Title: A Prospective, Multicenter, Observational Study in Relapsed and/or Refractory Multiple Myeloma Patients Treated with Ixazomib plus Lenalidomide and Dexamethasone

NCT Number: NCT03433001

Statistical analysis plan Approve Date: 01-NOV-2021

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Note; This document was translated into English as the language on original version was Japanese.

A Prospective, Multicenter, Observational Study in Relapsed and/or Refractory Multiple Myeloma Patients Treated with Ixazomib plus Lenalidomide and Dexamethasone

（Study number: C16042）

Statistical Analysis Plan

（Ver.3.0; NOV 01, 2021）

Secondary Sponsor: Takeda Pharmaceutical Company Limited

1 TERMS AND ABBREVIATIONS

Summary Statistics: number, mean, standard deviation, minimum/maximum value, quartiles
CCI: charlson comorbility index

2 ANALYSIS SETS

Full Analysis Set (FAS): All patients who enroll into the study and who receive at least one dose of ixazomib. Patients with enrollment violation will be excluded.
Evaluable Analysis Set: All patients included in the FAS who have measurable lesions prior to the start of IRd therapy and who have at least one response evaluation after the start of IRd therapy.
Safety Analysis Set: All patients who enroll into the study who receive at least one dose of any drug used in IRd therapy (i.e. ixazomib, lenalidomide, or dexamethasone).

3 CONSIDERATIONS FOR ANALYSIS

- Significance level
  5% (one-sided test)
- Confidence coefficient
  For only primary analysis, 90% (two-sided estimation)
  Otherwise, 95% (two-sided estimation)
- Number of display digits
  The significant digit is the lowest digit included in each variable of data unless otherwise specified; if the values “160” and “160.1” are included, the first decimal place will be the significant digit.
  - Mean/Quartiles/Confidence interval
    Round off two digits below the effective digit of the data and display up to one digit below.
  - Standard deviation
    Round off the third digit below the effective digit of the data and display up to the second digit below.
  - Minimum/Maximum value
    Display up to the significant digit of data.
  - Proportion/Percentage
    Round off the second decimal place and display to the first decimal place.
  - P value
    Round off the 5 decimal places and display up to 4 decimal places.
    However, when p value is less than 0.0001, it represents as "p <0.0001."

4 OTHER DATA HANDLING

➢ Duration

- Duration (day)

Target Date – Start Date + 1

➢ TEAE

- TEAE (treatment-emergent adverse event)
  AE that occurred from the start of IRd treatment until 30 days after the end of IRd treatment or the start of next treatment, whichever occurs first.

➢ Relative dose intensity (RDI)

- RDI

$$\text{RDI}(\%) = \frac{(\text{Actual dose})/(\text{Actual number of cycle days})}{(\text{Scheduled dose})/(\text{Scheduled number of cycle days})} \times 100$$

The actual number of cycle days shall be (next cycle start date) - (relevant cycle start date) if there is a next course, or the number of scheduled cycle days if there is no next course. The number of scheduled cycle days and dose for each drug should be set as following table.

Drug		Length of cycle	Dose
IRd	Ixazomib	28	4.0mg×3
	Lenalidomide		25mg×21
	Dexamethasone		40mg×4

➢ Frailty

The score of frailty should be set as following table. As a sensitivity analysis, changes in age categories may be considered.

Items		Score
Age	75<=	0
	76<= - <=80	1
	<=81	2
ADL	4<=	1
	<=5	0
IADL	5<=	1
	<=6	0
CCI	1<=	0
	<=2	1

The total score will be classified as follows.

Fit：0

Intermediate fitness：1

Frail：>=2

➢ Cytogenetic risk

Patients are classified into High risk group and Standard risk group, or Expanded high risk group and Modified Standard risk group according to the pattern of chromosome aberrations at the time of recurrence.

- High risk group
  Patients with abnormalities in either one of del17p, t(4;14) or t(14;16)
- Standard risk group
  All other patients

- Expanded high risk group
  Patients with abnormalities in either one of del17p, t(4;14), t(14;16) or 1q gain
- Modified Standard risk group
  All other patients

➢ Renal function

Calculation for the estimation of eGFR, published by the Japanese Society of Nephrology (2008):

For men:

eGFR (mL/min/1.73 m^2) = 194 * serum creatinine [mg/dL]$^{-1.094}$ * age [years] $^{-0.287}$

For Women:

eGFR (mL/min/1.73 m^2) = 194 * serum creatinine [mg/dL]$^{-1.094}$ * age [years]$^{-0.287}$×0.739

Cockcroft-Gault equation for the estimation of Ccr:

For men:

Ccr= ((140-age [years])×weight [kg])/(72×serum creatinine [mg/dL])

For women:

Ccr= ((140-age [years])×weight [kg])/(72×serum creatinine [mg/dL])×0.85

Renal function will be classified according to baseline CCr as following table.

Renal function	CCr
Normal	90≦
Mild	60≦ < 90
Moderate	30≦ < 60
Severe	< 30

➢ Handling of values below or above the quantitative limit

- Serum free light chain (FLC)

If FLC κ or FLC λ is below the limit of quantification, the limit of quantification is imputed. κ/λ ratio is calculated using the imputed value.

➢ International Staging System (ISS)

- Staging criteria (according to Study Protocol Appendix C)

Stage I: (Serum β2-microglobulin <3.5 mg/L) and (Serum albumin ≥3.5 g/dL)

Stage II: Neither Stage I or Stage III

There are two definitions of Stage II:

(serum β2-microglobulin <3.5 mg/dL) and (serum albumin <3.5 g/dL), or

serum β2-microglobulin 3.5– <5.5 mg/dL (irrespective of serum albumin concentration)

Stage III: Serum β2-microglobulin ≥5.5 mg/L

* The clinical stage (ISS) at the recurrence (at the start of treatment) is calculated from the clinical laboratory values. If the patient does not fall into Stage III and any one of serum β2-microglobulin and serum albumin is missing, the patient should not be classified.

➢ Censoring scheme

- Overall survival (OS)

Situation	**Date of event expression or censoring**	**Outcome**
Death	Date of death	event
Discontinuation	Date of discontinuation	-
Next antitumor treatment started*	Date of start of next treatment	censoring / -
Alive	Last confirmed date of survival	censoring

For the start of next antitumor treatment, analyze both the case of not censoring and the case of censoring.

- Progression Free survival (PFS)

Situation	**Date of event expression or censoring**	**Outcome**
Incomplete or no baseline assessments	Date of first treatment	censoring
Progression	Assessment date	event
Death	Date of death	event
Discontinuation	Date of discontinuation	-
Next antitumor treatment started	Date of start of next treatment	censoring
No progression	Last confirmed date at which patients are progression-free	censoring

- Time to Next Treatment (TTNT)

Situation	**Date of event expression or censoring**	**Outcome**
Incomplete or no baseline assessments	Date of first treatment	censoring
Progression	Assessment date	-
Death	Date of death	event
Next antitumor treatment started	Date of start of next treatment	event
Continued study treatment	Last observed date	censoring
Discontinued and no information of next treatment	Last observed date	censoring

Last observed date; last date of the date of discontinuation, the date of last dose of study treatment or the date of final assessment

- Duration of Response (DOR)

DOR is defined for the patients assessed as ≥PR (including patients where two consecutive assessments have not been made) according to the IMWG criteria (2014 version)

Situation	**Date of event expression or censoring**	**Outcome**
Incomplete or no baseline assessments	-	NA
Progression	Assessment date	event
Death	Date of death	event
Discontinuation	Date of discontinuation	-
Next antitumor treatment started	Date of start of next treatment	censoring
No progression	Last confirmed date as not less than PR	censoring

➢ Handling of response assessment

Follow the Research Protocol, Appendix F, Response Criteria [IMWG Criteria (2014 version)]. However, in consideration of the actual clinical situation, the results of only one assessment also will be used for the evaluation that originally "Two consecutive assessments are needed".

➢ Other valuables to be derived

- Body surface area (BSA)

Body Surface Area (m^2) = Weight (kg) $^{0.425}$ × Height (cm) $^{0.725}$ × 0.007184

5 PATIENTS, DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

5.1 Disposition of Patients

5.1.1 Study Information

Analysis Set:
All patients obtained informed consent

Analysis Variables:
The earliest date of informed consent
The latest date of the last visits
Version of MedDRA
Version of SAS

Analysis Methods:
(1) Output above items.

5.1.2 Eligibility of Patients

Analysis Set:
All patients obtained informed consent

Analysis Variables:
Eligibility [yes, no (reasons)]

Analysis Methods:
(1) Frequency count

5.1.3 Exit Status of Patients

Analysis Set:
Full Analysis Set

Analysis Variables:
Exit status [complete, incomplete (reasons)]

Analysis Methods:
(1) Frequency count
(2) Cross table of the number of cycle and the reason for discontinuation
The number of cycles in which any of the drugs of IRd is administered will be used.

5.1.4 Protocol Deviations and Analysis Datasets

5.1.4.1 Protocol Deviations

Analysis Set:
All patients obtained informed consent

Analysis Variables:
Protocol Deviations
[Major GCP Violations, Deviations of Protocol Entry Criteria, Deviations of Discontinuation Criteria, Deviations Related to Treatment Procedure or Dose, Deviations Concerning Excluded Medication or Therapy, Deviations to Avoid Emergency Risk, Other Deviations]

Analysis Methods:
(1) Summarize the number of patients who have deviated from the protocol, classify the deviations into above category, and show the breakdown of deviations. Patients applicable for multiple categories will be counted in each category.

5.1.4.2 Analysis Datasets

Analysis Set:
All patients obtained informed consent

Analysis Variables:
Protocol deviation related to analysis set [Inclusion, Exclusion]
Inclusion or Exclusion for each analysis set
Full Analysis Set
Evaluable Analysis Set
Safety Analysis Set

Analysis Methods:
Patients applicable for multiple categories will be counted once in each category.
(1) Frequency count about the determination of inclusion for each analysis set
(2) Frequency count of the number of patient included for each analysis set

5.1.4.3 Patient Flow Diagram

Analysis Set:
All patients obtained informed consent

Analysis Variables:
All patients obtained informed consent

All eligible patients
Inclusion or Exclusion for each analysis set
Full Analysis Set
Evaluable Analysis Set
Safety Analysis Set

Analysis Methods:
(1) Patient flow diagram

5.2 Patients Characteristics

5.2.1 Demographics and Other Baseline Characteristics

Analysis Set:
Full Analysis Set, Evaluable Analysis Set, Safety Analysis Set

Analysis Variables:
Age（year）[Min<= - <=65、65< - <=75、75< - <=Max]
Sex [Male、Female]
Height（cm）
Weight（kg）
BMI（kg/m^2）
BSA（m^2）
M-protein isotype [IgG κ・λ, IgA κ・λ, IgD κ・λ, IgE κ・λ, IgM κ・λ, Bence Jones type κ・λ, non-secretory type, unknown, others]
Clonal bone marrow plasma cell percentage (%)
Immunophenotyping: CD20, CD56 (positive, negative, not conducted)
Clinical stage according to ISS at initial diagnosis [Stage I, II, III]
Clinical stage according to ISS at disease recurrence (at first treatment) [Stage I, II, III]
Chromosome abnormality at the initial diagnosis [t (4;14), t (14;16), t (11;14), del17p, 1q gain]
Chromosomal abnormalities at disease recurrence (at first treatment) [t (4;14), t (14;16), t (11;14), del17p, 1q gain]
Whether imaging tests are performed [Conducted, Not conducted]
Presence of Bone Lesion [yes, no]
Presence of Extramedullary Masses [yes, no]
Extramedullary Masses [Bone-delivered, Soft tissue-delivered or others]
Prior antineoplastic therapies [Conducted, Not conducted]
Prior radiation therapy [Conducted, Not conducted]
Prior hematopoietic stem cell transplantation [Conducted, Not conducted]
M-protein in blood samples and urine samples
Serum FLC (free light chain) (FLC κ, FLC λ, κ/λ ratio [Min<= - <0.26, 0.26=< - <=1.65, 1.65< - <=Max]))

ECOG performance status [0, 1, 2, 3, 4]
Cytogentic risk[High risk、Standard risk], [Expanded high risk, Modified standard risk]
Renal function[Normal , Mild, Moderate, Severe]

Analysis Methods:
(1) Frequency count of categorical data and summary statistics of continuous data
Note：For patients whose M-protein isotype: type of light chain is "κ", FLC κ will be calculated. For patients whose M-protein isotype: type of light chain is "λ", FLC λ will be calculated.

5.2.2 Cytogenetic Abnormalities

Analysis Set:
Full Analysis Set, Evaluable Analysis Set, Safety Analysis Set

Analysis Variables:
Chromosomal abnormalities at disease recurrence (at first treatment) [t (4;14), t (14;16), t (11;14), del17p, 1q gain]

Analysis Methods:
(1) Distribution of chromosomal abnormal cell percentages
The distribution of chromosomal abnormal cell percentages is shown in the histogram.
(2) Frequency count of positive patients of chromosomal abnormalities
The thresholds shall be set as follows,
del17p: 5%
t(4;14)、t(14;16)、t(11;14)、1q gain: 3%

(3) Frequency count of patterns of chromosomal abnormalities
To examine the frequency of combinations of multiple chromosome abnormalities, a frequency count by possible chromosome abnormal pattern will be performed.

5.2.3 Comorbidity

Analysis Set:
Full Analysis Set

Analysis Variables:
Charlson comorbidity index（CCI）;
Myocardial infarction (history, not ECG changes only)
Congestive heart failure
Peripheral disease (includes aortic aneurysm ≥ 6 cm)
Cerebrovascular disease: CVA with mild or no residua or TIA

Dementia
Chronic pulmonary disease
Peptic ulcer disease
Liver disease [Mild (without portal hypertension, includes chronic hepatitis), Moderate or severe]
Diabetes [Without end-organ damage (excludes diet-controlled alone),
With end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)]
Hemiplegia
Moderate to severe renal disease
Tumor without metastasis (exclude if > 5years from diagnosis)
Leukemia (acute or chronic)
Lymphoma
Metastatic solid tumor
AIDS (not just HIV positive)

*Items with information on severity should be tabulated by severity.

Components of Frailty (Age, ADL, IADL, CCI)
Frailty [Frail, Intermediate fitness, Fit]

Analysis Methods:

(1) Frequency count of comorbidity
(2) Frequency count of components of frailty
(3) Frequency count[Min<= - <=1、2<= - <=Max] and summary statistics of CCI score

5.2.4 Prior Therapy

Analysis Set:
Full Analysis Set

Analysis Variables:
Prior Antineoplastic Therapies [Bortezomib, Carfilzomib, Lenalidomide, Pomalidomide, Prednisolone, Dexamethasone, Melphalan, Adriamycin, Cyclophosphamide, Elotuzumab, Daratumumab, Panobinostat, Vincristine, Other]
Number of collected prior regimen [1, 2, 3, 4……]
Prior Regimen（Pattern of prior antineoplastic therapies）
Reason for termination by prior regimen（Pattern of prior antineoplastic therapies） [PD or 'other']
Best Response by prior regimen（Pattern of prior antineoplastic therapies） [CR, sCR, …]

Analysis Methods:
For method (1) and (3), analysis will be performed by one previous drugs, two or more previous regimens and all previous regimens.

(1) Frequency count of prior antineoplastic therapies

Sorted by frequency. If the antineoplastic therapies is used more than once to the same patient, it will be counted as one case.

(2) Summary of the number of prior regimens

The number of collected antineoplastic therapy regimens will be calculated for each patient, and frequency count and summary statistics will be calculated.

(3) Summary of prior regimens

For high frequency regimens, the frequency of the regimen, the reason for termination and the response for each regimen will be tabulated.

5.2.5 Supportive Therapy

Analysis Set:
Full Analysis Set

Analysis Variables:
Supportive Therapy [varicella zoster, P. jirovecii infection (e.g. ST combination drug)]

Analysis Methods:
(1) Frequency count

Sorted by frequency. If the antineoplastic therapies is used more than once to the same patient, it will be counted as one case.

5.2.6 Next-line Treatment

Analysis Set:
Full Analysis Set

Analysis Variables:
Next-line Treatment [Bortezomib, Carfilzomib, Lenalidomide, Pomalidomide, Prednisolone, Dexamethasone, Melphalan, Adriamycin, Cyclophosphamide, Elotuzumab, Daratumumab, Panobinostat, Vincristine, Other]

Analysis Methods:
(1) Frequency count

Sorted by frequency. The denominator is the number of patients in the analysis set for which one of the next-line treatments was selected.

6 EFICACY ANALYSIS

6.1 Primary Endpoint and Analytical Methods

Analysis Set:
Full Analysis Set

Analysis Variables:
PFS from the start of study Treatment

Analysis Methods:
PFS is defined as the period from the first dose of treatment to the time of confirmed PD or confirmed death (regardless of the cause of death), whichever is earlier. Patients who are still alive and progression-free will be censored at the last confirmed date at which they are progression-free. PFS for the FAS will be estimated using the Kaplan-Meier method, and the quartiles and two-sided 95% confidence intervals will be calculated using the double logarithmit transformation method of Brookmeyer and Crowley.

6.2 Supplemental Analysis for Primary Endpoint

Analysis Set:
Evaluable Analysis Set

Analysis Variables:
PFS from the start of study Treatment

Analysis Methods:
6.1 Analysis will be repeated for Evaluable Analysis Set.

6.3 Secondary Endpoints and Analytical Methods

6.3.1 PFS rate at 12 and 24 Months from the Start of Study Treatment

Analysis Set:
Full Analysis Set

Analysis Variables:
PFS rate at Month 12 and 24 from the start of study Treatment

Analysis Methods:
(1) PFS rate at Month 12, 24 and the two-sided 95% confidence interval will be estimated by Kaplan-Meier method. The confidence interval is constructed based on the variance calculated by Greenwood's formula for the double logarithmically transformed PFS rate, and then calculated by exponential transformation.

6.3.2 Subgroup analysis of PFS from the Start of Study Treatment

Analysis Set:
Full Analysis Set, Evaluable Analysis Set

Analysis Variables:
PFS from the start of study Treatment

Strata:
Frailty adjusted group [Fit, Intermediate fitness, Frail]
Cytogenetic risk group [High risk, Standard risk]
Cytogenetic risk group [Expanded High risk, Modified Standard risk]
Chromosomal abnormalities at disease recurrence (at first treatment) [del17p, 1q gain]
Clinical stage according to ISS at disease recurrence (at first treatment) [Stage I, II, III]
Number of regimens [1, 2, 3 or more]
RDI by drug [<80%, >=80%]
Best response [at least VGPR, PR or worse]
Prior antineoplastic therapies* [Treated, Not treated]
*Bortezomib, Carfilzomib, Lenalidomide, Pomalidomide, Elotuzumab, Daratumumab
Renal function [Normal, Mild, Moderate, Severe]
Determination of prior treatment efficacy [Clinical relapse, Paraprotein relapse, Other]

Analysis Methods:
(1) PFS for each strata will be estimated using similar methodology to that used for analysis of primary analysis. PFS rate at Month 12, 24 and the two-sided 95% confidence interval will be estimated using Kaplan-Meier method.

(2) Median PFS and the two-sided 95% confidence interval for each strata will be estimated using Brookmeyer and Crowley methodology and display with forest plot.

6.3.3 OS from the Start of Study Treatment

Analysis Set:
Full Analysis Set

Analysis Variables:
OS from the start of study Treatment

Analysis Methods:

(1) OS is defined as the period from the first dose of treatment to the time when death (regardless of the cause of death) is confirmed. Patients who are still alive will be censored at the last confirmed date of survival or the date of data cut-off, whichever is earlier. OS for the FAS will be estimated using the Kaplan-Meier method, and the quartiles and two-sided 95% confidence intervals will be calculated using the double logarithmic transformation method of Brookmeyer and Crowley.

(2) OS for each strata will be estimated using similar methodology in (1).

(3) Median OS and the two-sided 95% confidence interval for each strata will be estimated using Brookmeyer and Crowley methodology and display with forest plot.

6.3.4 Best Response

Analysis Set:
Full Analysis Set, Evaluable Analysis Set

Analysis Variables:
Cumulative Best Response

Analysis Methods:
(1) Best response is defined as the cumulative numbers of patients who achieve each level of best response, as defined by the IMWG criteria (2014 version), after each cycle of treatment. A histogram (or similar) showing the numbers of patients achieving different levels of best response will be created after each cycle of treatment.

6.3.5 Time to Next Treatment（TTNT）

Analysis Set:
Full Analysis Set

Analysis Variables:
TTNT

Analysis Methods:
(1) TTNT is defined as the period from the first dose of treatment to the time of next-line treatment or confirmed death (regardless of the cause of death), whichever is earlier. Patients who are still alive and no next-line treatment will be censored at the last confirmed date at last observed date. TTNT for the FAS will be estimated using similar methodology to that used for analysis of PFS.

6.3.6 Duration of Therapy（DOT）

Analysis Set:
Full Analysis Set

Analysis Variables:
DOT

Analysis Methods:
(1) DOT is defined as the treatment duration of IRd therapy. Summary statistics will be calculated. In continuing patients, it is the end of the last cycle with or without drug interrupt. For discontinued patients, the period is defined as the date of IRd initiation to the date of decision to discontinue or the date of the last dose of ixazomib, whichever is later.

6.3.7 Proportion of Patients Continuing Treatment at 12 and 24 Months from the Start of Study Treatment

Analysis Set:
Full Analysis Set

Analysis Variables:
Proportion of patients continuing treatment with ixazomib at 12 and 24 months from the start of study Treatment

Analysis Methods:
(1) The proportion of patients who are not discontinued at 12 and 24 months after the start of treatment, and the two-sided 95% confidence intervals, will be calculated. Exact confidence intervals will be calculated based on a binomial distribution.

6.3.8 Overall Response Rate（ORR）

Analysis Set:
Full Analysis Set

Analysis Variables:
ORR

Analysis Methods:
(1) The ORR is defined as the proportion of patients who achieve a best response of PR or better according to the IMWG criteria (2014 version) after the start of the study treatment. The ORR and 95% confidence interval will be calculated. Exact confidence intervals will be calculated based on a binomial distribution.

6.3.9 Very Good Partial Response (VGPR) or More

Analysis Set:
Full Analysis Set, Evaluable Analysis Set

Analysis Variables:
Very Good Partial Response (VGPR) or more

Analysis Methods:
(1) The percentage of patients achieving a VGPR or better, according to the IMWG criteria (2014 version), after the start of the study, and 95% confidence interval will be calculated. Exact confidence intervals will be calculated based on a binomial distribution.

6.3.10 Patient Reported Outcome Health-related Quality of Life（HRQol）: EORTC-QLQ-C30/MY-20

Analysis Set:
Full Analysis Set

Analysis Variables:
EORTC QLQ-C30

- Five functional scales (physical, role, emotional, cognitive, social)
- A global health/quality of life scale
- Three symptom scales (tiredness, nausea and vomiting, pain)
- Six single items (dyspnea, insomnia, anorexia, constipation, diarrhea, economic difficulty)

EORTC QLQ-MY20

- Four independent subscales
- Two functional subscales (body image, future perspective)
- Two symptom subscales (multiple myeloma symptoms, treatment adverse effects)

Analysis Methods:
(1) Scores will be calculated for each subscale according to the EORTC Scoring Manual, and summary statistics and 95% confidence intervals will be calculated for each treatment cycle.
(2) Line plot (Mean±SD) will be presented graphically as plots over time.
(3) Summary statistics for change from cycle 1, plus the mean and 95% confidence intervals, will be calculated.

6.3.11 Proportion of Patients with CR who Achieve Minimal Residual Disease (MRD) Negativity in Bone Marrow

Analysis Set:
Full Analysis Set

Analysis Variables:
Percentage of MRD positive cells [=>10^{-4}, 10^{-5}<= - <10^{-4}, 10^{-6}<= - <10^{-5}, 10^{-7}<= - <10^{-6}]
Percentage of patients achieving MRD negativity [<10^{-4}, <10^{-5}, <10^{-6}]

Analysis Methods:
The same analysis will be performed for the SRL-flow method and the Adaptive. However, since the quantitative limit of the SRL-flow method is 10^{-6}, the smallest category of positive cell rate is tabulated as "less than 10^{-6}".

(1) The percentage of corresponding each category will be calculated. 95% confidence interval of percentage of patients achieving MRD negativity will be calculated. Exact confidence intervals will be calculated based on a binomial distribution. If a patient is MRD-positive at their first evaluation and MRD-negative after re-examination, the patient will be considered to be MRD-negative and corresponding percentage of MRD positive cells will be used for calculation of the percentage of MRD positive cells

6.3.12 Relative Dose Intensity（RDI）

Analysis Set:
Full Analysis Set

Analysis Variables:
RDI

Analysis Methods:
(1) Summary statistics for RDI for Ixazomib, Lenalidomide and Dexamethasone, will be calculated by cycle.
(2) Time plot of Analysis (1) will be outputted.
(3) Summary statistics for RDI for Ixazomib, Lenalidomide and Dexamethasone, will be calculated for overall period.

6.3.13 Imaging Evaluation

Analysis Set:
Full Analysis Set

Analysis Variables:
Bone evaluation
Extramedullary Masses

Analysis Methods:

(1) The percentage of patients with new bone lesions or extramedullary masses and the two-sided 95% confidence intervals will be calculated. Exact confidence intervals will be calculated based on a binomial distribution.

(2) For the patients with extramedullary masses, frequency count of findings about extramedullary masses will be outputted.

6.3.14 M-protein

Analysis Set:

Full Analysis Set

Analysis Variables:

M-protein measurement (SPEP/UPEP [24-hour urine collection], serum free light chain measurement)

Best response of SPEP/UPEP percent change

Analysis Methods:

(1) Summary statistics and 95% confidence interval of mean will be calculated.

(2) Summary statistics for change from cycle 1 plus the 95% confidence interval of mean will be calculated.

(3) The percent change of SPEP/UPEP is achieved when SPEP/UPEP is the lowest value by patients. Summary statistics for percent change from cycle 1 plus the 95% confidence interval of mean will be calculated.

6.3.15 Duration of Response（DOR）

Analysis Set:

Full Analysis Set

Analysis Variables:

DOR

Analysis Methods:

(1) DOR is defined as the time from the date of first documentation of response ≥PR according to the IMWG criteria (2014 version) to the date of first documentation of PD or death due to any cause. DOR for patients in the FAS who achieve PR or better at any time during the study will be estimated using the Kaplan-Meier method, and the quartiles and 95% confidence intervals will be calculated by the double logarithmic transformation method of Brookmeyer and Crowley. Patients who achieve PR or better and have not experienced PD will be censored from the date when their response was confirmed as not being worse than PR.

6.3.16 Examination of Prognostic Factors Regarding PFS, OS, TTNT and DOR

Analysis Set:
Full Analysis Set

Analysis Variables:
PFS, OS, TTNT and DOR

Analysis Methods:
If necessary, regression analysis using the Cox proportional hazards model will be performed as an exploratory analysis. Univariate analysis using the selected factors individually as fixed effects and multivariate analysis with appropriate variable selection will be considered, and the hazard ratios and their confidence intervals and p-values will be output from the estimated parameters. Candidate factors shall be as follows.

1. Cytogenetic risk group: High Risk
2. Components of Frailty adjusted group (Age, ADL, IDAL, CCI)
3. Prior antineoplastic therapies* [Treated, Not treated]

*Bortezomib, Carfilzomib, Lenalidomide, Pomalidomide, Elotuzumab, Daratumumab

4. Determination of prior treatment efficacy [Clinical relapse, Paraprotein relapse]
5. Number of regimens [1, 2, 3 or more]
6. ECOG performance status [0, 1, 2, 3, 4]
7. LDH
8. SEX
9. Extramedullary Masses
10. Prior hematopoietic stem cell transplantation
11. M-protein isotype [IgG κ・λ, IgA κ・λ, IgD κ・λ, IgE κ・λ, IgM κ・λ, Bence Jones type κ・λ, non-secretory type, unknown, others]
12. Serum FLC (free light chain) (FLC κ, FLC λ, κ/λ ratio [Min<= - <0.26, 0.26=< - <=1.65, 1.65< - <=Max]))
13. Renal function

7 SAFETY ANALYSIS

7.1 Frequency of Treatment-Emergent Adverse Event

7.1.1 Overview of Treatment-Emergent Adverse Event

Analysis Set:
Safety Analysis Set

Analysis Variables:
TEAE

Category：
Relationship to IRd treatment [Related, Not related]
Relationship to study drug [Related, Not related]
Grade [Grade1 – Grade5]

1) Frequency count of All TEAEs
2) Frequency count of IRd Treatment-related TEAEs
3) Frequency count of Study Drug-related TEAEs
4) Frequency count of Grade 3 or Higher TEAEs
5) Frequency count of IRd Treatment-related Grade 3 or Higher TEAEs
6) Frequency count of All TEAEs by Grade
7) Frequency count of IRd Treatment-related TEAEs by Grade
8) Frequency count of Study Drug-related TEAEs by Grade
9) Frequency count of TEAEs Resulting in Discontinuation of Treatment
10) Frequency count of Serious TEAEs
11) Frequency count of Non-serious TEAEs
12) Frequency count of TEAEs Resulting in Death

Note for calculation of incidence rate:
・For tabulation by grade
If a patient had two or more adverse events in the same category with different severities, then the event with the maximum severity was used for that patient. The denominator of incidence rate is the number of patients in analysis set.
・Otherwise
If a patient had two or more adverse events in the same category with different severities, then the event with the maximum severity was used for that patient. The denominator of incidence rate is the number of patients in analysis set.

7.1.2 Output of Treatment-Emergent Adverse Event

Analysis Set:

Safety Analysis Set

Analysis Variables:
TEAE

Category：
Relationship to IRd treatment [Related, Not related]
Relationship to study drug [Related, Not related]
Grade [Grade1 – Grade5]

TEAE will be coded using MedDRA and will be summarized by Preferred Term (PT) and System Organ Class (SOC). Analysis output will be sorted SOC alphabetically and PT frequency.

1) Frequency count of All TEAEs by SOC and PT
2) Frequency count of IRd Treatment-related TEAEs by SOC and PT
3) Frequency count of Study Drug-related TEAEs by SOC and PT
4) Frequency count of Grade 3 or Higher TEAEs by SOC and PT
5) Frequency count of IRd Treatment-related Grade 3 or Higher TEAEs by SOC and PT
6) Frequency count of All TEAEs by Grade by SOC and PT
7) Frequency count of IRd Treatment-related TEAEs by Grade by SOC and PT
8) Frequency count of Study Drug-related TEAEs by Grade by SOC and PT
9) Frequency count of TEAEs Resulting in Discontinuation of Treatment by SOC and PT
10) Frequency count of Serious TEAEs by SOC and PT
11) Frequency count of Non-serious TEAEs by SOC and PT

TEAE that excludes serious TEAE, and the incidence rate exceeds 5 % will be outputted.

12) Frequency count of TEAEs Resulting in Death by SOC and PT

Note for calculation of incidence rate:

・For tabulation by grade

If a patient had two or more adverse events in the same SOC (or with the same PT) with different severities, then the event with the maximum severity was used for that patient. The denominator of incidence rate is the number of patients in analysis set.

・Otherwise

Patient with two or more AEs in the same SOC (or with the same PT) is counted only once for that SOC (or PT). The denominator of incidence rate is the number of patients in analysis set.

7.2 Laboratory Results

Descriptive summary of laboratory data analyzed for safety analysis set.

8 LISTINGS

Details will be specified in TFL Shells.

9 CONSIDERATIONS ON STATISTICAL ANALYSIS

9.1 Covariate

Not applicable

9.2 Handling of Dropouts or Missing Data

Missing values shall not be imputed unless otherwise noted.

9.3 Criteria for Interim Analysis and Early Discontinuation

All planned analysis will be performed at 12 month after the last patient enrollment.

9.4 Multicenter Studies

Analyses for consideration of medical institution will not be performed.

9.5 Multiple Comparisons/Multiplicity

No adjustments for multiplicity are planned.

9.6 Consideration of Subgroups

The subgroups is considered in 6.3.2.

10 REVISION HISTORY

This document is a translation of the 3rd Japanese version.