Statistical Analysis Plan for

A SINGLE ARM PHASE II STUDY OF HIGH-DOSE WEEKLY CARFILZOMIB PLUS CYCLOPHOSPHAMIDE AND DEXAMETHASONE IN THE TREATMENT OF RELAPSED MULTIPLE MYELOMA AFTER 1-3 PRIOR THERAPIES

Academic CRO Protocol Number: MYX.1
Lead Group Protocol Number: MCRN-003

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1. OVERVIEW

This document is to describe the statistical analysis plan for MYX.1, and serves as the guideline for the analyses generated for writing the study report of this trial.

The data will be collected and cleaned by Canadian Cancer Trials Group (CCTG) according to the data management plan for this study. A senior biostatistician in CCTG will perform all analyses, and prepare a final statistical analysis report.

1.1 Objectives

This is a single arm phase II, investigator initiated, multicentre trial run through the Myeloma Canada Research Network. The primary objective is to determine the overall response rate after 4 cycles of weekly high-dose carfilzomib, cyclophosphamide and dexamethasone (CCD regimen) in patients with relapsed multiple myeloma after 1-3 prior regimens.

1.2 Timeline

The clinical cut-off date of final analysis is June 15th, 2018. The database will be locked for on July 13, 2018 for final analysis. The results will be available for 2018 abstract submission.

1.3 Data Collection

Data are collected and entered by CCTG, Kingston, Ontario. Procedures for data collection, data editing and data transfer are described in the data management plan.

2. RESULTS

Analysis population: All treated patients will be included in this analysis.

Baseline evaluations are those collected closest, but prior to, or on the first day of study medication, unless otherwise specified.

When either day or month of a date is missing, the missing day and/or month will be imputed by the midpoints within the smallest known interval. For example, if the day of the month is missing for any date used in a calculation, the 15th of the month will be used to replace the missing day. If the month and day of the year are missing for any date used in a calculation, the first of July of the year will be used to replace the missing day.

All comparisons between treatment arms will be carried out using a two-sided test at an alpha level of 5% unless otherwise specified. No formal adjustments will be made for the multiplicity of inferences for multiple clinical endpoints.

2.1 Accrual

Number (%) of patients per study center (Table 1) (All patients).

2.2 Eligibility status

Number (%) of eligible and ineligible patients and reasons of ineligibility (Table 2) (All patients).

2.3 Duration of follow-up

Median (range) duration of followup up will be reported using inverse OS method (Table 3).

2.4 Patient Characteristics

Number (%) of patient characteristics (Table 4) (Treated patients):

- Age (40-49, 50-59, 60-69, >=70)
- Age (Median, Range, Q1, Q3, Mean, SD)
- Sex
- ECOG performance status
- Number of prior therapy
- Myeloma Subtype – IgA, IgG, IgD LC only
- Stem Cell Transplant – Yes/No
- Baseline Genetics
- ISS stage
- Revised-ISS stage (using most current CG data and LDH from the time of study entry)
- % Proteosome Inhibitor exposed (either bortezomib or ixazomib)
- % Proteosome Inhibitor refractory
- % IMID (lenalidomide or pomalidomide or thalidomide) exposed
- % IMID refractory
- % of clonal plasma cells
- Participated in the millenoium study: Yes vs No

2.5 Efficacy

2.5.1 Response rates

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease

progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) as summarized in Table 11 of the study protocol. Response sub-category includes Stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Minimal Response (MR), Stable Disease (SD) and Progressive Disease (PD)

Number and (%) of disease response (sCR/CR/VGPR/PR/MR/SD/PD) will be reported in Table 5.

Overall response rate after 4 cycles of tretment will be calculated by number of (sCR + CR + VGPR + PR) / number of all treated patients. The corresponding 95% confidence interval for the overall response rate will be calculated by Normal approximation method.

Note: For patients with PD who were off treatment before cycle 4 will be considered as PD for cycle 4 response. Patients with other categories who off treatment before cycle 4 will be considered as in-evaluable for cycle 4 response.

Response rates of sCR, CR, VGPR, PR, MR, SD, PD and the corresponding 95% CI will also be reported separately.

Response rate according to baseline genetics will also be reported.

Best overall response will not be reported in this analysis but will be reported in a follow-up analysis.

2.5.2 Overall Survival (OS)

For patients who have died, overall survival is calculated in months from the day of registration to date of death. Otherwise, overall survival is censored at the last day the patient is known alive (LKA).

Two-year OS rate and the corresponding 95% CI will be estimated. KM curve of overall survival will be reported in Figure 1.

Cause of death and reason of censoring will be listed on Table 6.

2.5.3 Progression free survival (PFS)

Progression free survival (PFS) is defined as from the time of registration to the time of objective relapse for patients who achieved sCR, CR, VGPR or PR; to the time of progression of disease for

patients who maintained SD; to the time of symptomatic relapse or progression confirmed by imaging and/or necessitating institution of new treatment for myeloma; or to the time of death from any cause, whichever comes first. For patients who have not relapsed, progressed, or died, PFS is censored on the date of the last disease assessment.

Two-year PFS rate and the corresponding 95% CI will be estimated. KM curve of PFS will be reported in Figure 2.

Note: PFS will not be reported in current final analysis and will be analyzed later.

Type of PFS event and reason of censoring will be list on table 7.

2.6 Drug Exposure

Cumulative dose (mg) is the sum of each study medication doses received.

Mean, SD, Median, Q1, Q3, minimum and maximum of total amount for each of three drugs will be reported for patients who received at least one dose of carfilzomib, cyclophosphamide and dexamethasone treatment (based on standard IND algorithm) (Table 8)

Relative Dose Intensity (%)

Relative Dose Intensity for cyclophosphamide = Actual total dose / planned dose x 100%
Note: Relative dose intensity does not apply to Carfilzomib and Dexamethasone.

Mean, SD, Median, Q1, Q3, minimum and maximum of relative dose intensity, number and % of patients with relative dose intensity > 90% for each drug will be reported (Table 9).

Dose reduction, modification and discontinuation

The number and % of patients with at least one dose reduction, dose modification and dose discontinuation for each drug will be summarized for each of the three drugs (Table 10a). Reasons for dose reduction, dose modification and dose discontinuation for each drug will be reported.

Number of dose reduction (Mean, SD, median, Q1, Q3, min, max) per patient will be report for each drug. (Table 10b)

2.7 Toxicity

Post baseline Non-Hem Adverse Events (Table 11)

The number and % of patients with the following vascular, thromboembolic and cardiac adverse events (grade 1 or higher) will be reported:

- TTP
- PE/DVT
- Stroke
- Hypertension
- MI
- CHF event
- Unexplained dyspnea
- Renal failure

Hem Adverse Events (Table 12)

Biochemical Adverse Events (Table 12)

AE will be reported up to cycle 5 of treatment for this analysis.

2.8 Off treatment

Number (%) of patients off protocol treatment for each drug. (Table 13)

Death on trial (Table 14)

Number (%) of death and the reason of death (e.g, related or un-related to protocol treatment) will be reported.

SAE (Table 15).
Note: All SAE will be reported.

3. TABLES AND FIGURES

Figure 1. KM for OS

Figure 2. KM for PFS