

Janssen Research & Development

Statistical Analysis Plan

**Daratumumab plus Cyclophosphamide, Bortezomib and Dexamethasone (Dara-CyBorD)
in Previously Untreated and Relapsed Subjects with Multiple Myeloma**

Protocol 54767414MMY2012; Phase 2

JNJ-54767414 (daratumumab)

Authors: [REDACTED]
Date: 12 February 2018

Status: Approved
Date: 12 February 2018
Prepared by: Janssen Research & Development
Document No.: EDMS-ERI-157307205

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

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

TABLE OF CONTENTS

| | |
|------------------------------------------------------------|-----------|
| TABLE OF CONTENTS | 2 |
| ABBREVIATIONS | 4 |
| 1. INTRODUCTION..... | 5 |
| 1.1. Trial Objectives | 5 |
| 1.1.1. Primary Objective | 5 |
| 1.1.2. Secondary Objectives..... | 5 |
| 1.1.3. Exploratory Objective..... | 5 |
| 1.2. Trial Design | 5 |
| 1.3. Statistical Hypotheses for Trial Objectives..... | 6 |
| 1.4. Sample Size Justification | 6 |
| 1.5. Randomization and Blinding | 7 |
| 2. GENERAL ANALYSIS DEFINITIONS | 7 |
| 2.1. Visit Windows..... | 7 |
| 2.2. Pooling Algorithm for Analysis Centers..... | 7 |
| 2.3. Analysis Sets..... | 7 |
| 2.4. Definition of Subgroups..... | 8 |
| 2.5. Study Day and Relative Day | 9 |
| 2.6. Baseline Measurement | 9 |
| 2.7. Unique Lab value | 9 |
| 2.8. Imputation of Missing/Partial Dates | 10 |
| 2.8.1. Missing/Partial Adverse Event Onset Date..... | 10 |
| 2.8.2. Missing/Partial Adverse Event End Date..... | 10 |
| 2.8.3. Partial Multiple Myeloma Diagnosis Date | 11 |
| 2.8.4. Partial Concomitant Medication Start/End Date | 11 |
| 2.9. General Analysis Method | 11 |
| 3. INTERIM ANALYSIS AND DATA REVIEW COMMITTEE | 12 |
| 3.1. Interim Analysis..... | 12 |
| 3.2. Data Review Committee | 12 |
| 4. SUBJECT INFORMATION..... | 12 |
| 4.1. Demographics and Baseline Characteristics | 12 |
| 4.2. Disposition Information..... | 13 |
| 4.3. Extent of Exposure..... | 13 |
| 4.4. Protocol Deviations | 14 |
| 4.5. Pre-study and Concomitant Therapies | 14 |
| 5. EFFICACY | 14 |
| 5.1. Analysis Specifications..... | 14 |
| 5.1.1. Level of Significance..... | 14 |
| 5.1.2. Data Handling Rules..... | 14 |
| 5.2. Primary Efficacy Endpoint | 15 |
| 5.2.1. Definition | 15 |
| 5.2.2. Analysis Methods..... | 15 |
| 5.3. Secondary Efficacy Endpoints | 15 |
| 5.3.1. Progression-Free Survival | 15 |
| 5.3.1.1. Definition..... | 15 |
| 5.3.1.2. Analysis Methods | 16 |
| 5.3.2. Time to Disease Progression (TTP) | 16 |
| 5.3.2.1. Definition..... | 16 |
| 5.3.2.2. Analysis Methods | 16 |
| 5.3.3. Overall Survival (OS)..... | 17 |
| 5.3.3.1. Definition..... | 17 |

| | | |
|-----------|--------------------------------------------|-----------|
| 5.3.3.2. | Analysis Methods | 17 |
| 5.3.4. | Overall Response Rate (ORR) | 17 |
| 5.3.4.1. | Definition | 17 |
| 5.3.4.2. | Analysis Methods | 17 |
| 5.3.5. | Duration of Response (DOR) | 17 |
| 5.3.5.1. | Definition | 17 |
| 5.3.5.2. | Analysis Methods | 18 |
| 5.3.6. | Time to Response | 18 |
| 5.3.6.1. | Definitions | 18 |
| 5.3.6.2. | Analysis Methods | 18 |
| 5.4. | Subgroup Analyses | 18 |
| 6. | SAFETY | 19 |
| 6.1. | Adverse Events | 19 |
| 6.2. | Clinical Laboratory Tests | 20 |
| 6.3. | Vital Signs and Physical Examination | 21 |
| 6.4. | ECOG Performance Status | 22 |

ABBREVIATIONS

| | |
|-------------|--------------------------------------------------------------------------|
| AE | Adverse Event |
| ASCT | Autologous Stem Cell Transplantation |
| C1D1 | Cycle 1 Day 1 |
| C1D2 | Cycle 1 Day 2 |
| CTC | Common Toxicity Criteria |
| Dara-CyBorD | Daratumumab Plus Cyclophosphamide, Bortezomib And Dexamethasone |
| DRC | Data Review Committee |
| DPS | Data Presentation Specification |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| HDT | High-Dose Chemotherapy |
| IMWG | International Myeloma Working Group |
| ISS | International Staging System |
| MedDRA | Medical Dictionary For Regulatory Activities |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria For Adverse Events |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAEs | Treatment-Emergent Adverse Events |
| ULN | Upper Limit Normal |
| WHO | World Health Organization |

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the planned analysis for study protocol 54767414MMY2012: Daratumumab plus Cyclophosphamide, Bortezomib and Dexamethasone (Dara-CyBorD) in Previously Untreated and Relapsed Subjects with Multiple Myeloma.

1.1. Trial Objectives

1.1.1. Primary Objective

The primary objective is to evaluate complete response + very good partial response (CR+VGPR) rate following 4 cycles of induction therapy of daratumumab plus CyBorD (Dara-CyBorD), in previously untreated subjects, and in relapsed subjects with multiple myeloma, as defined by the International Myeloma Working Group (IMWG) criteria.

1.1.2. Secondary Objectives

The secondary objectives are to evaluate, in previously untreated subjects and in relapsed subjects with multiple myeloma:

- Overall response rate (ORR including CR+VGPR+partial response [PR])
 - Following 4 cycles of Dara-CyBorD induction therapy
 - At the end of 4 to 8 cycles of Dara-CyBorD induction therapy
 - Post-transplant (in subjects who undergo high dose therapy and autologous stem cell transplantation)
 - At the end of 12 cycles of daratumumab maintenance therapy
- Time to VGPR or better
- Time to PR or better
- Progression-free survival (PFS) rate: at 1 year and 3 years
- Overall survival (OS) rate: at 1 year and 3 years
- Safety and tolerability of Dara-CyBorD
- Safety profile of split-dose initial infusions of daratumumab administered as 8 mg/kg on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 2 (C1D2).

1.1.3. Exploratory Objective

An exploratory objective is to evaluate the clinical efficacy of Dara-CyBorD in molecular subgroups, including: del17p, del13, t(4;14), t(11;14), t(14;16).

1.2. Trial Design

This is a multicenter, single-arm, Phase 2 study, evaluating the combination of Dara-CyBorD in subjects with previously untreated multiple myeloma irrespective of eligibility for HDT and ASCT and subjects with relapsed multiple myeloma following one prior line of therapy.

Approximately 100 subjects will be enrolled into this study with at least 40 previously untreated multiple myeloma subjects. Due to slow enrollment of subjects with relapsed multiple myeloma following one prior line of therapy, this cohort is closed to enrollment in Amendment 2 of the protocol.

Subjects will be assigned to receive Dara-CyBorD as induction on a 28-day cycle length. All subjects will receive 4 to 8 cycles of oral cyclophosphamide 300 mg/m² on Days 1, 8, 15, and 22; subcutaneous (SC) bortezomib 1.5 mg/m² on Days 1, 8, and 15; and oral or IV dexamethasone 40 mg weekly. Subjects will concurrently receive daratumumab on 28-day cycles (8 mg/kg IV on C1D1, C1D2; 16 mg/kg IV on Cycle 1, Days 8, 15, 22; Cycle 2, Days 1, 8, 15, 22; Cycles 3-6, Days 1,15; Cycles 7-8, Day 1; Maintenance, Day 1 for 12 cycles).

Treatment phases consist of induction therapy with 4 to 8 cycles of Dara-CyBorD, consolidation therapy with HDT/ASCT for eligible subjects, and maintenance therapy. Following induction and/or consolidation therapy with ASCT, subjects will receive maintenance therapy with daratumumab alone for twelve 28-day cycles or until disease progression (whichever occurs first). Maintenance therapy for subjects who have ASCT should begin approximately 90 days after ASCT. Follow-up for all subjects will continue up until 36 months after the start of induction therapy (Cycle 1 Day 1).

Throughout the study, subjects will be monitored closely for adverse events, laboratory abnormalities, and clinical response, as specified in the Time and Events Schedule of the protocol. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE Version 4.03) will be used to grade toxicity throughout the study.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is that CR+VGPR rate following 4 cycles of induction therapy of Dara-CyBorD in previously untreated subjects is higher than 60%, and in relapsed subjects is higher than 30%, as defined by the IMWG criteria. The hypotheses are as follow:

For previously untreated subjects:

$$H_0: p \leq 0.6 \quad \text{vs} \quad H_A: p > 0.8$$

For relapsed subjects:

$$H_0: p \leq 0.3 \quad \text{vs} \quad H_A: p > 0.5 ,$$

where p is the proportion of subjects with CR+VGPR.

1.4. Sample Size Justification

The historical CR+VGPR rate after 4 cycles of CyBorD induction therapy is 60% in previously untreated multiple myeloma subjects. Thirty-three (33) enrolled subjects will provide 80% power at a 5% 1-sided significance level to detect an absolute 20% increase over 60% with Dara-CyBorD.

The historical CR+VGPR rate after 4 cycles of CyBorD induction therapy is 30% in previously relapsed multiple myeloma subjects. Thirty-five (35) enrolled subjects will provide 80% power at a 5% 1-sided significance level to detect an absolute 20% increase over 30% with Dara-CyBorD.

With the planned enrollment of 100 subjects, with a minimum of 40 newly diagnosed multiple myeloma subjects, at least 80% power will be achieved to detect an absolute 20% increase in the untreated cohort at the 5% 1-sided significance level. In Amendment 2 of the study protocol, enrollment of subjects in the relapsed cohort is closed and expected not to exceed 15 subjects. No inferential statistics will be performed for the relapsed cohort.

1.5. Randomization and Blinding

This is a single-arm study where all enrolled subjects will be treated with the same treatment combination of Dara-CyBorD. There is no randomization and unblinding is not required.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

For analyses of data by cycle, if data are collected by date (e.g., AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study treatment administration data. The start date of a particular cycle is defined as the date of the first scheduled dose of any component of the study treatment, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or the minimum of last study treatment date plus 30 days or subsequent anti-myeloma therapy minus 1 day, if the end of treatment visit date is not available.

In general, if data (e.g., laboratory and vital sign etc.) are collected by cycle, the nominal cycle will be used to summarize data.

2.2. Pooling Algorithm for Analysis Centers

Data from participating centers in the study will be pooled together for analyses purpose.

2.3. Analysis Sets

The following analysis sets are defined.

- Full analysis set (FAS): is defined as enrolled subjects who have provided informed consent and met the study eligibility criteria. Analyses of demographics, baseline characteristic and time-to-event variables (e.g., PFS and OS) will be based on this population.
- Safety analysis set: is defined as enrolled subjects who received at least 1 dose (partial or complete) of study treatment (Daratumumab, Cyclophosphamide, Bortezomib or Dexamethasone). This population will be used for all safety related analyses.

- Response-evaluable set: is defined as subjects who have measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post baseline disease assessment. Measurable disease is defined as follows:
 - Serum M-protein level ≥ 1.0 g/dL or urine M protein level ≥ 200 mg/24 hours; or
 - Immunoglobulins A, D, E or M multiple myeloma: serum M-protein level ≥ 0.5 g/dL or urine M-protein level ≥ 200 mg/24 hours; or
 - Light chain multiple myeloma without measurable disease in the urine: serum Ig FLC ≥ 10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio

Analyses of the primary endpoint of CR+VGPR response and secondary response-related endpoints such as ORR and duration of response will be based on this population.

2.4. Definition of Subgroups

The following subgroup analyses may be performed for the newly diagnosed patients for the primary endpoint, PFS, and OS, depending on the number of subjects in each subgroup as shown in Table 1.

Table 1: Subgroup Analyses of Efficacy Endpoints

| Subgroup | Definition |
|---------------------------|-----------------------------|
| Sex | Male, Female |
| Age | <65 years, ≥ 65 years |
| Type of MM | IgG, Non-IgG |
| ECOG performance score | 0, ≥ 1 |
| Cytogenetics ^a | high risk vs. standard risk |

^a Includes: del17p, del13, t(4;14), t(14;16), and t(11;14). High risk and standard risk defined below.

For each of the del17p, del13, t(4;14), t(14;16) and t(11;14), the cytogenetic abnormality finding for a subject can be classified into the following 3 groups:

- Yes (abnormality): if there is any abnormality finding from FISH testing by bone marrow aspirate
- No: there is no abnormality finding
- Not done: the testing is not done.

For cytogenetics profile, two cytogenetic risk categories are defined as:

- High risk: An abnormality finding in any of del17p, del13, t(4;14), and t(14;16).
- Standard risk: No abnormality findings in all of del17p, del13, t(4;14) and t(14;16).

Additionally, patients who have consolidation therapy with HDT/ASCT after 4 to 8 cycles induction therapy of Dara-CyBorD is considered as a separate ASCT subgroup for analysis purpose.

Given that enrollment in the relapsed group is stopped early, subgroup analyses will not be performed for the relapsed group.

2.5. Study Day and Relative Day

Study treatment refers to Daratumumab, Cyclophosphamide, Bortezomib and Dexamethasone (Dara-CyBorD). Study drug refers to Daratumumab.

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

The first study treatment date is defined as the earliest date of non-zero dose of the following administration: Daratumumab, Cyclophosphamide, Bortezomib or Dexamethasone. The last study treatment date is defined as the latest date of non-zero dose of the 4 treatment administrations.

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

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

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

A subject is considered as treated in a cycle if he/she receives any nonzero dose of Daratumumab, Cyclophosphamide, Bortezomib or Dexamethasone in that cycle.

2.6. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study treatment administration (including time if time is available, with exception of parameters associated with disease-related efficacy assessment such as SPEP, UPEP, kappa, lambda, kappa/lambda ratio, serum calcium, and albumin).

2.7. Unique Lab value

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

2.8. Imputation of Missing/Partial Dates

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

Additional imputation rules may be specified in the data presentation specification (DPS).

2.8.1. Missing/Partial Adverse Event Onset Date

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

- When month and year are present and the day is missing,
 - If the onset month and year are the same as the month and year of first study treatment, the day of first study treatment is imputed. If the imputed start date is later than end date, the day-component of the AE end date (possibly imputed) is imputed
 - If the onset month and year are not the same as the month and year of first study treatment, then the first day of the month is imputed
- When only a year is present or no components of the onset date are present,
 - If the onset year is the same as the year of first study treatment. If AE end date is available and is prior to first study treatment, the day and month of AE end date are imputed. Otherwise, the day and month of first study treatment are imputed
 - If the onset year is different from the year of first study treatment, the 1st of January is imputed
- If the onset date is completely missing, the date of first study treatment is imputed as the onset date.

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

2.8.2. Missing/Partial Adverse Event End Date

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

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

- If the imputed date is later than the date of death (if available), the date of death will be used as the imputed date instead.

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

2.8.3. Partial Multiple Myeloma Diagnosis Date

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

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

2.8.4. Partial Concomitant Medication Start/End Date

In case of partially missing concomitant medication start/end dates, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed.

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

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

2.9. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range (maximum and minimum). Categorical variables will be summarized using frequency and percentage. For time-to-event variables including PFS, OS, etc., Kaplan-Meier method will be used for descriptive summaries and KM plots.

Summary tabulations for baseline characteristics, safety parameters including AEs and lab will be presented for newly diagnosed subjects, relapsed subjects and all subjects combined as side-by-side columns. For efficacy parameters, summary tabulations will be presented for newly diagnosed subjects and relapsed subjects only (no display for all subjects).

3. INTERIM ANALYSIS AND DATA REVIEW COMMITTEE

3.1. Interim Analysis

There is no interim efficacy analysis planned for this study. However, three interim safety analyses are planned. The first interim safety analysis will occur after at least 20 subjects are treated for at least 1 cycle of study treatment (or discontinue before the end of Cycle 1). The second interim safety analysis will occur after at least 50 subjects complete cycle 1 of study treatment (or discontinue before the end of Cycle 1) with a focus on infusion related reactions during cycle 1. The third interim safety analysis will occur after at least 50 subjects are treated for at least 4 cycles (or discontinue before the end of Cycle 4). A separate SAP was prepared that outlines the interim safety analyses. All three planned interim safety analyses have completed.

3.2. Data Review Committee

An internal Data Review Committee will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study. The committee will meet periodically to review interim safety data and will also perform the predetermined interim safety review as detailed in Section 3.1, Interim Analysis. After the review, the committee will make recommendations regarding the continuation of the study. The details will be provided in a separate committee charter.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

The following parameters will be summarized using full analysis set:

- Demographic and baseline characteristic variables: age (continuous), age category (< 65 years, 65 to < 75 years, and ≥75 years), sex, ethnicity, race, weight (kg), height (cm), and ECOG performance status (0, 1, 2)
- Baseline disease characteristics: type of myeloma (IgA, IgD, IgE, IgG, IgM, light chain, biclonal, Serum free light chain only), ISS staging (I, II, III), cytogenetics profile (del17p, del13, t(4;14), t(11;14), t(14;16)), time since initial diagnosis (years), Line of prior therapy (0, 1), number of lytic bone lesions (None, 1-3, 4-10, more than 10), presence of diffuse myeloma-related osteopenia (Yes, No), number extramedullary plasmacytomas (0, ≥1), bone marrow % plasma cells (10, 10 – 30, >30),
- Disease related laboratory values: hemoglobin (g/L), hemoglobin category (< 80 g/L, 80 – 100 g/L, >100 g/L), platelets (giga/L), platelets category (< 75, ≥ 75), calcium (mmol/L), calcium category (>ULN, ≤ ULN), corrected calcium (mmol/L), corrected calcium category (> ULN, ≤ ULN), creatinine(umol/L), creatinine category (> ULN, ≤ ULN), creatinine clearance (mL/min), creatinine clearance category (> 60 mL/min, 30 - 60 mL/min, < 30 mL/min), beta2 microglobulin (mg/L), beta2 microglobulin category (< 3.5 mg/L, 3.5 – < 5.5 mg/L, ≥ 5.5 mg/L), albumin (g/L), and albumin category (< 35 g/L, ≥ 35 g/L)
- Baseline laboratory tests: Summary statistics as well as frequencies of CTC toxicity grade will be provided for the following parameters:

- Hematology: white blood cell (WBC) count, platelets (giga/L), lymphocytes, neutrophils, red blood cell (RBC) count, hematocrit.
- Serum chemistry: potassium, total bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), ionized calcium.
- General ongoing medical history by body system as reported on eCRF. A listing will be generated for ongoing medical history.
- The incidence of subjects receiving radiotherapy, systemic therapy, or palliative supportive care for second primary malignancy will be provided.
- Baseline vital signs: pulse, systolic blood pressure, and diastolic blood pressure.
- Baseline ECG overall interpretation: normal, abnormal and clinically significant, or abnormal and not clinically significant.

4.2. Disposition Information

The number of subjects (%) who discontinued study treatment will be summarized using the full analysis set, together with reasons of discontinuation reported on eCRF. The number of subjects who discontinued from study and the reported reasons on eCRF will be presented similarly.

An overview of subject disposition in the study will be provided too. The overview includes a summary of total number of subjects who are enrolled into each treatment group, the number (%) of subjects who entered into each treatment phase, and their status (completed, DC and on-going) in each phase (induction, ASCT, maintenance, and follow-up) will be provided.

4.3. Extent of Exposure

Extent of exposure to study treatments will be summarized based on the full analysis set including the following:

- The number and percentage of subjects treated within each cycle.
- Duration of study treatment, defined as the number of months from the date of the first administration of study treatment to the date of the last dose.
- The duration of Daratumumab infusion (hours) for first infusion, second infusion, and subsequent infusions
- Total dose administered overall for Daratumumab (mg/kg), Cyclophosphamide (mg/m²), Bortezomib (mg/m²), or Dexamethasone (mg).
- Dose intensity for each treatment, which is calculated as the sum of total doses (mg/kg, or mg/m², or mg) received in all cycles divided by the number of treatment cycles.
- Relative dose intensity (%), which is defined as the ratio of the total actually received dose and total planned dose. Total planned dose is calculated as the sum of planned dose level over the number of recorded infusions or dose administrations (zero & non-zero dosing records included).
- Number of subjects with cycle delay, dose skipped (not administered), adjusted, and stopped for Daratumumab, Bortezomib, and Dexamethasone and dose reduced for Cyclophosphamide, as well as the respective reasons.

4.4. Protocol Deviations

The incidence of major protocol deviations will be summarized based on the full analysis set. A listing of all major protocol deviations will be provided.

4.5. Pre-study and Concomitant Therapies

Pre-study therapies are therapies administered up to 30 days before first dose of study treatment. Concomitant therapies are therapies recorded throughout the study beginning with start of the first dose of study drug until 30 days following completion of the last dose of study drug. Medications will be summarized by World Health Organization (WHO) drug therapeutic class and generic medication name using the full analysis set. Pre- and post-infusion medications will also be summarized separately. This will be provided using the full analysis set.

Additionally, number of subjects who received HDT/ASCT after 4 to 8 cycles of induction therapy with Dara-CyBorD will be summarized, and their stem cell yield will be summarized.

5. EFFICACY

The primary analysis will be performed after all enrolled subjects have completed 4 cycles of induction therapy, disease evaluation or have been discontinued from study treatment by this time point. A final data analysis, to update secondary endpoints and safety, will occur at the end of study when all subjects have completed follow-up at 36 months after the start of induction therapy, or until death or withdrawal of consent for study participation, whichever occurs first.

Response to study treatment and progressive disease will be evaluated by a validated computer algorithm to calculate IMWG response. As a sensitivity analysis, investigator assessments of response and disease progression using the IMWG response criteria will also be performed.

All response related efficacy analyses will be based on the Response-evaluable set and time to events including PFS, time to disease progression (TTP), OS and time to response analyses will be based on the full analysis set.

5.1. Analysis Specifications

5.1.1. Level of Significance

The primary hypothesis is to be tested at a 1-sided 0.05 significance level for the previously untreated subjects. All 95% confidence interval presented will be 2-sided.

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint values.

5.2. Primary Efficacy Endpoint

5.2.1. Definition

The primary endpoint is the proportion of subjects achieving either a complete response (CR) or a very good partial response (VGPR), [CR+VGPR], following 4 cycles of induction therapy with Dara-CyBorD, as determined by the validated computer algorithm using the IMWG criteria.

5.2.2. Analysis Methods

The number and percentage of subjects with [CR+VGPR] response achieved after 4 cycles of induction therapy will be tabulated. The proportion of [CR+VGPR] response will be compared to a reference value of 0.6 at a 1-sided 0.05 significance level using a normal approximation to the binomial distribution for the previously untreated subjects. In Amendment 2 of the study protocol, enrollment of subjects in the relapsed cohort is closed and expected not to exceed 15 subjects. No inferential statistics will be performed for the relapsed subjects. In addition, a 2-sided 95% confidence interval for [CR+VGPR] will be provided.

A sensitivity analysis of [CR+VGPR] rate after 4 cycles of induction therapy based on investigator assessment according to the IMWG response criteria will be performed.

5.3. Secondary Efficacy Endpoints

5.3.1. Progression-Free Survival

5.3.1.1. Definition

PFS is defined as the duration from the date of first dose (start of induction) to the date of first documented evidence of progressive disease based on the computerized algorithm according to the IMWG response criteria or death due to any cause, whichever occurs first. Subjects who start subsequent antimyeloma therapies for multiple myeloma without disease progression will be censored at the last disease assessment before the start of subsequent therapies. Subjects who withdrew consent from the study before disease progression will be censored at the last disease assessment before withdrawal of consent to study. Subjects who are lost to follow-up will be censored at the last disease assessment before subjects are lost to follow-up. Subjects who have not progressed and are still alive at the cutoff date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at the first dose date.

Determination of dates of PFS event and dates for censoring is summarized in [Table 2](#) as follows.

Table 2: PFS Event and Censoring Method

| Situation | Date of Progression or Censoring | Outcome |
|-----------|----------------------------------|---------|
|-----------|----------------------------------|---------|

| | | |
|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Disease progression prior to start of subsequent antimyeloma therapy | Earliest date that indicates disease progression | PFS event |
| Death prior to start of subsequent antimyeloma therapy | Date of death | PFS event |
| No post-baseline disease assessment | First dose date | Censored |
| Other (e.g., withdrawal of consent to study participation, lost to follow-up, start of subsequent antimyeloma therapy etc.) | Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, or subsequent antimyeloma treatment | Censored |

5.3.1.2. Analysis Methods

Kaplan-Meier method will be used to estimate the distribution of PFS. The estimated median PFS with 95% CI will be provided. In addition, the number and percentage of subjects who had a PFS event or were censored will be reported. In addition, 1, 2, and 3-years PFS rates with 95% CI will be estimated by Kaplan-Meier method. Kaplan-Meier PFS curves will also be generated.

A sensitivity analysis of PFS, in which progressive disease is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner as described above.

5.3.2. Time to Disease Progression (TTP)

5.3.2.1. Definition

TTP is defined as the time between the date of first dose (start of induction) and the date of first documented evidence of confirmed PD, as defined in the IMWG response criteria. Subjects who start subsequent antimyeloma therapies for multiple myeloma without disease progression will be censored at the last disease assessment before the start of subsequent therapies. Subjects who withdraw consent to study or are lost to follow-up or die without disease progression will be censored at the last disease assessment. Subjects who have not progressed at the cutoff date for analysis will be censored at the last disease assessment. Subjects without any post-baseline disease assessment will be censored at the first dose date.

5.3.2.2. Analysis Methods

Similar statistical methods will be applied as described in Section 5.3.1 for PFS analysis.

A sensitivity analysis of TTP, in which progressive disease is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner.

5.3.3. Overall Survival (OS)

5.3.3.1. Definition

Overall survival (OS) is measured from the date of first dose (start of induction) to the date of death due to any cause. Subjects who withdraw consent from the study or are lost to follow-up will be censored at the time of withdrawal or lost to follow-up. Subjects who are still alive at the cutoff date for the analysis will be censored at the last known date of alive. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.3.3.2. Analysis Methods

Similar statistical methods will be applied as described in Section 5.3.1 for PFS analysis.

5.3.4. Overall Response Rate (ORR)

5.3.4.1. Definition

ORR is defined as the proportion of subjects who achieve a partial response or better (i.e., PR, VGPR, CR or sCR), according to IMWG response criteria.

5.3.4.2. Analysis Methods

Analysis of ORR will be based on the Response-evaluable set defined in Section 2.3. The number and percentage of subjects in the following response categories will be presented: stringent complete response (sCR), complete response (CR), sCR+CR, very good partial response (VGPR), partial response (PR), overall response (sCR+CR+VGPR+PR), minimal response (MR), overall response + MR (sCR, CR, VGPR, PR, and MR), stable disease (SD), progressive disease (PD), and not evaluable (NE). The corresponding 95% CI for each response category will also be provided. Analysis of ORR will be presented at the following time points:

- Following 4 cycles of induction therapy
- At the end of Dara-CyBorD induction therapy
- Post-transplant (in subjects who undergo high dose therapy and autologous stem cell transplantation)
- At the end of 12-cycles maintenance therapy

A sensitivity analysis of overall response rate, in which disease response is based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner.

5.3.5. Duration of Response (DOR)

5.3.5.1. Definition

Duration of response is defined for subjects with a confirmed response (PR or better) as the duration from the date of initial documentation of a response (PR or better) according to the IMWG criteria to the date of first documented evidence of progressive disease according to the

IMWG criteria or death due to progressive disease. Responders without disease progression will be censored at the censoring time point for TTP.

5.3.5.2. Analysis Methods

Analysis of DOR will be based on subjects who achieved a confirmed response of PR or better. Median DOR with 95% CI will be estimated based on the Kaplan-Meier method. Kaplan-Meier estimates will be generated and Kaplan-Meier curves for the duration of response will be produced.

A sensitivity analysis of DOR, in which disease response and progression are based on investigator assessment according to the IMWG response criteria, will be performed in a similar manner.

5.3.6. Time to Response

5.3.6.1. Definitions

Time to VGPR or better response (based on the computerized algorithm) is defined as the duration from the date of first dose (start of induction) to the date of initial documentation of VGPR or better, which was confirmed by a repeated measurement as required by the IMWG criteria. Subjects without confirmed response (VGPR or better) will be censored at the censoring date for TTP.

Time to PR or better response (based on the computerized algorithm) is defined as the duration from the date of first dose (start of induction) to the date of initial documentation of PR or better, which was confirmed by a repeated measurement as required by the IMWG criteria. Subjects without confirmed response (PR or better) will be censored at the censoring date for TTP.

5.3.6.2. Analysis Methods

Kaplan-Meier method will be used to estimate the cumulative distribution function of response over time using the full analysis set. Median time to response with 95% CI will be tabulated. Similar analyses will be conducted for time to VGPR or better response and time to PR or better response. Kaplan-Meier estimates and curves for both time to response variables will be provided.

In addition, for subjects who achieve a confirmed response, descriptive statistics (n, mean, standard deviation, median, range) will also be provided to summarize time to VGPR and time to PR or better response.

A sensitivity analysis of time to response based on investigator assessment according to the IMWG response criteria will be performed.

5.4. Subgroup Analyses

Subgroup analyses of the primary and selected secondary efficacy endpoints will be performed based on pre-specified subgroups defined in Section 2.4 in the newly diagnosed subject group.

Descriptive summaries and forest plot for the computer algorithm assessed response rate [CR+VGPR] will be provided for the subgroups specified in Section 2.4 for the previously untreated subjects. The subgroup analyses will be performed if there is adequate number of subjects in each subgroup.

The computer algorithm assessed PFS and OS will also be analyzed similarly for the subgroups using the methods described in section 5.3.1.2.

Additionally, the efficacy endpoint of best response will be summarized for subjects who received ASCT after 4-8 cycles of induction therapy.

6. SAFETY

Safety evaluation will include adverse events (AEs), death, clinical laboratory tests (hematology and serum chemistry), vital signs, physical exam findings, and ECOG performance status. Safety analyses will be performed based on the safety analysis set.

6.1. Adverse Events

AEs will be monitored throughout the study. All AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. For AE reporting, the verbatim term used in the electronic case report forms (eCRF) by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Unless otherwise specified, at each level of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs), which are defined as any AE that occurs after the first administration of study treatment (e.g., Daratumumab, Cyclophosphamide, Bortezomib, or Dexamethasone) through 30 days after the last study treatment administration or the day prior to start of subsequent therapy, whichever is earlier, or any AE that is considered reasonably related to study treatment regardless of the start date of the event, or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered reasonably related to study treatment by the investigator.

The incidence of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term, by maximum toxicity grade, and by relationship to study treatment administration. Specifically, the following AE summaries will be presented:

- A summary of TEAEs will be provided and will include the number and percentage (incidence) of subjects with any AE, subjects with any toxicity grade 3 or higher AE, subjects with any treatment-related AE, subjects with any toxicity grade 3 or higher treatment-related AE, subjects with any SAE, subjects with any treatment-related SAE, subjects with any AEs leading to study treatment discontinuation, subjects with any treatment-related AE leading to study treatment discontinuation, and subjects with any AE with outcome of death.
- Incidence of TEAEs by SOC, preferred term and toxicity grade (1-4)

- Incidence of TEAEs by SOC, preferred term and toxicity grade (1-2 and 3-4)
- Incidence of toxicity grade ≥ 3 TEAEs, by SOC, preferred term and toxicity grade (3 and 4)
- Study Treatment-Related Adverse Events
 - Incidence of Treatment-Related TEAEs by SOC, preferred term and toxicity grade (1-4)
 - Incidence of TEAEs related to daratumumab by SOC, preferred term and toxicity grade (1-4)
- Serious Adverse Events
 - Incidence of treatment-emergent SAEs, by SOC and preferred term
 - Incidence of treatment-emergent SAEs related to daratumumab by SOC and preferred term
- Infusion-related reaction
 - Infusion-related reactions (IRR) reported with daratumumab will be summarized by SOC and preferred term and maximum toxicity grade. Subjects with any infusion reactions associated with daratumumab will also be listed. The list will include subject ID, MedDRA preferred term/verbatim, study day of event, toxicity grade, relationship to study treatment, action taken with study treatment and outcome.
- Incidence of TEAEs leading to any study treatment discontinuation (Daratumumab, Cyclophosphamide, Bortezomib, or Dexamethasone) by SOC, preferred term and toxicity grade will be provided. For subjects who discontinued any study treatment due to AEs, a list including subject ID, preferred term/verbatim term, study day of AE, AE toxicity grade, relationship to study treatment, action taken with study treatment and outcome will be provided.
- Incidence of TEAEs leading to any treatment cycle delays or dose modifications of at least one of the study treatments (Daratumumab, Cyclophosphamide, Bortezomib, or Dexamethasone) by SOC, preferred term and toxicity grade will be summarized. Dose modifications include dose skipping (not administered) or dose adjustment or dose stopped (applicable to Daratumumab, Bortezomib, or Dexamethasone).
- Deaths: The number of subjects who died during study and within 30 days of last dose will be summarized. The primary cause of death recorded on eCRF page will also be summarized. A listing of subjects whose primary cause of death is at least one AE during the study will be provided
- Secondary malignancy: A listing of subjects who reported second primary malignancies during the study will be provided. This listing will include diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and pathology diagnosis (biopsy, aspirate, etc.) information whenever a second primary malignancy is observed. In addition, cumulative study treatment exposure, the treatment for second primary malignancy and the outcome information will also be presented in the listing.

6.2. Clinical Laboratory Tests

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

Hematology:

- hemoglobin
- neutrophils and lymphocytes
- red blood cell (RBC) count
- platelet count
- white blood cell (WBC) count with absolute

Chemistry:

| | |
|---------------------------------------|----------------------------------------|
| - sodium | - total bilirubin |
| - potassium | - alkaline phosphatase |
| - creatinine and creatinine clearance | - uric acid |
| - glucose | - calcium and albumin-adjusted calcium |
| - aspartate aminotransferase (AST) | - phosphate |
| - alanine aminotransferase (ALT) | - albumin |
| - chloride | - bicarbonate |
| - blood urea nitrogen (BUN) | - gamma-glutamyltransferase (GGT) |
| - lactic acid dehydrogenase (LDH) | - total protein |
| - magnesium | |

Descriptive statistics (mean, standard deviation (SD), median, and range) will be used to summarize observed laboratory values and their change from baseline at each scheduled visit during the study. Line plot of mean with standard error for each laboratory analyte over time will be displayed for hemoglobin, neutrophils, lymphocytes, platelets, WBC, AST, ALT, and creatinine.

The worst toxicity grade in hematology and chemistry during treatment will be summarized by toxicity grade. Shift tables from baseline to worst toxicity grade during the study will be provided for laboratory parameters listed above. These tables will summarize the number of subjects with each baseline CTC grade and changes to the maximum CTC grade.

A listing of subjects with any laboratory results outside the reference ranges (any grade 3 and above laboratory results) will be provided.

6.3. Vital Signs and Physical Examination

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point.

Physical examination with abnormal findings as well as those reported to be clinically significant will be summarized by body system and time point.

6.4. ECOG Performance Status

Frequencies of ECOG performance status (0, 1, 2, >2) over time will be summarized. In addition, shift from baseline to worst score during treatment may be provided.

SIGNATURES

Signed by

██████████

██████████

Date

12Feb2018, 20:03:35 PM, UTC

18Feb2018, 16:24:12 PM, UTC

Justification

Document Approval

Document Approval