ≥ PR.
- TTP: is defined as the time from the date of randomization to the date of the first documented confirmed PD.
- Duration of clinical benefit (DOCB): defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause. DOCB is defined only for patients with a confirmed MR or better.
- Best response during the study (sCR, CR, VGPR, PR, MR, stable disease [SD] or PD) using the IMWG-URC
- Primary and secondary endpoint as assessed by Investigators

## 3.4 Exploratory Objectives

- To assess and compare the primary and secondary endpoints in various subgroups of Arm A and Arm B

- To evaluate the melphalan pharmacokinetic (PK) parameters during treatment with melflufen, the impact of covariates on this relationship and the inter-occasion variability in melphalan exposure (Arm A)
- To assess the relationship between melphalan exposure and effect on safety and efficacy variables, including PFS and ORR, in Arm A
- To assess minimal residual disease (MRD) in patients that achieve a CR (Arm A and Arm B).
- To assess functional status and well-being based on patient reported outcome (PRO) assessment

### *3.4.1 Exploratory Endpoints*

- PK parameters of melphalan (Arm A)
- Proportion of patients with MRD (yes/no) for patients that achieve a CR
- Value and change from baseline in EORTC QLQ-C30 summary score, each scale of the EORTC QLQ-C30, each scale of the MY20, EQ-5D utility score, each dimension of the EQ-5D, and the VAS of the EQ-5D
- Maximum post-baseline health related quality of life (HRQoL) scores (EORTC Global Health Status, EORTC summary score, EQ-5D-3L health utility score, EQ VAS)
- Relationship between concurrent IMWG response and time to maximum HRQoL score

Additional exploratory analyses of endpoints related to pharmacokinetics and HRQoL will be described separately.

## 4 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on comparing the melflufen + dexamethasone (MEL+DEX) arm and the pomalidomide + dexamethasone (POM+DEX) arm in terms of PFS. The sample size estimation is based on the following assumptions:

- Power = 90 %
- Significance level = 0.05 two-sided
- Hazard ratio = 0.70 (MEL+DEX / POM+DEX)
- Distribution of survival = Exponential
- Accrual time = 24 months

- Follow up time = 6 months after last patient randomized
- Total study time = 30 months
- Early censor rate = approximately 15 %
- Time to full recruitment speed = 6 months
- Median PFS for POM+DEX = 3.6 months (FDA Pomalyst Prescribing Information 2015)

Based on these assumptions the final analysis should take place when 339 patients have experienced a PFS event.

# 5 NON-INFERIORITY CHOICE OF MARGIN

According to EU guidelines, the choice of non-inferiority margin is based on a combination of statistical reasoning and clinical judgment (Guideline of the choice of the non-inferiority margin EMEA/CPMP/EWP/2158/99). The proposed comparator has, in a previous Phase 3 trial, shown superiority over an active control (high-dose dexamethasone) with a PFS HR of 0.45 (2-sided 95% confidence interval 0.35-0.59) (Pomalidomide Celgene EPAR 2013). The upper limit of the confidence interval (0.59) would then correspond to a HR of 1.69 (1/0.59). A non-inferiority trial comparing melflufen and dexamethasone versus pomalidomide and dexamethasone where the upper limit of the 95% confidence interval is less than 1.69 can then be interpreted as superiority over high-dose dexamethasone since the 95% confidence interval of the melflufen study will not overlap with the 95% confidence interval of the historical study data. Since high dose dexamethasone is an active compound, the difference against a hypothetical placebo would be even larger.

Even though a non-inferiority margin of 1.69 might satisfy the statistical regulatory requirements, it would allow melflufen and dexamethasone to be substantially worse than the pomalidomide and dexamethasone comparator arm and this is clearly not clinically acceptable. In the current trial a non-inferiority margin of 1.2 will be used. With the planned sample size, this margin will ensure that the point estimate of the HR will be 1 or better (≤ 1). A non-inferiority margin of 1.2 will thus ensure a roughly similar or better efficacy of melflufen versus pomalidomide with the respect to the primary endpoint of PFS.

# 6 ANALYSIS POPULATIONS

## 6.1 Enrolled Analysis Set

The Enrolled analysis set is defined as all subjects who are assigned a unique patient number by Interactive Response Technology system at the time of

enrollment (signing of consent). This analysis set includes randomized subjects and non-randomized subjects, identified as screen failures. The Enrolled analysis set will be the primary population for the summaries of disposition. Randomized subjects will be summarized according to the treatment assigned at randomization.

## 6.2 Full Analysis Set (FAS)

The Full analysis set (FAS) is defined as all subjects who are randomized. Subjects will be analyzed according to the treatment assigned at randomization. The primary analysis (PFS) will be performed using the FAS.

## 6.3 Safety Analysis Set

The Safety analysis set is defined as all subjects who received at least one dose of melflufen, pomalidomide, or dexamethasone. The Safety analysis set will be the primary population for the summaries of all exposure and safety data. Subjects will be summarized according to the treatment actually received.

## 6.4 Per Protocol Analysis Set

The Per Protocol analysis set is defined as all subjects who received at least one dose of melflufen, pomalidomide, or dexamethasone, and have a baseline assessment of disease status and at least one post-baseline assessment for disease response. Subjects who have major protocol deviations, related to critical eligibility criteria, the assessment of efficacy or the safety of the subject that could significantly impact the interpretation of study results, will be excluded from the Per Protocol analysis set. The supporting analysis of the primary and secondary efficacy endpoints will be evaluated using the Per Protocol analysis set. Subjects will be analyzed according to the treatment actually received.

## 6.5 Patient Reported Outcomes Analysis Set

HRQoL assessments were added at the time of protocol version 4.1. Only participants who enroll on or after protocol version 4.1 and have completed the same PRO questionnaire at baseline and post-baseline and will be included in the PRO analysis set. Subjects will be analyzed according to the treatment actually received.

## 6.6 Pharmacokinetic (PK) Analysis Set

The PK analysis set is defined as all subjects in FAS who received at least 1 dose of melflufen and have 3 samples with measurable concentrations in at least one treatment cycle.

Analyses will be performed according to the treatment actually received.

# 7 DATA MANAGEMENT

## 7.1 Data Cutoff

The cutoff will be set and described in the Data Management Plan.

Data pertaining to any assessments performed as part of a visit per the data cutoff date for a patient, and any AE or CM starting or ending before or on that data cutoff date for a patient, will be included in the database for the CSR.

## 7.2 Data Validation

Data will be validated according to the Data Management Plan (DMP). Prior to the data cutoff, the study data will be reviewed for any data inconsistencies and major protocol deviations. Any data inconsistencies remaining after the data cutoff will be documented according to the DMP and Clinical Data Interchange Standards Consortium (CDISC) requirements. Any changes made regarding analysis sets or analytic definitions after the data cutoff will be documented and referred to in the CSR.

## 7.3 Data Standards

Study datasets will be developed according to CDISC Study Data Tabulation Model (SDTM) Implementation Guide Version 3.2. All datasets used for the analyses and presentations of summary results will be developed according to CDISC analysis data model (ADaM) Implementation Guide Version 1.1. The source data for all ADaM datasets will be SDTM datasets.

# 8 ANALYTIC DEFINITIONS

Definitions of terms used for the calculation of derived variables and general terms used for the analyses are provided in this section.

## 8.1 General

### *8.1.1 Study Day 1*

Study Day 1 corresponds to the date of the first dose of any study drug.

### *8.1.2 Study Day*

Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to Study Day 1. For events, assessments, and interventions after Study Day 1, study day represents the elapsed number of days from Study Day 1, inclusive:

*Study Day n = (Date of assessment – Date of Study Day 1) + 1 day*

Study Day −1 will be the day before Study Day 1, and in general for assessments prior to Study Day 1, study day is defined as:

*Study Day n = (Date of assessment – Date of Study Day 1)*

For listings (such as for adverse events) that include the derivation of "days since last dose," this is defined as event date – date of last dose. Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

### *8.1.3 Baseline*

Unless otherwise specified, the baseline value is defined as the most recent assessment prior to administration of the first dose of study drug, melflufen, pomalidomide, or dexamethasone. For randomized not treated patients, the baseline value is defined as the most recent assessment prior to randomization.

### *8.1.4 Unscheduled Visits*

All results not taken at a scheduled timepoint are unscheduled. Unscheduled assessments are labelled as 'Unscheduled' in the listings and will include the study day from first dose of all dates.

Because unscheduled assessments are not associated with any scheduled timepoint, they are excluded from all summaries by timepoint. Unscheduled assessments will be considered when deriving myeloma response parameters as described in Section 8.7.

The study protocol accepts a time window of ± 3 days for scheduled visits and assessments (visit window). In the event multiple protocol-specified assessments are reported within the same visit window the value reported for the scheduled visit should be used in summaries by timepoint (i.e. clinical safety labs and vital signs), and if this value is missing or unknown the earliest reported value of unscheduled assessments within the visit window should be used. Derivations using multiple assessments should be based on assessments from the same visit.

### *8.1.5 HRQoL Visits*

Baseline value for a HRQoL assessment is defined as the most recent assessment prior to administration of the first dose of study drug, melflufen, pomalidomide, or dexamethasone.

HRQoL assessments are to be administered prior to dosing on Day 1 of each cycle while on treatment. The HRQoL visits will be derived as Cycle X Day 1, where X is the cycle number of the HRQoL assessment date. The latest HRQoL assessment prior to melflufen/pomalidomide Cycle X Day 1 dose date will be used for analyses.

The End of Treatment HRQoL assessment will be derived as the first assessment after the last dose of melflufen or pomalidomide.

HRQoL assessments are to be administered monthly after end of treatment with each PFS follow up visit. The HRQoL PFS follow up assessments will be labeled as "QOL PFS FU Month X", where X is derived as the HRQoL assessment date within ±7 days of (End of Treatment Date + (X × 30 days)). For example, QOL PFS FU Month 2 will be the HRQoL PFS follow up assessment within 53 to 67 days of End of Treatment Date.

OS FUP visit will not be summarized as they are not consistently administered to patients, only as indicated.

### *8.1.6 Duration*

Duration can be expressed in days, weeks, months, years, or minutes as appropriate.

- **Days** – Duration expressed in days between one date (date1) and another later date (date2) are calculated using the following formula:

  *duration in days = (date2-date1+1).*

- **Weeks** – Durations expressed in weeks between one date (*date1*) and another later date (*date2*) are calculated using the following formula:

  *duration in weeks = (date2-date1+1)/7.*

- **Months** – Durations expressed in months between one date (*date1*) and another later date (*date2*) are calculated using the following formula:

  *duration in months = (date2-date1+1)/30.4375.*

- **Years** – Durations expressed in years between one date (*date1*) and another later date (*date2*) are calculated using the following formula:

  *duration in years = (date2-date1+1)/365.25.*

- **Minutes** – Durations expressed in minutes between one timepoint (*time1*) and another later timepoint (*time2*) are calculated using the following formula: duration in minutes = (time2-time1)/60.

## 8.2 Medical Coding

### *8.2.1 MedDRA*

Events recorded as medical history or adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Preferred term (PT) and system organ class (SOC) will be summarized.

### *8.2.2 WHO Drug Dictionary*

All prior systemic cancer therapies as recorded on the Multiple Myeloma History - Prior Systemic Cancer Drug Therapy CRF page and prior and concomitant medications as recorded on the Concomitant Medications CRF will be coded using WHO Drug Dictionary (WHO DD) Enhanced version September 2020. Medications are coded to Anatomical/Therapeutic/Chemical (ATC) drug class level 4 and preferred drug names. If ATC drug class level 4 code is unavailable, level 3 is used; if level 3 coding is unavailable, level 2 is used.

## 8.3 Patient Characteristics

### *8.3.1 Age*

Age is calculated as the integer duration from the date of birth to the date of informed consent, if age is not recorded in the electronic case report form (eCRF). Age will be categorized as <65, 65 - <75, and ≥75 (years) and separately per the randomization strata <75 and ≥75 (years).

### *8.3.1 Body Surface Area*

Body surface area (BSA) will be calculated based on patients' height in centimeters (Ht) and weight in kilograms (Wt) at study entry using the Mosteller formula, i.e. $\{Ht*Wt/3600\}^{0.5}$. BSA will categorized into subgroups with BSA below or above median BSA for FAS.

### *8.3.2 Geographic Region*

Geographic location of study site will be categorized as United States of America, Europe and Rest of World. Rest of World includes Russia, Israel, Korea and Taiwan.

## 8.4 Disease Characteristics

### *8.4.1 Time Since Initial Diagnosis*

Time since initial diagnosis in years at study entry will be defined as duration from diagnosis to first dose of study. Partial dates will be imputed according to Section 10.1.

### *8.4.2 Time Since Most Recent Relapse*

Time since most recent relapse in months at study entry will be defined as duration from date of most recent documented progressive disease to randomization. Partial dates will be imputed according to Section 10.1.

### *8.4.3 Prior and Concomitant Medications*

Concomitant medications are defined as medications with start date or end date on or after the date of first dose and start date before the date of the last dose + 30 days or are ongoing at the time of first dose. Prior medications are defined as medications with a stop date before the date of first dose of study drug.

For the purpose of determining if a medication should be noted as a concomitant medication, the imputation rules stated in Section 10.1 will be used. Imputed dates will not be presented in the listings.

Patients may have more than one medication per ATC level and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level.

Transfusions will be defined as WHO DD preferred names of “Platelets” or “Red blood cells”. Growth factor agents will be defined as WHO DD Standardized Drug Groupings (SDG) “Colony stimulating factors”.

### *8.4.4 Therapeutic Drug Classes*

Proteasome inhibitor (PI) is defined as WHO DD SDG “Antineoplastic proteasome inhibitors”.

Immunomodulatory drug (IMiD) is defined as SDG “Antineoplastic thalidomide analogues”.

Anti-CD38 monoclonal antibodies (mAb) is defined as SDG “Antineoplastic CD38 antigen inhibitors”.

Other mAb is defined as SDG “Monoclonal antibodies – antineoplastics” excluding SDG “Antineoplastic CD38 antigen inhibitors”.

Alkylators is defined as SDG “Antineoplastic alkylating drugs”.

Other antineoplastic drugs for the treatment of multiple myeloma will be referred to as “Other”.

Any experimental or investigational drugs that are not covered by WHO DD will be reviewed manually and classified as one of the above therapeutic drug classes if applicable. Classifications will be documented as part of database lock procedures and further described in the CSR.

### *8.4.5 Prior Regimens*

A prior regimen is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one regimen. A new regimen starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new regimen also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease. [Rajkumar 2011]

Number of prior regimens per patient will be the ‘Total Lines of Therapy’ as reported by investigator on the Multiple Myeloma History – Prior Systemic Cancer Therapy Summary CRF.

### *8.4.6 Refractory Status*

A patient is defined as refractory to a drug within a prior regimen if the patient fulfills any of the following criteria [Rajkumar 2011]:

1. Reason for termination was PD
2. Best response was PD or SD
3. Relapse or progression occurred within 60 days from last administration

Double-class refractory is defined as refractory to at least one PI and at least one IMiD.

Triple-class refractory is defined as refractory to at least one PI, at least one IMiD, and at least one Anti-CD38 mAb.

### *8.4.7 Transplants*

A front-line transplant is defined as the transplant indicated for the first line of therapy. This can be single or tandem transplant. Planned tandem autologous or autologous-allogeneic are considered as one transplant.

A salvage transplant is defined as any transplant given following failure of front-line therapy. Planned tandem autologous or autologous-allogeneic are considered as one transplant.

Time from autologous transplant to relapse is the duration in years from date of transplant (or date of first transplant if given in tandem) to date of relapse. Time from autologous transplant to relapse will be categorized as <1 year, 1 - <1.5 years, 1.5 – 2 years, >2 years.

### *8.4.8 Cytogenetic Risk Groups*

Genetic subtypes from cytogenetics analysis by fluorescence in situ hybridization (FISH) will be categorized into risk groups as follows [Sonneveld 2016]:

- High-risk group: consists of patients who have the genetic subtype t(4; 14), t(14:16), deletion 17p, gain 1q (+1q), t(14,20) , and gain (1q21).[1]
- Standard-risk group: consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk
- Unknown: consists of patients for whom the procedure was not done or unevaluable.

### *8.4.9 International Staging System (ISS)*

ISS Stage and Revised ISS (R-ISS) Stage will be used as reported in CRF [Palumbo, 2015], see Table 1.

[1] The addition of subtypes gain 1q (+1q), t(14,20) were added to the IMWG definition of high risk cytogenetics [Sonneveld 2016] as an update to initial IMWG guideline [Rajkumar 2011]. As this definition was changed during the study and the protocol did not require testing of the additional high-risk cytogenetic abnormalities, these additional subtypes may be underrepresented.[2] IMWG defined measurable serum M-protein as ≥ 1.0 g/dL [Rajkumar 2011].

***Table 1: Standard Risk Factors for MM and the Revised ISS (R-ISS)***

| **Standard Risk Factors for MM and the Revised -ISS (R-ISS)** | |
|---|---|
| **Prognostic Factor** | **Criteria** |
| **ISS Stage** | |
| **Stage I** | Serum B2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL |
| **Stage II** | Not ISS stage I or III |
| **Stage III** | Serum B2-microglobulin ≥ 5.5 mg/L |
| **Chromosomal abnormalities (CA) by interphase by florescent in situ hybridization (iFISH)** | |
| **High-Risk** | Presence of del(17p) and/or translocation of t(4:14) and/or translocation of t(14:16) |
| **Standard-Risk** | No high-risk CA |
| **Lactase Dehydrogenase (LDH)** | |
| **Normal** | Serum LDH < upper limit of normal (ULN) |
| **High** | Serum LDH > ULN |
| **A new model for risk stratification of MM R-ISS** | |
| **Stage I** | ISS stage I and standard-risk CA by iFISH and normal LDH |
| **Stage II** | Not R-ISS stage I or III |
| **Stage III** | ISS stage III and either high-risk CA by iFISH or LDH |

ISS as reported in CRF will be referred to as 'ISS' {I, II, III, Unknown, Not Done}.

R-ISS as reported on the CRF will be referred to as 'R-ISS' {R-I, R-II, R-III, Unknown, Not Done}.

### *8.4.10 Monoclonal Protein Spike (M-protein)*

M-protein is assessed from serum and urine protein electrophoresis test (SPEP/UPEP), and/or serum free light chain (sFLC).

Measurable M-protein at screening and baseline are defined as follows:

- Measurable SPEP is defined as M-protein ≥ 0.5 g/dL.[2]
- Measurable UPEP is defined as M-protein ≥ 200 mg/24 hr.
- Measurable sFLC is defined as involved FLC ≥ 10 mg/dL with abnormal Kappa/Lambda ratio (defined as values outside 0.26-1.65).

[2] IMWG defined measurable serum M-protein as ≥ 1.0 g/dL [Rajkumar 2011].

If the sFLC kappa/lambda ratio is >1.65, kappa is the involved sFLC, and lambda is the uninvolved sFLC. If the kappa/lambda ratio is <0.26, lambda is the involved sFLC, and kappa is the uninvolved sFLC. Difference in sFLCs (dFLC) is defined as (Involved sFLC – Uninvolved sFLC) and is used for response assessment according to IMWG [Rajkumar 2011].

Maximum percent decrease of M-protein or dFLC as summarized in waterfall plots is defined as maximum decrease from baseline to lowest level (nadir) per patient divided by baseline level, expressed as percent. Maximum percent decreases of less than -100% will be set to -100%.

When estimating maximum percent decrease; If both SPEP and UPEP are measurable at baseline, SPEP will be used. If only SPEP is measurable, SPEP will be used. If only UPEP is measurable UPEP will be used. If neither SPEP and UPEP are measurable, FLC will be used.

#### *8.4.11 Plasma Cell Involvement*

Bone marrow plasma cell involvement (%) as assessed by aspiration and biopsy will use the higher value in cases of discrepancy and referred to as maximum plasma cell involvement. Maximum plasma cell involvement will be categorized as (<30%, 30 - <60%, ≥60%).

#### *8.4.12 Presence of Bone Lesions and Extramedullary Disease (EMD)*

Presence of bone lesions and/or EMD at baseline will be defined the Multiple Myeloma Status at Study Entry CRF, or Multiple Myeloma Status at Diagnosis CRF if not available at study entry, and if not available from investigator assessments of imaging at study entry, recorded on the Bone Lesion Assessment-Screening and Extramedullary Plasmacytoma Evaluation-Screening CRFs.

### 8.5 Protocol Deviations

Major protocol deviations related to the eligibility, efficacy, or safety of the subject that could significantly impact the interpretation of study results will be identified prior to database lock and may include, but are not limited to:

- Subjects who missed one or more assessments that have a significant effect on the evaluation of efficacy or safety
- Subjects who did not satisfy critical inclusion and exclusion criteria
- Subjects who received the wrong treatment or incorrect dose

Major protocol deviations will be summarized by deviation type for the Full analysis set.

Patients with major protocol deviations leading to exclusion from the Per Protocol analysis set will be indicated.

## 8.6 Myeloma and Safety Laboratory Assessments (Hematology, Coagulation, and Serum Chemistry)

### *8.6.1 Unit Conversion*

Reported units will be converted to standard units according to CDISC controlled terminology using the conversion factors shown in Table 2.

***Table 2. Conversion factors for laboratory units***

| Analyte | Original reported unit | Standard unit | Conversion factor |
|---|---|---|---|
| **Myeloma Laboratory Assessments** | | | |
| Urine Monoclonal Protein Spike | mg/24hrs | mg/day | 1 |
| Serum Monoclonal Protein Spike | g/dL | g/dL | 1 |
| Kappa/Lambda Free Light Chain | Ratio | RATIO | 1 |
| Beta-2 Microglobulin | mg/dL | mg/L | Multiplied by 10 |
| Immunoglobulins (A, D, E, G, M), Kappa Free Light Chain, Lambda Free Light Chain, | mg/dL | mg/dL | 1 |
| **Hematology** | | | |
| WBC differentials (Basophils, Eosinophils, Monocytes, Lymphocytes, Neutrophils) | % | % | 1 |
| Platelets, WBC and WBC differentials (Basophils, Eosinophils, Monocytes, Lymphocytes, Neutrophils) | 10^9/L, x10^9/L, K/µL, K/CUMM, x10^3/µL, K/mcL | 10^9/L | 1 |

| Analyte | Original reported unit | Standard unit | Conversion factor |
|---|---|---|---|
| Platelets, WBC and WBC differentials (Basophils, Eosinophils, Monocytes, Lymphocytes, Neutrophils) | /uL, cells/mm3, cells/µL, cells/uL | 10^9/L | Divided by 1000 |
| RBC | 10^12/L, x10^12/L, M/µL, M/CUMM, MIL/CUMM, x10^6/µL, M/mcL | 10^12/L | 1 |
| RBC | /uL, cells/mm3, cells/µL, cells/uL | 10^12/L | Divided by 1000000 |
| Hematocrit | % | % | 1 |
| Hemoglobin | g/L | g/L | 1 |
| Hemoglobin | g/dL | g/L | Multiplied by 10 |
| **Serum Chemistry** | | | |
| ALT, AST, ALP, LDH | U/L, IU/L | U/L | 1 |
| Albumin | g/L | g/L | 1 |
| Albumin | g/dL | g/L | Multiplied by 10 |
| Bicarbonate/CO2, Chloride, Potassium, Sodium | mmol/L | mmol/L | 1 |
| Bicarbonate/CO2, Chloride, Potassium, Sodium | mEq/L | mmol/L | 1 |
| Total Bilirubin | umol/L, µmol/L | umol/L | 1 |
| Total Bilirubin | mmol/L | umol/L | Multiplied by 1000 |
| Total Bilirubin | mg/dL | umol/L | Multiplied by 17.1037 |
| Calcium | mmol/L | mmol/L | 1 |
| Calcium | mg/dL | mmol/L | Multiplied by 0.2495 |
| Creatinine | umol/L, µmol/L | umol/L | 1 |
| Creatinine | mg/dL | umol/L | Multiplied by 88.4017 |

| Analyte | Original reported unit | Standard unit | Conversion factor |
|---|---|---|---|
| Creatinine | mmol/L | umol/L | Multiplied by 1000 |
| Glucose | mmol/L | mmol/L | 1 |
| Glucose | mg/dL | mmol/L | Multiplied by 0.05556 |
| Glucose | g/L | mmol/L | Multiplied by 5.556 |
| Magnesium | mmol/L | mmol/L | 1 |
| Magnesium | mEq/L | mmol/L | Multiplied by 0.5 |
| Magnesium | mg/dL | mmol/L | Multiplied by 0.4114 |
| Phosphate | mmol/L | mmol/L | 1 |
| Phosphate | mg/dL | mmol/L | Multiplied by 0.3226 |
| Total Protein | g/L | g/L | 1 |
| Total Protein | g/dL | g/L | Multiplied by 10 |
| Uric Acid/Urate | umol/L, µmol/L | umol/L | 1 |
| Uric Acid/Urate | mg/dL | umol/L | Multiplied by 59.4849 |
| Uric Acid/Urate | mmol/L | umol/L | Multiplied by 1000 |
| Urea Nitrogen/Blood Urea Nitrogen (BUN) | mmol/L | mmol/L | 1 |
| Urea Nitrogen/Blood Urea Nitrogen (BUN) | mg/dL | mmol/L | Multiplied by 0.3571 |
| Coagulation | | | |
| INR | Ratio | RATIO | 1 |
| Prothrombin Time | s, sec | sec | 1 |
| Prothrombin Time | % | -- | No conversion |

### *8.6.2 Derived Laboratory Parameters and Subgroups*

Creatinine clearance (ml/min) will be derived using the following equation:

$$CrCl = K \times \{140 - age \times weight\} / \{72 \times serum\ creatinine\}$$

where K is 1 for males and 0.85 for females, age is integer years, weight in kg, and serum creatinine in mg/dL [Cockroft 1976]. Age at the date of serum creatinine assessment will be used. Weight at the assessment date or nominal visit as serum creatinine will be used.

For hypocalcemia and hypercalcemia (as defined from laboratory ranges), serum calcium values and normal ranges will be corrected using the formula:

*Corrected calcium = Serum calcium mg/dL + 0.8 × (4 - serum albumin g/dL)*

β2 microglobulin (mg/L) will be categorized as < 3.5, 3.5 – 5.5 and > 5.5.

Platelet count (10^9/L) will be categorized as <75, 75 – 100, >100 – 150, and >150.

ANC (10^9/L) will be categorized as <1.0, 1.0 – 1.5, and >1.5.

Hemoglobin (g/L) will be categorized as <80, 80 – 100, >100.

Lactase dehydrogenase (LDH) will be categorized as <1.5xULN and ≥1.5xULN, where ULN=upper limit of normal range based on reference ranges provided from each site.

Albumin (g/dL) will be categorized as <3.5, and ≥3.5.

Creatinine clearance (ml/min) will be categorized as <45, ≥45 - <60, ≥60 - <90, ≥ 90.

### *8.6.3 Toxicity Grades*

The following laboratory test results will be assigned toxicity grades using NCI CTCAE version 4.03:

- Hematology
  - Hemoglobin (increase, decrease)
  - Platelets (decrease)
  - WBC (increase, decrease)
  - ANC (decrease)
  - Lymphocyte Count (increase, decrease)
- Serum Chemistry
  - Alanine transaminase (ALT) (increase)
  - Aspartate transaminase (AST) (increase)
  - Alkaline Phosphatase (increase)
  - Total Bilirubin (increase)
  - Creatinine (increase)
  - Corrected Calcium (increase, decrease)

- Glucose (increase, decrease)
- Albumin (decrease)
- Uric Acid/Urate (increase)
- Magnesium (increase, decrease)
- Phosphorus/Phosphate (decrease)
- Potassium (increase, decrease)

## 8.7 Myeloma Response Parameters

The primary analysis of tumor response and progression-dependent endpoints will be based the Independent Review Committee (IRC). All tumor response and progression-depended endpoints will be assessed using the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) [Rajkumar 2011].

### *8.7.1 Progression Free Survival (PFS)*

PFS is defined as the duration in months from randomization until first evidence of confirmed disease progression. Disease progression is defined according to IMWG-URC as PD or death due to any cause, whichever occurs first. PFS will be right-censored according to the conventions described in Table 3.

***Table 3: Conventions for Censoring of PFS***

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No post baseline response assessments | Date of randomization | Censored |
| Non-protocol systemic anticancer therapy started before documentation of PD or death | Date of last response assessment prior to start of new anticancer therapy | Censored |
| Death or PD after more than 1 consecutively missed response assessment | Date of last response assessment without documentation of PD that is before the first missed visit | Censored |
| Unconfirmed PD as the final response assessment | Date of latest PD assessment | Progressed |
| Alive and without PD documentation | Date of last response assessment | Censored |
| Death or PD between scheduled response assessments | Date of death or preceding response assessment showing PD, whichever occurs first | Progressed |
| Death before first response assessment | Date of death | Progressed |

These conventions are adapted from the December 2018 FDA Guidance for Industry, 'Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics', and on the April 2015 FDA Guidance for Industry 'Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics'. If a patient initiates a non-protocol systemic anticancer therapy, after randomization, prior to any response assessment, the patient will be censored at the time of initiation of the non-protocol systemic anticancer therapy. If a patient dies more than 60 days after last assessment or randomization, the patient will be considered as missing more than 1 consecutive response assessment.

Event-free rates will be defined using Kaplan-Meier (K-M) product-limits and categorized by consecutive periods of 3 months from treatment start.

Confirmed disease progression is defined as two consecutive response assessments resulting in PD at any time. Response assessments that are not done or incomplete and occur between consecutive PD results will be excluded when deriving PFS. If a second response assessment can only be obtained after the start of a subsequent therapy consisting of a non-protocol cancer therapy, it may be used as a confirmation of PD.

### *8.7.2 Response Rates*

The overall response rate (ORR) is defined as the proportion of patients for whom the best overall confirmed response is stringent complete response (sCR),

complete response (CR), very good partial response (VGPR), or partial response (PR).

The clinical benefit rate (CBR) will be defined as the proportion of patients with the best overall confirmed response of minimal response (MR) or better.

Stable disease (SD) will be defined as the proportion of patients with the best overall confirmed response of SD.

Disease stabilization will be defined as the proportion of patients with the best overall confirmed response of SD or better.

'Best overall confirmed response' is the best response achieved on study based on two consecutive assessments according to IMWG-URC.

Responses of not evaluable (NE) will be determined if no measurable disease at baseline or no post-baseline response assessment. No post-baseline response will be presented separately for patients still on study at the time of the data cut or if patient has withdrawn from study.

### *8.7.3 Overall Survival*

OS is defined as the time in months from randomization to date of death due to any cause. Patients who are alive will be censored at the last follow up visit or data cut-off date for patients still on-study.

### *8.7.4 Duration of Response (DOR)*

DOR will be estimated for patients who achieve a PR or better. DOR is defined as the duration in months from first documentation of a confirmed response to first evidence of confirmed disease progression or death due to any cause.

Disease progression, and dates of progression and censoring, will be determined as described for the analysis of PFS (Section 8.7.1).

### *8.7.5 Time to Response (TTR)*

TTR will be estimated for patients with confirmed responses of PR or better. TTR is defined as the duration in months from randomization to the first occurrence of a response of PR or better.

### *8.7.6 Time to Progression (TTP)*

TTP will be estimated for patients with confirmed PD. TTP is defined as the duration in months from randomization to first evidence of disease progression.

Disease progression, and dates of progression and censoring, will be determined as described for the analysis of PFS (Section 8.7.1), with the exception that

patients who die will be censored as of the last response assessment prior to death.

### *8.7.7 Duration of Clinical Benefit (DOCB)*

Duration of clinical benefit will be estimated for patients whose best confirmed response is MR or better. Duration is defined as the time in months from first post-baseline documentation of a confirmed MR or better to disease progression or death due to any cause.

### *8.7.8 Long Term Follow-up for PFS and OS*

According to the study protocol, patients who discontinue therapy for reasons other than disease progression should continue to have monthly disease assessments done until confirmed progression or initiation of subsequent therapy.

Following confirmed disease progression or initiation of subsequent therapy, follow-up for overall survival status, second primary malignancies and subsequent therapy will take place every three months +/- 7 days for 24 months.

## 8.8 Patient Reported Outcomes / Health related quality of life (HRQoL)

Health related quality of life (HRQoL) assessments were added at the time of protocol version 4.1. HRQoL analyses will use the PRO analysis set.

Domains of focus will include summary score, global health status, physical functioning, emotional functioning, fatigue and pain (EORTC QLQ-C30), disease symptoms and side effects of treatment (EORTC QLQ-MY20) and EQ-5D health utility and VAS analyses.

### *8.8.1 EQ-5D-3L*

The EQ-5D-3L questionnaire converts 5 dimensions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) of patient-reported, current-day health status into a “health utility” score. For the EQ-5D questionnaire, each dimension is scored on a Likert-type scale with 3 available levels of response and scores ranging from 1 to 3, “no problems,” “some problems,” and “extreme problems,” respectively. For EQ-5D health utility values will be mapped in accordance with the EQ-5D manual using United Kingdom as value set. The EQ VAS scores are anchored on 100 = best imaginable health and 0 = worst imaginable health.

The maximum EQ-5D-3L health utility score and EQ VAS will be calculated as the highest scores from post-baseline to end of treatment. The time to maximum

score will be calculated as the time (months) from randomization to the first occurrence of a maximum score.

### *8.8.2 EORTC QLQ-C30 and QLQ-MY20*

The scoring for the EORTC instruments will be done according to the procedures described by their respective EORTC Scoring Manual.

EORTC QLQ-C30 and QLQ-MY20 raw scores will be transformed into a range from 0 to 100. For EORTC QLQ-C30 Global Health Status and functional domains (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning), a higher score indicates better function, and for symptom domains (Fatigue, Nausea & vomiting, Pain, Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, Financial Difficulty), a lower score indicates fewer symptoms. For EORTC QLQ-MY20, higher scores represent better functioning for future perspective and body image, and higher scores representing worse impact for disease symptoms and side effects of treatment.

The EORTC QLQ-C30 Summary Score is calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale are not included). Prior to calculating the mean, the symptom scales need to be reversed to obtain a uniform direction of all scales. The summary score should only be calculated if all of the required 13 scale scores are available (using scale scores based on the completed items, provided that at least 50% of the items in that scale have been completed.

The maximum EORTC QLQ-C30 summary score will be calculated as the highest score from post-baseline to end of treatment.

The time to maximum EORTC QLQ-C30 summary score will be calculated as the time (months) from randomization to the first occurrence of a maximum score.

The maximum EORTC QLQ-MY20 summary score will be calculated as the highest score from post-baseline to end of treatment.

The time to maximum EORTC QLQ-MY20 summary score will be calculated as the time (months) from randomization to the first occurrence of a maximum score.

## 8.9 PK Parameters for Melphalan

PK parameters for melphalan will be derived using non-compartmental analysis in Phoenix WinNonLin® and transferred to Precision.

The following PK parameters will be calculated.

- $C_{max}$: Maximum observed concentration.

- $AUC_{last}$: Area under the concentration versus time curve from start of infusion to the last data point with measurable concentration.
- $AUC_{inf}$: Area under the concentration versus time curve from start of infusion to infinity.
- $t_{½}$: Elimination half-life.

## 8.10 Exposure

The study drugs for this study are melflufen, pomalidomide, and dexamethasone.

### *8.10.1 Overall Study Drug Exposure*

Duration of treatment with study drug in weeks is defined as the longer of (date of last dose + 28 days – date of first dose + 1 for melflufen), (date of last dose + 1 day – date of first dose + 1 for pomalidomide) or (date of last dose + 7 days – date of first dose + 1 for dexamethasone) divided by 7.

### *8.10.2 Melflufen Exposure*

Duration of melflufen treatment in weeks is defined as ((date of last dose + 28 days) – date of first dose + 1) divided by 7.

Melflufen treatment cycle is defined as cycle during which at least one dose of melflufen was administered. A treatment cycle starts on the date of melflufen administration.

Cumulative dose of melflufen in mg is the sum of all melflufen doses administered.

Average dose of melflufen in mg/week is defined as the cumulative dose divided by the duration of melflufen treatment.

The dose intensity of melflufen is defined as the ratio of the average dose of melflufen to the prescribed dose, where prescribed dose is 40 mg per 4 weeks = 10 mg/week and expressed as a percent.

A dose delay is defined as a consecutive dose of melflufen administered on day 32 or later following a preceding dose of melflufen. Dose delays will be categorized as delays in weeks as 1 (day 33 to 39), 2 (day 40 to 46), 3 (day 47 to 53), 4 (day 54 to 60), and >4 weeks (day 61 or later) for each cycle.

If a subject missed the cycle with a dose delay due to COVID-19, these dose delays will be summarized separately.

A dose reduction is defined as a consecutive dose of melflufen lower than a preceding dose of melflufen.

#### 8.10.2.1 Kaplan-Meier Analysis of Melflufen Dose Modifications

Time to dose modification is defined from the treatment start date to the start date of the first dose modification (Date of first dose modification – date of the first dose of melflufen + 1), where a dose modification is either a subsequent dose reduced from preceding dose or a subsequent dose administered after day 32 from preceding dose whichever occurs first. Those patients who do not experience an event will be censored at the date of last melflufen dose plus 28 days, end of study date, data cutoff date, or death date, whichever is earlier.

Time to dose delay is defined from the treatment start date to the start date of the first dose delay (Date of first dose delay– date of the first dose of melflufen + 1), where a dose delay is a subsequent dose administered after day 32 from preceding dose. Those patients who do not experience an event will be censored at the earliest of the date of last melflufen dose plus 28 days, end of study date, data cutoff date, or death date.

Time to dose reduction is defined from the treatment start date to the start date of the first dose reduction (Date of first dose reduction– date of the first dose of melflufen + 1), where a dose reduction is a subsequent dose reduced from preceding dose. Those patients who do not experience an event will be censored at the earliest of the date of last melflufen dose plus 28 days, end of study date, data cutoff date, or death date.

### *8.10.3 Pomalidomide Exposure*

Duration of pomalidomide treatment in weeks is defined as ((date of last dose +1 day) – date of first dose + 1) divided by 7.

Pomalidomide treatment cycle is defined as cycle during which at least one dose of pomalidomide was administered. A treatment cycle starts on the date of pomalidomide administration.

Cumulative dose of pomalidomide in mg is the sum of all pomalidomide doses administered.

Average dose of pomalidomide in mg/week is defined as the cumulative dose divided by the duration of pomalidomide treatment.

The dose intensity of pomalidomide is defined as the ratio of the average dose of pomalidomide to the prescribed dose, where prescribed dose is 4 mg per day for 21 days = 84 mg/month = 21 mg/week and expressed as a percent.

The planned dosing are days 1 through 21. A dose delay is defined as the next cycle of pomalidomide administered on day 32 or later of current cycle.

If a subject missed the cycle with a dose delay due to COVID-19, these dose delays will be summarized separately.

A dose reduction is defined as a consecutive dose of pomalidomide lower than a preceding dose of pomalidomide.

### *8.10.4 Dexamethasone Exposure*

Duration of dexamethasone treatment in weeks is defined as ((date of last dose +7 days) – date of first dose + 1) divided by 7.

Cumulative dose of dexamethasone in mg is the sum of all dexamethasone doses administered.

The dose intensity of dexamethasone is defined as the ratio of (cumulative dose divided by the duration of dexamethasone treatment) to the prescribed dose, where prescribed dose is 160 mg per 4 weeks = 40 mg/week for patients with age <75 years, or 80 mg per 4 weeks = 20 mg/weeks for patients with age ≥75 years, and expressed as a percent.

A dose delay is defined as a dose of dexamethasone administered on day 4 or later following the planned dosing days 1, 8, 15 and 22 respectively, and before the day of a planned subsequent dose. A missed dose of dexamethasone is a planned dose that is not given before the day of a planned subsequent dose (e.g. if planned dose on day 8 is not given before day 15).

A dose reduction is defined as a consecutive dose of dexamethasone lower than a preceding dose of dexamethasone.

### *8.10.5 Action Taken with Study Drug*

The protocol and eCRF use the terms dose held and dose delay. A dose held is the same as a dose delay. The term dose delay is used herein and will be used for the CSR.

Dose delays or dose reductions in summaries of scheduled study drug administration will be analyzed using the derived continuous variables described in Sections 8.10.2, 8.10.3, and 8.10.4, and not as reported in the CRF. The ‘Dose adjustment’ as reported in CRF {NO ACTION TAKEN, DOSE HELD, DOSE REDUCED, and DRUG PREMANENTLY DISCONTINUED} and dose adjustment according to CDISC Controlled terminology (CT) {DOSE NOT CHANGED, DOSE REDUCED, DRUG INTERRUPTED, and DRUG WITHDRAWN} will be included in listings. CRF entry ‘DOSE HELD’ correspond to CT ‘DRUG INTERRUPTED’, and CRF entry ‘DRUG PERMANENTLY DISCONTINUED’ correspond to CT ‘DRUG WITHDRAWN’.

## 8.11 Safety Evaluation

### *8.11.1 Adverse Events*

An **adverse event** (AE) is any untoward medical occurrence in a study patient administered an investigational product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the patient begins study therapy is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

Further details for the definition of AE is provided in study protocol section 9.1.1.

A **serious adverse event** (SAE) is defined as any AE, occurring at any dose that meets any one or more of the following criteria:

- Is fatal or immediately life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization

Further details for the definition of SAE is provided in study protocol section 9.2.1.

A **treatment-emergent adverse event** (TEAE) is an AE with an onset or increase in severity level after the initial dose of study drug and no later than day 30 after the last dose of study drug or initiation of new multiple myeloma therapy, whichever is sooner.

A **treatment-related adverse event** is an AE that is recorded by the investigator as possibly or probably related to either or both of melflufen/pomalidomide and dexamethasone. A melflufen related AE is an AE that is noted as possibly or

probably related to melflufen/pomalidomide independently of relationship with dexamethasone, and a dexamethasone related AE is an AE that is noted as possibly or probably related to dexamethasone independently of relationship with melflufen/pomalidomide.

Patients may have more than one adverse event per SOC and preferred term. At each level of patient summarization, a patient is counted once if he/she reported one or more adverse events at that level. For such cases, the maximum NCI CTCAE (version 4.03) toxicity grade and strongest causal relationship to study drug will be used in the incidence calculations.

### *8.11.2 Dose Modifications due to Adverse Event*

Dose delays or dose reductions in summaries of 'Action taken with study drug' due to AE will be analyzed as reported in the CRF {NO ACTION TAKEN, DOSE HELD, DOSE REDUCED, DRUG INTERRUPTED, and DRUG PREMANENTLY DISCONTINUED}. Listings will include Action taken as reported on CRF and Action taken as mapped according to CDISC Controlled terminology (CT) {DOSE NOT CHANGED, DOSE REDUCED, DRUG INTERRUPTED, and DRUG WITHDRAWN}.

### *8.11.3 Adverse Events of Special Interest*

AEs of special interest (AESIs) are TEAEs defined as follows:

- Neutropenia: Preferred terms of Neutropenia, Febrile neutropenia, Neutrophil count decreased, Neutropenic sepsis, Neutropenic infection, Cyclic neutropenia, Band neutrophil count decreased, Band neutrophil percentage decreased, Neutrophil percentage decreased, Agranulocytosis, Granulocyte count decreased, Granulocytopenia
- Thrombocytopenia: Broad search including in the Standardized MedDRA Query (SMQ) {"Haematopoietic thrombocytopenia"}
- Anemia: Broad search including in the SMQ {"Haematopoietic erythropenia"}
- Febrile neutropenia: PT {"Febrile neutropenia"}[3]
- Infections: SOC {"Infections and infestations"}
- Infective pneumonia: SMQ {"Infective pneumonia"}, including and excluding broad terms.

[3] PT "Febrile neutropenia" is listed as an individual PT and is also included in the SMQ "Haematopoietic leukopenia". Hence, that PT will be counted in the 2 separate AESIs.

- Hemorrhage: All terms included in the SMQs {“Haemorrhage terms, excluding laboratory terms”} and narrow terms included in the SMQ {“Haemorrhage laboratory terms”}
- Thrombocytopenia concomitant to hemorrhage: Hemorrhage with an onset date within ± 7 days of the onset and/or resolution date of a grade 3 or 4 thrombocytopenia.
- Neutropenia concomitant to infection: Infection with an onset date within ± 7 days of the onset and/or resolution date of a grade 3 or 4 neutropenia.
- Thromboembolism: SMQ {“Embolic and thrombotic events”}
- Central Nervous System Bleeding (CNS Bleeding): SMQ {“Haemorrhagic central nervous system vascular conditions”}
- Second Primary Malignancy (SPM): {SMQ “Malignant or unspecified tumours including SMQ Malignant tumours”}, as well as {SMQ “Tumours of unspecified malignancy”}, and high level term (HLT) {“Myelodysplastic syndromes”}, but will exclude high level group term (HLGT) {Plasma cell neoplasms”}.
- Myelodysplastic Syndrome (MDS): HLT Myelodysplastic syndromes, which includes PTs {5q minus syndrome, Chronic myelomonocytic leukaemia, Myelodysplastic syndrome, Myelodysplastic syndrome transformation, Myelodysplastic syndrome unclassifiable, Refractory anaemia with an excess of blasts, Refractory anaemia with ringed sideroblasts, Refractory cytopenia with multilineage dysplasia, Refractory cytopenia with unilineage dysplasia, or Sideroblastic anemia}
- Peripheral Neuropathy: Narrow terms included in the SMQ {“Peripheral neuropathy”}
- Tachyarrhythmias: Narrow terms included in the SMQ {“Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias)”}

### *8.11.4 Deaths*

Deaths will be categorized as occurring within 30 days of the last dose of study drug or more than 30 days after the last dose respectively. Deaths related study drug occurring more than 30 days after the last dose will also be categorized.

Early deaths will be defined as occurring within 60 days of first dose of study drug.

## 8.12 Subsequent Therapies

### *8.12.1 Grouping Therapies into SDGs*

Subsequent therapies are not codded according to WHO DD. Therefore, the following algorithm will be used to group each therapy's reported term to the respective SDG:

- First, test for a direct match between reported term and SDG terms (preferred term),
- Next, test for trade name match to SDG term (e.g. Revlimid to lenalidomide),
- Next, split reported terms out that have been recorded as combination therapies and repeat steps 1 and 2,
- Finally, identify misspellings (e.g., lenalidomid as lenalidomide) and repeat steps 1 and 2.

### *8.12.2 Missing Dates*

If a subject's subsequent therapy initiation start date is missing, end of study treatment date will be used.

### *8.12.3 Multiple Therapies*

For analysis purposes (e.g. censoring for overall survival), the date of a subject's first subsequent therapy will be used when multiple subsequent therapies have been initiated.

# 9 STATISTICAL METHODS

## 9.1 General Considerations

All statistical summaries and analyses will be performed in SAS® version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

Statistical analyses will be reported using summary tables, figures, and data listings. In general, summaries of all data will be presented by treatment arm: Melflufen + Dexamethasone and Pomalidomide + Dexamethasone. Summaries will also be provided for the total group (combined treatment arms) for all summaries, except efficacy.

Inferential statistical analyses will be performed as described below. Unless otherwise stated, the null hypothesis for all inferential analyses is that there is no difference between the treatment arms. The alternative hypothesis is that there is a difference. All tests will be two-sided, at an alpha level of 0.05. See Section 10.2 for a description of multiplicity adjustments.

For continuous variables, the number of patients with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum will be presented.

For discrete data, the frequency and percent distribution will be presented. Unless otherwise indicated, percentages will be calculated based upon the number of patients in the applicable analysis set in each study group as the denominator. Graphical methods will be used, as appropriate, to illustrate study endpoints.

Confidence intervals, when presented, will be constructed at the 95% level and will be provided for each treatment group and differences between treatment groups. For binomial variables, exact distribution methods will be employed. The distribution of time-to-event endpoints will be summarized by the K-M method. Quartiles including median will be estimated by K-M method along with their 95% confidence intervals based on a log(-log(survival)) distribution.

Assuming raw or derived variables are recorded to “x” decimal places; range will be presented to x decimal places; mean, median, and quartiles to x+1; and SD and confidence intervals to x+2 decimal places. Presented decimal places should however not be greater than 4.

Percentages will be presented to 1 decimal place, with the exception of 0, which will be presented without percent, and 100, which will be presented without decimal places. Categorization of a variable based on percentages will be done before rounding.

Tables that summarize categorical data will present data as “0”, if the number of events is zero. Denominators for percentages will be based on the number of patients with non-missing data in the population used in each column. A “missing” category will be included for any parameter for which information is missing, without a percentage.

Individual patient data recorded on the electronic case report forms (eCRFs) and any derived data will be presented by study group and by patient in data listings.

## 9.2 Disposition of Patients

The population of primary interest for the summary of disposition is the Enrolled analysis set. The following patient disposition information will be summarized:

- Number of screened patients (Total group only)
- Number of patients not randomized (Total group only)
- Reason for not being randomized (Total group only)
- Number of randomized subjects (FAS)
- Number of randomized and treated subjects
- Number of treated subjects (Safety analysis set)
- Number (%) of subjects evaluable for response with no major protocol deviations (Per Protocol analysis set)
- Number (%) of treated patients who discontinued treatment
- Primary reason for treatment discontinuation
- Number (%) of treated patients in long-term PFS follow-up
- Number (%) of treated patients in long-term OS follow-up
- Number (%) of treated patients who discontinued the study
- Primary reason for study discontinuation
- Number (%) of subjects evaluable for HRQoL analyses (PRO analysis set)
- Number (%) of subjects evaluable for PK/PD analyses (PK analysis set)

Treatment discontinuations due to AE specific to COVID-19 or other pandemic-related reasons will be presented separately.

Time on study in months will be calculated as (last known date of contact minus date of randomization plus one)/30.4375. Time on treatment in months will be calculated as (last treatment date minus first treatment date plus one)/30.4375. KM estimates of the distribution of the time-to-study discontinuation and time-to-treatment discontinuation will be tabulated and graphed by treatment arm. The tabulation will include the KM estimate of the medians, 25th and 75th percentiles, and corresponding 95% CIs, if estimable. The tabular and graphical summaries will include the at-risk counts for every visit.

In addition, the number and percentage of subjects who complete scheduled visits will be presented for the FAS. In addition, visit compliance will be presented by calendar year and month to evaluate the effect of COVID-19 pandemic on visit completion.

The number and percentage of subjects randomized by geographical region and site will also be presented by treatment arm for the FAS. The same summary will be presented by calendar year and month.

A summary table will be produced of the randomization stratification factors from the interactive response technology (IRT) and the combined stratum groups:

- Age (≥ 75 years of age versus < 75 years of age)
- Number of lines of prior therapy (2 versus 3-4 prior lines)
- ISS Score (1 versus ≥ 2)
- Stratum Group 1: Age ≥ 75 years of age, 2 lines of prior therapy, ISS Score = 1
- Stratum Group 2: Age ≥ 75 years of age, 3-4 lines of prior therapy, ISS Score = 1
- Stratum Group 3: Age ≥ 75 years of age, 2 lines of prior therapy, ISS Score ≥ 2
- Stratum Group 4: Age ≥ 75 years of age, 3-4 lines of prior therapy, ISS Score ≥ 2
- Stratum Group 5: Age < 75 years of age, 2 lines of prior therapy, ISS Score = 1
- Stratum Group 6: Age < 75 years of age, 3-4 lines of prior therapy, ISS Score = 1
- Stratum Group 7: Age < 75 years of age, 2 lines of prior therapy, ISS Score ≥ 2
- Stratum Group 8: Age < 75 years of age, 3-4 lines of prior therapy, ISS Score ≥ 2

In addition, in case the site accidentally stratified a patient using the wrong stratification value, the derived stratification value reported in the eCRF data versus the one the site entered in the IRT during randomization process will be presented.

For analysis purposes, subject disposition, as outlined above, will be presented for each prior autologous stem cell transplant subgroup (<2.5 years, 2.5-5 years, <5 years, >5 years, and no transplant).

### 9.3 Protocol Deviations

All protocol deviations will be collected by the clinical research associates. Major protocol deviations leading to exclusion from the Per Protocol analysis set, will be summarized by deviation type for the FAS.

All protocol deviations will also be provided in a listing. Separate listings for major protocol deviations, COVID-19 pandemic-related protocol deviations, and major COVID-19 pandemic-related protocol deviations will also be provided.

## 9.4 Demographic, Baseline Characteristics, and Prior Therapy

### *9.4.1 Demographic and Baseline Characteristics*

The following demographic and baseline characteristics will be summarized for the Full, Safety, and Per Protocol analysis sets.

- Age (years) and age categories
- Sex
- Race
- Ethnicity
- Baseline ECOG performance status
- Baseline fertility status
- Baseline weight (kg)
- Baseline BSA ($m^2$)

For analysis purposes, subject demographics, as outlined above, will be presented for each prior autologous stem cell transplant subgroup (<2.5 years, 2.5-5 years, <5 years, >5 years, and no transplant).

### *9.4.2 Medical History*

The number (%) of patients who experienced a prior disease or disorder will be summarized by SOC, PT, and treatment arm using the FAS. Summaries will be ordered by descending order of total incidence of SOC and PT within each SOC.

Any medical history of COVID-19 will be presented as separate PTs specific to COVID-19 or coronavirus.

### *9.4.3 Disease Characteristics*

The following disease characteristics at diagnosis will be summarized for the Full, Safety, and Per Protocol analysis sets based on data recorded on the Multiple Myeloma History at Diagnosis CRF:

- Stage of disease (ISS and R-ISS)
- Heavy chain and light chain status, heavy chain and light chain combinations (e.g., IgG-lambda, IgG-kappa)
- Presence of bone lesions
- Presence of extramedullary disease

- Cytogenetic risk groups (as determined by FISH)
    - Each cytogenetic abnormality by FISH

The following disease characteristics at baseline/study entry will be summarized for the FAS:

- Stage of disease (ISS, R-ISS)
- Time from diagnosis to randomization in years
- Time from most recent relapse to randomization in months
- Type of measurable disease
- SPEP, UPEP, Kappa/Lambda values
- Heavy chain and light chain status, heavy chain and light chain combinations
- Maximum plasma cell involvement (%)
- Presence of bone lesions
- Presence of extramedullary disease
- Cytogenetic risk groups (as determined by FISH)
    - Each cytogenetic abnormality by FISH
- Laboratory Assessments
    - β2 microglobulin as values and categories
    - Platelet count as values and categories
    - ANC as values and categories
    - Hemoglobin as values and categories
    - LDH as values and categories
    - Albumin as values and categories
    - Creatinine
    - Creatinine clearance (mL/min) as values and categories
    - Corrected calcium

### *9.4.4 Prior Myeloma Therapy*

The following information related to prior myeloma therapy will be summarized for the Full, Safety, and Per Protocol analysis sets:

- Number of regimens of prior treatment for multiple myeloma

- Best response to last (most recent) line of prior therapy
- Best response to second to last line of prior therapy
- Number (%) of subjects who are refractory to lenalidomide 25 mg vs. lenalidomide < 25 mg (10 mg or 15 mg) during last (most recent) line of prior therapy or administered within 18 months prior to randomization.
- Refractory (refractory versus relapsed-refractory) status to lenalidomide during last (most recent) line of prior therapy or administered within 18 months prior to randomization.
- Number (%) of patients with at least one prior regimen including a therapeutic drug class, i.e. IMiD, PI, Alkylators, anti-CD38 mAb, Other mAb, and Other.
- Number (%) of patients who are refractory to a prior regimen including a therapeutic drug class.
- Number (%) of patients who received an IMiD and PI (double-class)
- Number (%) of patients who received an IMiD, PI, and anti-CD38 mAb (triple-class)
- Number (%) of patients who are double-class refractory (IMiD and PI)
- Number (%) of patients who are triple-class refractory (IMiD, PI, and anti-CD38 mAb)
- Number (%) of patients who are refractory to most recent prior regimen
- Number (%) of patients per last prior therapeutic class.
- Number (%) of patients refractory to any agent per last prior therapeutic class.
- Number (%) of patients who are refractory to IMiD, PI, Alkylators, anti-CD38 mAb, Other mAb, or Other per the most recent prior regimen by therapeutic classes.
- Number (%) of patients with at least one prior autologous transplant, and number (%) of patients with at least two prior autologous transplants
- Number of prior autologous transplants
- Number (%) of patients with ≥ 2 autologous transplants
- Number (%) of patients with an allogenic transplant, regardless of whether it was a tandem transplant
- Time (years) from front line transplant to relapse

- Number (%) of patients with prior radiotherapy

### *9.4.5 Prior and Concomitant Medications*

Concomitant medications will be summarized by ATC level 2, ATC level 4, and preferred name as counts and percentages using the FAS. The summaries will be ordered by descending frequency of ATC class and preferred name within each ATC class in the total group. Prior medications will be summarized in the same manner.

A separate summary table will summarize the number and percentage patients with transfusions and taking growth factor agents.

## 9.5 Efficacy Analyses

The primary population for all efficacy analyses will be the FAS. Additional select analyses will use the Per Protocol analysis set as indicated below. All tumor response and progression-depended endpoints will be assessed using the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) [Rajkumar 2011].

### *9.5.1 Primary Efficacy Analysis: Progression Free Survival*

The primary analysis of PFS will be performed using a log rank test stratified by the randomization stratification factors to compare treatment group survival distributions based on the FAS. K-M estimates of the survival distributions of the time-to-event based on log(-log(survival)) distribution will be tabulated and graphed by treatment arm. The tabulation will include the K-M estimate of the medians, 25th and 75th quartiles, and corresponding 95% CIs, if they can be estimated. The tabular and graphical summaries will include the at-risk counts. The number and percent of subjects censored, reason for censoring, and with events will be presented. The median PFS will be estimated for each treatment arm from the 50th percentile of the corresponding K-M estimates. The 95% CI for median PFS will be constructed using the method of Brookmeyer [Brookmeyer and Crawley,1982].

Potential follow-up for PFS will be summarized by treatment arm for the FAS using the reverse K-M method where the censoring variable is inverted [Schemper and Smith, 1996]. The median potential follow-up time will be summarized.

The hazard ratio and 95% CI will be determined based on a semi parametric Cox proportional hazards regression model stratified by randomization strata to estimate the magnitude of the effect. Ties will be handled using the Efron methodology.

In addition to a significant p-value for the treatment comparison based on the log rank test, the superiority of Melflufen + Dexamethasone versus Pomalidomide + Dexamethasone will be demonstrated if the upper limit of the 95% confidence interval for the hazard ratio is < 1.0.

Non-inferiority of Melflufen + Dexamethasone versus Pomalidomide + Dexamethasone will be demonstrated if the upper limit of the 95% confidence interval for the hazard ratio is < 1.2. This assessment is relevant for non-FDA submissions.

"Swim lane" plots based on PFS will be provided for the FAS analysis set. The plots will be stacked by day of first documentation of the different response levels (SD, MR, PR, VGPR, CR, sCR) on study.

#### 9.5.1.1 Sensitivity Analyses for PFS

The following sensitivity analyses will be performed for PFS.

##### 9.5.1.1.1 Unstratified Analysis

In addition to the stratified primary analysis of PFS, the unstratified log rank test and Cox proportional hazards regression model will be used to obtain the unstratified p-values and estimate of the hazard ratio. This analysis will be based on the FAS.

##### 9.5.1.1.2 PFS Adjusted for Version of Protocol

The analysis of PFS will be performed as specified above in Section 9.5.1 adding a fixed effect for protocol version (enrolled prior to version 3.0 versus after implementation of version 3.0) and will be based on the FAS.

##### 9.5.1.1.3 Initiation of Non-Protocol Anti-Cancer Therapy Treated as PFS Event

In this sensitivity analysis, initiation of non-protocol anti-cancer therapy will be treated as a PFS event whereby PFS is broadly defined as duration from randomization to documented disease progression, initiation of non-protocol anti-cancer therapy, or death, whichever occurs earlier. The data censoring rules are the same as those for the primary analysis of PFS except that the use of non-protocol anti-cancer therapy will be treated as an event rather than a mechanism for censoring. The analysis method will be the same as that for the primary PFS analysis. This analysis will be based on the FAS.

#### 9.5.1.1.4 Death or Progression Immediately After More than 1 Consecutively Missed Disease Assessment Visit Treated as a PFS Event

In this sensitivity analysis, death or progression immediately after more than 1 consecutively missed disease assessment visit will be treated as a PFS event. The data censoring rules are the same as those for the primary analysis of PFS except that the death or progression immediately after more than 1 consecutively missed disease assessment visit will be treated as an event rather than a mechanism for censoring. The analysis method will be the same as that for the primary PFS analysis. This analysis will be based on the FAS.

#### 9.5.1.1.5 Initiation of Non-Protocol Anti-Cancer Therapy Treated as neither a PFS Event nor a Censoring Event

In this sensitivity analysis, the use of non-protocol anti-cancer therapy will be treated as neither a PFS event nor a censoring event. The data censoring rules are the same as those for the primary analysis of PFS except that the initiation of non-protocol anticancer therapy will be excluded as a mechanism for censoring. The analysis method will be the same as that for the primary PFS analysis. This analysis will be based on the FAS.

#### 9.5.1.1.6 Analysis based on Scheduled Assessment Dates instead of Actual Assessment Dates

In this sensitivity analysis, the impact on the analysis of PFS due to potential systematic difference in disease assessments between treatment arms will be assessed. The estimated scheduled dates based on the protocol specified disease assessment window will be used instead of the actual assessment dates. If the actual assessment date does not correspond to a scheduled assessment date, the next scheduled assessment date will be used. Other than that, the censoring rules and the analysis method will be the same as those for the primary PFS analysis. This analysis will be based on the FAS.

#### 9.5.1.1.7 Per Protocol Analysis

PFS will be analyzed in the same way as the primary analysis but will be based on the Per Protocol analysis set.

#### 9.5.1.1.8 COVID-19

In order to evaluate the effect of the COVID-19 pandemic the following sensitivity analyses will be performed based on FAS.

Patients will be categorized based on whether randomization occurred on or after versus before October 1, 2019. October 1, 2019 was chosen to allow 6 months pre-pandemic follow-up in the subgroup of patients enrolled before October 1, 2019.

Regional restrictions due COVID-19 pandemic may have caused delays in response assessments regardless of whether a subject contracted COVID-19. The following sensitivity analyses due to COVID-19 pandemic will be performed to assess the impact of delays in response assessments:

- For the censoring rule “Death or PD after more than 1 consecutively missed response assessment”,
  - 2 consecutively missed assessments will be used instead of 1
  - 3 consecutively missed assessments will be used instead of 1
- For the censoring rule “Unconfirmed PD as the final response assessment”, if the subject discontinued due to COVID-19 pandemic, the subject will be censored at the date of discontinuation instead of counted as progressed.

To assess the impact of subjects who contracted or potentially contracted COVID-19, the following sensitivity analyses will be performed:

- Subjects who have a fatal AE due to COVID-19, will be censored at the AE start date instead of counted as progressed.
- Subjects who have a COVID-19 AE prior to progression will be censored at the start date of the AE.

To assess the impact of Pomalidomide + Dexamethasone subjects who had the drug delivered to their home instead of dispensing at the clinical site, the following sensitivity analyses will be performed:

- Pomalidomide + Dexamethasone subjects who had the drug delivered to their home, will be censored at the date of delivery if not progressed by that date.

### *9.5.2 Key Secondary Efficacy Analysis: Overall Response Rate (ORR)*

The key secondary efficacy analysis will compare Melflufen + Dexamethasone and Pomalidomide + Dexamethasone on the ORR, using a Cochran Mantel Haenszel (CMH) test stratified by the randomization stratification factors. The number and percentage, with two-sided 95% exact binomial confidence interval (Clopper-Pearson method [Fleiss, 1981]), of subjects in each category will be presented by arm. The proportional treatment difference with associated two-sided 95% CI will be presented.

ORR will be summarized for the Full and Per Protocol analysis sets.

See Section 10.2 for a description of multiplicity adjustments.

The following sensitivity analyses based on FAS will be conducted to assess the impact of COVID-19 pandemic:

- Pomalidomide + Dexamethasone subjects who had the drug delivered to their home, only response assessment up to the date of delivery will be included.
- Subjects who have an AE due to COVID-19, only response assessments up to the start date of the COVID-19 AE will be included.

Patients will also be categorized based on whether randomization occurred on or after versus before October 1, 2019. October 1, 2019 was chosen to allow 6 months pre-pandemic follow-up in the subgroup of patients enrolled before October 1, 2019.

In addition to the stratified analysis, the unstratified CMH will also be presented based on the FAS.

### *9.5.3 Key Secondary Efficacy Analysis: Overall Survival (OS)*

OS will be estimated and summarized using the same method as for PFS (Section 9.5.1), including median potential follow-up time.

OS will be summarized for the Full and Per Protocol analysis sets.

See Section 10.2 for a description of multiplicity adjustments.

To assess the impact of subjects who contracted or potentially contracted COVID-19, the following sensitivity analyses will be performed:

- Subjects who have a fatal AE due to COVID-19, will be censored at the AE start date.
- Subjects who have an AE due to COVID-19 prior to death will be censored at the start date of the AE.

To assess the impact of Pomalidomide + Dexamethasone subjects who had the drug delivered to their home instead of dispensing at the clinical site, the following sensitivity analyses will be performed:

- Pomalidomide + Dexamethasone subjects who had the drug delivered to their home, will be censored at the date of delivery.

Patients will also be categorized based on whether randomization occurred on or after versus before October 1, 2019. October 1, 2019 was chosen to allow 6 months pre-pandemic follow-up in the subgroup of patients enrolled before October 1, 2019.

### *9.5.4 Other Secondary Efficacy Analyses*

The analysis of subgroups is specified as an other secondary endpoint, see Section 9.5.6 for complete details on prospectively defined subgroups.

The analyses based on investigator is specified as an other secondary endpoint, see Section 9.5.7 for complete details on prospectively defined analyses based on investigator assessments.

#### 9.5.4.1 Duration of Response (DOR)

DOR will be summarized by treatment group for patients who achieve a PR or better. DOR will be summarized for the Full and Per Protocol analysis sets.

For exploratory and descriptive purposes only, the distributions of DOR will be analyzed using the same methods as for PFS (Section 9.5.1).

The same COVID-19 pandemic-related sensitivity analyses described for PFS (Section 9.5.1.1.8) will also be performed for DOR.

#### 9.5.4.2 Clinical Benefit Rate (CBR)

CBR will be estimated and summarized using the same methods as for ORR (Section 9.5.2). CBR will be summarized for the Full and Per Protocol analysis sets.

#### 9.5.4.3 Time to Response (TTR)

TTR will be summarized by treatment group without hypothesis testing. TTR will be summarized for the Full and Per Protocol analysis sets.

#### 9.5.4.4 Time to Progression (TTP)

The distribution of TTP will be estimated and summarized using the same methods as for PFS (Section 9.5.1).

TTP will be summarized for the Full and the Per Protocol analysis sets.

#### 9.5.4.5 Duration of Clinical Benefit

Duration of clinical benefit will be summarized by treatment group for patients whose best confirmed response is MR or better. Duration of clinical benefit will be summarized for the Full and the Per Protocol analysis sets.

For exploratory and descriptive purposes only, the distributions of DOCB will be analyzed using the same methods as for PFS (Section 9.5.1).

#### 9.5.4.6 Best Confirmed Response

Best confirmed response will be estimated and summarized using the same methods as for ORR (Section 9.5.2). Best confirmed response will be summarized for the Full and Per Protocol analysis sets.

### *9.5.5 Exploratory Efficacy Analyses*

#### 9.5.5.1 MRD in Patients that Achieve CR or Better

The number and percentage of patients with MRD or not in patients who achieve CR or better will be presented. MRD will be defined based on external vendor assessment.

#### 9.5.5.2 Changes in M-protein

"Waterfall" plots will display the maximum percent decrease in the M-protein being used to determine response for all patients. Bars will be stacked per best responses.

#### 9.5.5.3 HRQoL

Results and change from baseline at each scheduled visit for the EQ-5D-3L health utility score, each of the 5 dimensions, and the EQ VAS will be summarized with descriptive statistics. In addition, the maximum post-baseline scores will be summarized.

Results and change from baseline at each scheduled visit for the EORTC QLQ-C30 summary score, global health status, functional domains, and symptom scales and EORTC QLQ-MY20 5 domains will be summarized with descriptive statistics. In addition, the maximum post-baseline scores will be summarized.

The time to maximum HRQoL score will be summarized with descriptive statistics by concurrent IMWG response categories. Concurrent is defined as occurring within 7 days of the PRO assessment. If there are multiple response assessments within 7 days, then choose the assessment closest to the date of PRO assessment. If there are 2 response assessments on the same date then worst response is selected.

### *9.5.6 Analyses by Subgroups*

Exploratory analyses of subgroups are planned to evaluate the robustness of results.

PFS, ORR, DOR, OS, CBR, duration of clinical benefit, best confirmed response, TTR, and TTP will also be summarized for the following bulleted subgroups.

In addition, forest plots presenting the hazard ratio and 95% confidence interval for efficacy endpoints PFS, DOR, OS, TTR, TTP, and DOCB will be provided for the following subgroups. The summaries will be based on the Full analysis set.

- Age
  - <65, ≥65 years
  - <75, ≥75 years
- Sex (male, female)
- BSA (below or above median BSA for FAS)
- Race (White, All Other Races)
- Geographic region (United States of America, Europe, Rest of World)
- Number of prior regimens (2, 3-4)
- ISS at baseline (I, II or III)
- R-ISS at baseline (R-I, R-II or R-III)
- Refractory to lenalidomide in last line versus refractory in earlier line
- Refractory status:
  - Refractory to an alkylator (yes, no)
  - Refractory to an anti CD38 mAb (yes, no)
  - Refractory to a PI and IMiD but not to an anti CD38 mAb (yes, no)
- Presence of Extramedullary Disease at Baseline (yes, no)
- Prior autologous stem cell transplant (yes, no)
- Maximum plasma cell involvement (%) at baseline, as assessed with bone marrow assessment (<30, 30 - <60, ≥60)
- Baseline creatinine clearance (ml/min) (<45, 45 - < 60, 60 - < 90, ≥90)
- Baseline LDH (<1.5×ULN, ≥1.5×ULN)
- Baseline albumin (g/L) (<35, ≥35)
- Cytogenetic risk groups as determined by FISH (standard risk, high risk, unknown)
- Version of protocol (enrollment prior to version 3.0 versus after implementation of version 3.0)

In addition to the above subgroup analyses, PFS, OS, and ORR will be summarized by time from prior autologous stem cell transplant to randomization at the following levels:

- <2.5 years
- 2.5 – 5 years
- <5 years
- >5 years
- No transplant

### *9.5.7 Assessments by Investigator*

Summaries of PFS, ORR, DOR, CBR, duration of clinical benefit, best confirmed response, TTR, and TTP will be repeated for the assessments performed by the investigator. These summaries will be provided for both the Full and the Per Protocol analysis sets.

Summaries of PFS, ORR, DOR, CBR, and duration of clinical benefit by subgroups of disease characteristics (Section 9.5.5.1) will be repeated for the assessments performed by the investigator and provided for the FAS only.

A summary table of concordance between Investigator and IRC will be presented.

## 9.6 PK Parameters for Melphalan

Analyses of PK parameters will be based on the PK analysis set.

PK parameters of melphalan per treatment cycle will be summarized as continuous variables using descriptive statistics, including geometric mean and CV.

Additional exploratory analyses, including covariates and the inter-occasion variability, will be described in a separate plan.

## 9.7 Safety Analysis

All analyses of safety will be based on the Safety analysis set.

### *9.7.1 Exposure*

All analyses of exposure will be based on the Safety analysis set.

#### 9.7.1.1 Overall Study Drug Exposure

Duration of treatment will be summarized as a continuous variable using descriptive statistics.

Treatment cycles and patients dosed by cycle will be summarized as counts and percentages, and as a continuous variable using descriptive statistics.

#### 9.7.1.2 Melflufen Exposure

Duration of treatment, treatment cycles, cumulative dose, infusion time, average dose, and dose intensity will be summarized as continuous variables using descriptive statistics.

Number of patients dosed, treatment cycles (overall and per dose), patients with dose modifications, cycles with dose modifications, cycles with dose reduction after dose delay of 3 weeks or longer, reason for dose reduction, patients with dose delay by cycle and categories of delay, and patients with dose reductions by cycle, will be summarized as counts and percentages.

The number patients with dose delays due to COVID-19 pandemic will also be summarized.

K-M estimates of the survival distributions of the time to dose modifications will be tabulated and graphed by treatment arm. The tabulation will include the K-M estimate of the medians, 25th and 75th quartiles, and corresponding 95% CIs, if they can be estimated. The tabular and graphical summaries will include the at-risk counts. The number and percent of subjects censored, reason for censoring, and with events will be presented.

#### 9.7.1.3 Pomalidomide Exposure

Duration of treatment, treatment cycles, cumulative dose, average dose, and dose intensity will be summarized as continuous variables using descriptive statistics.

Number of patients dosed, treatment cycles (overall and per dose), patients with dose modifications, cycles with dose modifications, reason for dose reduction, patients with dose delay by cycle and categories of delay, and patients with dose reductions by cycle, will be summarized as counts and percentages.

Where applicable, the number patients who had their study drug delivered, instead of dispensed at the site, due to COVID-19 pandemic will also be summarized.

#### 9.7.1.4 Dexamethasone Exposure

Duration of treatment, number of doses, cumulative dose, and dose intensity will be summarized as continuous variables using descriptive statistics.

Dose modifications and reasons for permanent discontinuation will be summarized as counts and percentages.

### *9.7.2 Adverse Events*

Number and percentage of patients with TEAEs will be summarized overall by treatment arm by categories of maximum severity, relationship with study drug (either, melflufen/pomalidomide, and dexamethasone), seriousness and dose modifications of study drug (either, melflufen/pomalidomide, and dexamethasone).

Number and percentage of TEAEs will be summarized by treatment arm by SOC and PT by categories of severity, relationship with study drug, seriousness and dose modifications of study drug. A separate summary of non-hematological TEAEs will be summarized by treatment arm by SOC and PT by maximum severity. Non-hematological AEs are defined as all AEs excluding the SOC "Blood and Lymphatic System disorders" and the HLGT “Haematology investigations (incl blood groups)” from the SOC “Investigations” (keeping the rest of the “Investigations” SOC). All summaries of TEAEs will include event counts.

Number and percentage of patients with TEAEs will be summarized for melflufen arm by MedDRA SOC and PT at frequencies of Very common (≥10%); Common (≥1 to <10%); Uncommon (≥0.01 to <1%); Rare (≥0.001 to <0.01%); Very rare (<0.001%).

Summaries that are displayed by SOC and PT will be ordered by descending order of incidence per SOC and PT within each SOC for the total group.

Any AEs related to COVID-19 will be presented as separate PTs specific to COVID-19 or coronavirus.

Number and percentage of patients with TEAEs, SAEs, fatal TEAEs, and AEs leading to study drug discontinuation, by SOC and PT will also be summarized by subgroups listed in Section 9.7.10.

Separate listings of serious AEs, AEs leading to dose modification of melflufen/pomalidomide, AEs leading to discontinuation of melflufen/pomalidomide, AEs leading to dose modification of dexamethasone, or AEs leading to discontinuation of dexamethasone will be provided. AEs that are not treatment-emergent will be provided in listings.

### *9.7.3 Adverse Events of Special Interest*

All AESIs defined in Section 8.11.3 will be summarized as counts and percentages, overall and per severity grade by treatment arm. SMQ Infective pneumonia will be summarized using all terms and narrow terms only, separately.

AESIs neutropenia concomitant to infection and thrombocytopenia concomitant to hemorrhage will be summarized as counts and percentages by treatment arm.

For the AESIs of neutropenia, febrile neutropenia, thrombocytopenia, anemia, infections, infective pneumonia and hemorrhage, and thromboembolism, the maximum toxicity grade during each cycle and at the End of Treatment visit will be summarized respectively by treatment arm. These tables will be presented for three subsets of cycles during which the AESI's starts: 1) excluding last cycle per patient; 2) including the last cycle per patient; and 3) only the last cycle per patient.

### *9.7.4 Deaths*

Number of deaths and the cause of death, as collected on the Patient Death CRF, will be summarized by treatment arm and total as counts and percentages, overall, and as categorized. All deaths which occur on study are recorded on the Patient Death CRF, i.e. on treatment and off treatment. The total number of deaths will not be equivalent to the number of fatal TEAEs.

A listing of all deaths will be provided.

### *9.7.5 Hematology, Serum Chemistry, and Coagulation*

Results and change from baseline at each scheduled visit for all hematology, serum chemistry, and coagulation parameters will be summarized by treatment arm with descriptive statistics. Corresponding line series plots of average values will also be provided by treatment arm.

Toxicity grade of applicable parameters will be summarized by treatment arm as counts and percentages in shift tables of baseline versus worst toxicity grade through the End of Treatment visit. Number of patients with grade 3 or higher toxicity will be summarized as counts and percentages by cycle. A separate listing of all laboratory results corresponding to grade 3 or 4 will be provided.

For hemoglobin, leukocytes (WBC), lymphocytes, ANC and platelet count, the maximum toxicity grade recorded during each cycle and at the End of Treatment visit will be summarized separately.

For ANC and platelet count, results and change from the Day 1 pre-infusion value at Days 8, 15, and 22 during each cycle will be summarized as descriptive statistics by treatment arm.

Time, in days, to first occurrence of grade 3 or 4 neutropenia (ANC), time to first grade 4 neutropenia (ANC), time to first occurrence of grade 3 or 4 thrombocytopenia (platelet count), and time to first grade 4 thrombocytopenia (platelet count) will be summarized descriptively by treatment group. Time, in days, to resolution of first grade 3 or 4 neutropenia (ANC), time to resolution of first grade 4 neutropenia (ANC), time to resolution of first grade 3 or 4 thrombocytopenia (platelet count), and time to resolution of first grade 4 thrombocytopenia (platelet count) will be summarized descriptively by treatment group. Resolution is defined as less than grade 3 for grade 3 or 4 analyses and less than grade 4 for grade 4 analyses. Duration of grade 3 or 4 neutropenia (ANC), duration of grade 4 neutropenia (ANC), duration of grade 3 or 4 thrombocytopenia (platelet count), and duration of grade 4 thrombocytopenia (platelet count) by cycle will also be summarized descriptively. Duration in days will be calculated from first lab date in the cycle with grade 3 or 4 to the next result in the same cycle less than grade 3 (or less than grade 4 for grade 4 only analyses) plus 1. Per protocol a patient should not initiate a new cycle if ANC or platelet count has a CTCAE grade 3 or 4. In the cases where a new cycle was initiated despite having a grade 3 or 4 ANC or platelet count, the observations will be excluded.

### *9.7.6 Vital Signs and Weight*

Results and change from baseline for weight, blood pressure, pulse, respiratory rate and temperature will be summarized by treatment arm by visit. Results and change from pre-infusion to post-infusion for blood pressure, pulse, respiratory rate and temperature will be summarized by treatment arm and cycle. The nominal pre and post infusion timepoints on the CRF will be used as vital signs assessment time is not collected.

### *9.7.7 ECOG Performance Status*

ECOG performance status will be summarized by treatment arm as counts and percentages using shift tables of baseline versus worst performance status during study. The number of patients with improvement of ≥1 unit and ≥2 units respectively at the last available visit and at the End of Treatment visit will be summarized as counts and percentages.

### *9.7.8 Physical Examination*

Physical examination results will be listed without summary.

### *9.7.9 12-Lead Electrocardiograms*

QTc-Fridericia (QTcF) interval results and changes from baseline will be summarized by treatment arm with descriptive statistics at baseline and End of Treatment visit. QTcF is calculated in the database as $QTcF = QT / (RR)^{1/3}$ assuming units of milliseconds.

### *9.7.10 Analyses by Subgroups*

Analysis of TEAEs, AESIs, SAEs, fatal TEAEs, TEAEs leading to discontinuation, and TEAEs leading to dose modifications will be provided by the following subgroups:

- Age
  - <65, ≥65 years
  - <75, ≥75 years
- Sex (male, female)
- BSA (below or above median BSA for FAS)
- Race (White, All Other Races)
- Geographic region (United States of America, Europe, Rest of World)
- Prior Autologous Transplant (Yes, No)
- Time from Prior Autologous Stem Cell Transplant to Randomization
  - <2.5 years
  - 2.5 – 5 years
  - <5 years
  - >5 years
  - No transplant

## 10 STATISTICAL/ANALYTICAL ISSUES

### 10.1 Handling of Dropouts or Missing Data

#### *10.1.1 Efficacy Assessments*

The handling of dropouts and missing disease status assessments for the efficacy variables is described in their definitions. Table 3 describes how dropouts and missing data impact the calculation of the time to event variables. Missing data will not be estimated or carried forward for any of the other summaries.

### *10.1.2 Safety Assessments*

#### 10.1.2.1 Adverse Events

Adverse events with missing relationship are considered related for purposes of summaries. Imputed relationship will not be included in the listings.

Adverse events with missing severity are considered severe (grade 3) for purposes of summaries. Imputed severity will not be included in the listings.

Adverse events with missing action taken with study drug are excluded from analyses.

#### 10.1.2.2 Laboratory Assessments

The following imputations will be made for missing reported units:

- Beta-2 Microglobulin, FLCs
    - Values less than 10: mg/L
    - Values greater than or equal to 1000: µg/L
- Creatinine clearance: mL/min
- ALT, AST, Alkaline Phosphatase: U/L
- Albumin
    - Values less than 10: g/dL
    - Values greater than or equal to 10: g/L
- INR: RATIO
- Prothrombin Time (PT): seconds (sec)
- Hematocrit
    - Values greater than 1: %
    - Values less than or equal to 1: RATIO
- Hemoglobin
    - Values less than 30: g/dL
    - Values greater than or equal to 30: g/L
- RBC: 10^12/L.
- Platelets:
    - Values less than 1000: 10^9/L.

- Values greater than or equal to 1000: /µL

- WBC
  - Values less than 20: 10^9/L.
  - Values greater than or equal to 20: /µL
- WBC differential counts
  - Values less than 10: 10^9/L.
  - Values greater than or equal to 100: /µL

Prothrombin times reported as %, which will not be imputed, will be omitted from summaries.

### *10.1.3 Dates and Times*

If only a partial date is available and is required for a calculation (e.g., time since diagnosis, time since most recent relapse, determination of whether a medication is concomitant or an AE is treatment-emergent), the following standards will be applied:

- Start dates (e.g., AE onset date or start date of medication, date of diagnosis, date of relapse)

  For missing start day only - Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.

  For missing start day and month - Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
- Stop dates (e.g., AE resolution date or stop date of medication)
  For missing stop day only - Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31)

  For missing stop day and month - Day and month will be imputed as the last day of the year (i.e., 31 December)

If a patient is known to be dead, but the death date is unknown, the death date will be imputed as the survival status contact date where the patient was known to have died.

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2011, 2009).

If time is not available but is required for a calculation (e.g., timing of AE vs study drug administration) the most conservative approach should be used, i.e. assuming that the time of AE was after study drug administration or that the time of concomitant medication was after AE.

#### *10.1.4 Dates for Prior Autologous Transplant Subgroup*

If only a partial date is available and is required for a calculation (e.g., time since prior autologous transplant to randomization), the following standards will be applied:

- Start dates

  For missing start day only - Day will be imputed as the 15$^{th}$ day of the month.

  For missing start day and month - Day and month will be imputed as the first day of the July (i.e., 1 July).

### 10.2 Multiplicity/Multiple Comparisons

For the primary and the key secondary efficacy analyses, the overall 2-sided level of significance will be alpha = 0.05. The hypothesis testing of key secondary endpoints will be conducted using a gatekeeping procedure based on a closed fixed-sequence test, provided the primary efficacy endpoint comparison is statistically significant at an alpha level 0.05. If this comparison is not statistically significant, then the comparison of key secondary efficacy endpoints will be considered nominal, descriptive and exploratory. This procedure controls the study-wise type I error and is described below.

1. First Melflufen + Dexamethasone and Pomalidomide + Dexamethasone will be compared with respect to the primary efficacy endpoint. If the comparison achieves statistical significance at the 2-sided 0.05 level in favor of Melflufen + Dexamethasone, then
2. Melflufen + Dexamethasone and Pomalidomide + Dexamethasone will be compared with respect to ORR. If the comparison achieves statistical

significance at the 2 sided 0.05 level in favor of Melflufen + Dexamethasone, then
3. Melflufen + Dexamethasone and Pomalidomide + Dexamethasone will be compared with respect to OS.

If at any step defined above, the comparison is not statistically significant at the 2-sided 0.05 level, then the remaining comparisons in the stated hierarchy will be considered nominal, descriptive and exploratory. The study-wise type I error will be maintained with the above closed procedure.

## 10.3 Interim Analysis and Data Monitoring

### *10.3.1 Interim Analysis*

No interim analyses are planned.

### *10.3.2 Data Monitoring Committee*

An independent DMC will perform surveillance of efficacy/safety balance at regular intervals during the study, using summaries and listings that will be unblinded to the assigned treatment arm. All activities and processes surrounding the DMC will be outlined in the DMC Charter.

### *10.3.3 Independent Review Committee (IRC)*

An Independent Review Committee (IRC) will assess all tumor responses and progression as detailed in the IRC Charter. The IRC members will be blinded to all treatment data and perform their reviews in closed-meeting sessions. All activities and processes surrounding the IRC will be outlined in the IRC Charter.

## 10.4 Changes to Protocol Planned Analyses

Per FDA feedback received 27APR2021, the following updates were made:

- Primary endpoint analysis based on stratified log-rank test
- DOR moved from key secondary objective/endpoint to other secondary objective/endpoint, removing it from multiplicity adjustment.
- Efficacy subgroup analyses and DOCB analyses clarified to be exploratory

The PK Analysis Set was added for evaluation of melphalan PK endpoints.

Exploratory analyses to evaluate the effect of the COVID-19 pandemic were added.

The protocol specifies that TTP will be summarized without analysis, however, TTP will be analyzed using K-M methods.

Duration of MR and SD will not be summarized separately.

Unstratified CMH analyses were added for consistency with time-to-event unstratified analyses.

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