Title: An Open-label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Ixazomib in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma Initially Treated with an Injection of Proteasome Inhibitor-Based Therapy

NCT Number: NCT03416374

Statistical analysis plan Approve Date: 01-NOV-2021

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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

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

An Open-label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Ixazomib in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma Initially Treated with an Injection of Proteasome Inhibitor-Based Therapy

（Study number: C16043）

Statistical Analysis Plan

（Ver.4.0; NOV 01, 2021）

Secondary Sponsor: Takeda Pharmaceutical Company Limited

1 TERMS AND ABBREVIATIONS

Summary Statistics: number, mean, standard deviation, minimum/maximum value, quartiles
VRd: bortezomib plus lenalidomide and dexamethasone
KRd: carfilzomib plus lenalidomide and dexamethasone
IRd: ixazomib plus lenalidomide and dexamethasone
CCI: charlson comorbility index

2 ANALYSIS SETS

Full Analysis Set (FAS): all patients who enroll in Treatment Period I and who receive at least one dose of any therapy during the Treatment Period
Evaluable Analysis Set: FAS excluding patients who did not assessed a single response assessment
Safety Analysis Set: all patients who enroll in Treatment Period I and who receive at least one dose of any therapy during the Treatment Period (Same as FAS)
Safety Analysis Set for Treatment Period II: all patients who enroll into Treatment Period II and who receive at least one dose of the study drug

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
  - 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)
  - For patients who discontinued during Treatment Period I, an AE that occurred from the start of study until the end of Treatment Period I
  - For patients who enrolled into Treatment Period II, an AE that occurred from the start of treatment in Treatment Period I until 30 days after the end of Treatment Period II or the start of next treatment, whichever occurs first
- TEAE after the First Dose of Study Drug
  In Treatment Period II, TEAEs will be regarded as any AEs that occur after the first dose of study drug.
- non serious TEAE
  TEAE that excludes serious TEAE (refer to Study protocol 10.1.3), and the incidence rate exceeds 5 %.

➢ Quality-Adjusted Life-Years (QALYs)

- modified QALY
  The global health/quality of life scale score from the EORTC-QLQ-C30 instrument will be converted into a utility value ranging from 0 to 1, and used to adjust the value of survival years; this value is defined as the modified QALY.

$$\text{modified QALY} = \sum_{j=2}^{J_i} \frac{(u_j + u_{j-1})}{2} \times t + \frac{(u_{J_i} + u_C)}{2} \times (t_C - t_{J_i})$$

J_i : The number assessment before the minimum follow-up time (t_C)
u_i : The utility value at any time point j

For limited follow-up, u_c can be estimated as utility at t_C using a trapezoidal estimate for the partial follow-up time.

$$u_C = u_{J_i} + \frac{(u_{J_i+1} - u_{J_i})}{(t_{J_i+1} - t_{J_i})} \times (t_C - t_{J_i})$$

➢ 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. For VRd, the scheduled dose should be defined according to the number of scheduled cycle days selected in the CRF.

Drug		Length of cycle	Dose
Period I-KRd (Cycle 1)	Carfilzomib	28	20mg/m^2×2 ＋27mg/m^2×4
	Lenalidomide		25mg×21
	Dexamethasone		40mg×4
Period I-KRd (After Cycle 2)	Carfilzomib	28	27mg/m^2×6
	Lenalidomide		25mg×21
	Dexamethasone		40mg×4
Period I-VRd(1)	Bortezomib	21	1.3mg/m^2×4
	Lenalidomide		25mg×14
	Dexamethasone		40mg×3
Period I-VRd(2)	Bortezomib	28	1.3mg/m^2×4
	Lenalidomide		15mg×18
	Dexamethasone		40mg×4
Period I-VRd(3)	Bortezomib	35	1.3mg/m^2×4
	Lenalidomide		15mg×21
	Dexamethasone		20mg×8
Period II	Ixazomib	28	4.0mg×3
	Lenalidomide		25mg×21
	Dexamethasone		40mg×4

➢ 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 period I) 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.

➢ Time allowance

- Time allowance for Month 12 after the start of treatment period I

In the analysis of the event rate without using the Kaplan-Meier method, the allowable of diagnoses and tests for event determination at 12 months is 52 weeks ± 4 weeks, and the event rate is calculated as follows.

<For analysis of PFS rate>
(1) No assessment at 52 ± 4 weeks, or only "NE"/"Unknown" during that period;
Included in denominator (Treated as PD)
(2) If one of two consecutive PD assessments was performed by 52 + 4 weeks;
PD
(3) Otherwise;
Progression Free Survival

<For analysis of modified PFS rate>
(1) No assessment at 52 ± 4 weeks, or only "NE"/"Unknown" during that period;
Included in denominator (Treated as PD)
(2) If one of two consecutive PD assessments was performed by 52 + 4 weeks;
PD
(3) If no results are available after a single PD assessment performed by 52 + 4 weeks;
Included in denominator (Treated as PD)
(4) Otherwise;
Progression free survival

➢ Censoring scheme

- Overall survival (OS)

Situation	**Date of event expression or censoring**	**Outcome**
Death	Date of death	event
Discontinuation of treatment period I	Date of discontinuation	-
Discontinuation of treatment period II	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 period I	censoring
Progression	Assessment date of the first of two consecutive assessments	event
Death	Date of death	event
Discontinuation of treatment period I	Date of discontinuation	-
Discontinuation of treatment period II	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

- modified PFS

Situation	**Date of event expression or censoring**	**Outcome**
Incomplete or no baseline assessments	Date of first treatment period I	censoring

Progression	Assessment date of the first of two consecutive assessments	event
Two consecutive PD assessments have not been obtained, but the final assessment is PD	Final assessment date	event
Death	Date of death	event
Discontinuation of treatment period I	Date of discontinuation	-
Discontinuation of treatment period II	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

- Duration of Response (DOR)

DOR is defined for the patients assessed as ≥PR according to the IMWG criteria (2014 version)

Situation	**Date of event expression or censoring**	**Outcome**
Incomplete or no baseline assessments	-	NA
Progression	Assessment date of the first of two consecutive assessments	event
Death	Date of death	event
Discontinuation of treatment period I	Date of discontinuation	-
Discontinuation of treatment period II	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

- modified DOR

modified DOR is defined for the patients assessed as ≥PR according to the IMWG criteria (2014 version)

Situation	**Date of event expression or censoring**	**Outcome**
Incomplete or no baseline assessments	-	NA

Progression	Assessment date of the first of two consecutive assessments	event
Two consecutive PD assessments have not been obtained, but the final assessment is PD	Final assessment date	event
Death	Date of death	event
Discontinuation of treatment period I	Date of discontinuation	-
Discontinuation of treatment period II	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

- Time to Next Treatment (TTNT)

Situation	**Date of event expression or censoring**	**Outcome**
Incomplete or no baseline assessments	Date of first treatment period I	censoring
Progression	Assessment date of the first of two consecutive assessments	-
Death	Date of death	event
Next antitumor treatment started	Date of start of next treatment	event
Continued study treatment	Last observed date	censoring
Discontinued during treatment period I and no information of next treatment	Start date of last cycle	censoring
Discontinued during treatment period II 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 Therapy (DOT)

Situation	**Date of event expression or censoring**	**Outcome**
Incomplete or no baseline assessments	Date of first treatment period I	censoring
Progression	Assessment date of the first of two consecutive assessments	-
Death	Date of death	-
Discontinuation of treatment period I	Date of discontinuation or date of last dose of proteasome inhibitor	event
Discontinuation of treatment period II	Date of discontinuation or date of last dose of Ixazomib	event
Continued study treatment	Last observed date	censoring

➢ 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 for Period I [yes, no (reasons)]
Eligibility for Period II [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:
Analysis will be performed by period I treatment (VRd, KRd) and overall.
(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 VRd, KRd, or 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:
Analysis will be performed by period I treatment (VRd, KRd) and overall.
(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:
Eligible Patients Period I

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

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall. 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

5.2 Patients Characteristics

5.2.1 Demographics and Other Baseline Characteristics

Analysis Set:
Full Analysis Set, Safety Analysis Set, Safety Analysis Set for Treatment Period II

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]
Clinical stage according to ISS at initial diagnosis [Stage I, II, III]
Clinical stage according to ISS at disease recurrence (at first treatment period I) [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 period I) [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]
The longest diameter and shortest diameter of the largest extramedullary plasmacytoma (mm)
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]

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.
(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 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)

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.
(1) Frequency count
(2) Frequency count[Min<= - <=1、2<= - <=Max] and summary statistics of CCI score

5.2.3 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']

Analysis Methods:

Analysis will be performed by period I treatment (VRd, KRd) and overall. 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.

5.2.4 Supportive Therapy

Analysis Set:
Full Analysis Set

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

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(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.

5.2.5 Next-line Treatment

Analysis Set:
Full Analysis Set

Analysis Variables:
Next-line Treatment

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(1) Frequency count

5.2.6 Follow-up Period

Analysis Set:
Full Analysis Set

Analysis Variables:
Follow-up period

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(1) reverse Kaplan-Meier method

Analysis will be performed by using reverse indicator of 6.2.1 ”OS from the start of study treatment period I” in order to estimate median of follow-up period.

(2) Analysis (1) will be repeated with patients dosed of study drug.

6 EFICACY ANALYSIS

6.1 Primary Endpoint and Analytical Methods

6.1.1 PFS rate at 12 Months from the Start of Study Treatment Period I

Analysis Set:
Full Analysis Set

Analysis Variables:
PFS rate at 12 Months from the Start of Study Treatment Period I

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall. Statistical test will be performed only for overall analysis.

(1) The primary endpoint of PFS rate at 12 months from the start of study Treatment Period I is defined as the proportion of patients who are alive and have not had disease progression at 12 months after the start date. The start date is defined as the date of first dose of treatment in Treatment Period I. Patients without 12-month imaging data for determining PD, or patients lost to follow-up, are included in the denominator; however, they are not treated as patients who have not had disease progression. For the primary endpoint analysis, the null hypothesis will be that the proportion of patients in the FAS who are alive and progression-free at 12 months after the start of Treatment Period I is ≤36%.The one-sided significance level will be 5%. Exact two-sided 90% confidence intervals will be calculated via binomial distribution. The same analysis will be performed by defining a modified PFS rate to account for the possibility that a new treatment is administered before two consecutive assessments, even though PD has been determined at one time. The evaluation was conducted under the assumption that all the patients were confirmed to have PD again, and the patients was treated as PD once determined to have PD.

6.1.2 Supplemental Analysis for Primary Endpoint

Analysis Set:
Evaluable Analysis Set

Analysis Variables:
PFS rate at 12 Months from the Start of Study Treatment Period I

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

6.2 Secondary Endpoints and Analytical Methods

6.2.1 OS from the Start of Study Treatment Period I

Analysis Set:

Full Analysis Set

Analysis Variables:
OS from the start of study Treatment Period I

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.
(1) OS is defined as the period from the first dose of treatment in Treatment Period I 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 rate at Month 3, 6, 9, 12, 15, 18, 21, 24, 27 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 OS rate, and then calculated by exponential transformation.

6.2.2 PFS from the Start of Study Treatment Period I

Analysis Set:
Full Analysis Set

Analysis Variables:
PFS from the start of study Treatment Period I

Strata:
Clinical stage according to ISS at disease recurrence (at first treatment period I) [Stage I, II, III]
Best response [at least VGPR, PR or worse]
Charlson comorbidity index（CCI） [Min<= - <=1、2<= - <=Max]

The following items may fall under each category in duplicate.
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 period I) [del17p, 1q gain]
Prior antineoplastic therapies* [Treated, Not treated]
*Bortezomib, Carfilzomib, Lenalidomide, Pomalidomide, Elotuzumab, Daratumumab

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(1) PFS is defined as the period from the first dose of treatment in Treatment Period I 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 similar methodology to that used for analysis of OS. The same analysis will be performed by defining a modified PFS to account for the possibility that a new treatment is administered before two consecutive assessments, even though PD has been determined at one time. The evaluation was conducted under the assumption that all the patients were confirmed to have PD again, and the patients was treated as PD once determined to have PD.

(2) PFS rate at Month 3, 6, 9, 12, 15, 18, 21, 24, 27 and the two-sided 95% confidence interval will be will be estimated using similar methodology to that used for analysis of OS.

(3) Analysis (1) and (2) will be repeated for each strata.

6.2.3 Very Good Partial Response (VGPR) or More

Analysis Set:
Full Analysis Set

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

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(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.

6.2.4 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:

Analysis will be performed by period I treatment (VRd, KRd) and overall. 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

(2) If there are patients who achieved CR in the treatment period I, the same analysis will be conducted focusing on patients who achieved CR in the treatment period II.

6.2.5 Best Response

Analysis Set:
Full Analysis Set

Analysis Variables:
Best Response

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(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.

(2) A shift table with the best response of Period I at the head of the table and the best response of Period II at the side will be created. Patients discontinued during period I will be tabulated as the best response of Period II “NA”.

6.2.6 Overall Response Rate（ORR）

Analysis Set:
Full Analysis Set

Analysis Variables:
ORR

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(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.

6.2.7 Proportion of Patients Continuing Treatment with Ixazomib at 12 Months from the Start of Study Treatment Period I

Analysis Set:
Full Analysis Set

Analysis Variables:
Proportion of patients continuing treatment with Ixazomib at 12 months from the start of study Treatment Period I

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(1) The proportion of patients who are continuing to receive study drug at 12 months after the start of treatment period I, and the two-sided 95% confidence intervals, will be calculated. Exact confidence intervals will be calculated based on a binomial distribution.

6.2.8 Duration of Response（DOR）

Analysis Set:
Full Analysis Set

Analysis Variables:
DOR

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(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 SD. The same analysis will be performed by

defining a modified DOR to account for the possibility that a new treatment is administered before two consecutive assessments, even though PD has been determined at one time. The evaluation was conducted under the assumption that all the patients were confirmed to have PD again, and the patients was treated as PD once determined to have PD.

(2) DOR rate at Month 3, 6, 9, 12, 15, 18, 21, 24, 27 and the two-sided 95% confidence interval will be will be estimated using similar methodology to that used for analysis of OS.

6.2.9 Time to Next Treatment（TTNT）

Analysis Set:
Full Analysis Set

Analysis Variables:
TTNT

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(1) TTNT is defined as the period from the first dose of treatment, which is based on proteasome inhibitor, in Treatment Period I 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 OS.

(2) TTNT rate at Month 3, 6, 9, 12, 15, 18, 21, 24, 27 and the two-sided 95% confidence interval will be will be estimated using similar methodology to that used for analysis of OS.

6.2.10 Duration of Therapy（DOT）

Analysis Set:
Full Analysis Set

Analysis Variables:
DOT

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(1) DOT is defined as the period from the first dose of treatment, which is based on proteasome inhibitor, in Treatment Period I to the time of discontinuation of study treatment or last dose of proteasome inhibitor, whichever is later. Patients who continue study treatment will be

censored at the last confirmed date at last observed date. DOT for the FAS will be estimated using similar methodology to that used for analysis of OS.

(2) DOT rate at Month 3, 6, 9, 12, 15, 18, 21, 24, 27 and the two-sided 95% confidence interval will be will be estimated using similar methodology to that used for analysis of OS.

6.2.11 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:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(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, Treatment Period I, plus the mean and 95% confidence intervals, will be calculated. For patients enrolled in Treatment Period II, summary statistics for change from cycle 1, Treatment Period II, plus the 95% confidence intervals of mean, will also be calculated.

6.2.12 Quality Adjusted Life Years: QALY

Analysis Set:
Full Analysis Set

Analysis Variables:
modified QALY

Analysis Methods:

Analysis will be performed by period I treatment (VRd, KRd) and overall.

(1) Summary statistics regarding modified QALYs will be calculated at 12 months from the start of study Treatment Period I

(2) Analysis (1) will be repeated without discontinued patients during treatment period I.

6.2.13 Health Care Resource Utilization: HCRU

Analysis Set:
Full Analysis Set

Analysis Variables:
Hospitalization events
Outpatient events

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.

(1) The exposure-adjusted rate of hospitalization events (per patient-months) and the duration of hospitalization will be calculated by treatment period and overall.

(2) The exposure-adjusted rate of outpatient events (per patient-months) will be calculated by treatment period and overall.

6.2.14 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 by treatment period and overall. For RDI of overall period, proteasome inhibitor (Bortezomib+Ixazomib, Carfilzomib+Ixazomib, Bortezomib/Carfilzomib+Ixazomib) will be combined.

6.2.15 Bone Evaluation

Analysis Set:

Full Analysis Set

Analysis Variables:
Bone evaluation

Analysis Methods:
Analysis will be performed by period I treatment (VRd, KRd) and overall.
(1) The percentage of patients with bone lesions and the two-sided 95% confidence intervals will be calculated. Exact confidence intervals will be calculated based on a binomial distribution.

6.2.16 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:
Analysis will be performed by period I treatment (VRd, KRd) and overall.
(1) Summary statistics and 95% confidence interval of mean will be calculated.
(2) Summary statistics for change from cycle 1, Treatment Period I, plus the 95% confidence interval of mean, will be calculated. For patients enrolled in Treatment Period II, summary statistics for change from cycle 1, Treatment Period II, plus the 95% confidence intervals of mean, will also 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, Treatment Period I, plus the 95% confidence interval of mean, will be calculated. For patients enrolled in Treatment Period II, summary statistics for percent change from cycle 1, Treatment Period II, plus the 95% confidence intervals of mean, will also be calculated.

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：
Grade [Grade1 – Grade5]

Analysis will be performed by period I treatment (VRd, KRd) and overall.

1) Frequency count of All TEAEs
2) Frequency count of Grade 3 or higher TEAEs
3) Frequency count of All TEAEs by grade
4) Frequency count of Serious TEAEs
5) Frequency count of TEAEs that Result 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 Overview of Treatment-Emergent Adverse Event after the First Dose of Study Drug

Analysis Set:
Safety Analysis Set for Treatment Period II

Analysis Variables:
TEAEs after the first dose of study drug

Categories：

Relationship to study drug	[Related, Not related]
Grade	[Grade1 – Grade5]

Analysis will be performed by period I treatment (VRd, KRd) and overall.

1) Frequency count of All TEAEs after the first dose of study drug
2) Frequency count of study drug related TEAEs after the first dose of study drug
3) Frequency count of grade 3 or higher TEAEs after the first dose of study drug
4) Frequency count of study drug related grade 3 or higher TEAEs after the first dose of study drug
5) Frequency count of All TEAEs after the first dose of study drug by grade
6) Frequency count of study drug related TEAEs after the first dose of study drug by grade
7) Frequency count of TEAEs resulting in discontinuation of treatment after the first dose of study drug
8) Frequency count of serious TEAEs after the first dose of study drug
10) Frequency count of TEAEs after the first dose of study drug that result in death

Note for calculation of incidence rate:
Same as 7.1.1

7.1.3 Output of Treatment-Emergent Adverse Event

Analysis Set:
Safety Analysis Set

Analysis Variables:
TEAE

Category：
Grade [Grade1 – Grade5]

Analysis will be performed by period I treatment (VRd, KRd) and overall.
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 Grade 3 or higher TEAEs by SOC and PT
3) Frequency count of TEAEs by SOC and PT by Grade
4) Frequency count of Serious TEAEs by SOC and PT
5) Frequency count of Non-serious TEAEs by SOC and PT
6) Frequency count of TEAEs that Result 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.

7.1.4 Output of Treatment-Emergent Adverse Event after the First Dose of Study Drug

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE after the First Dose of Study Drug

Categories：

Relationship to study drug	[Related, Not related]
Grade	[Grade1 – Grade5]

Analysis will be performed by period I treatment (VRd, KRd) and overall.

TEAE after the First Dose of Study Drug 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 TEAEs after the First Dose of Study Drug by SOC and PT
2) Frequency count of Study Drug-related TEAEs after the First Dose of Study Drug by SOC and PT
3) Frequency count of Grade 3 or higher TEAEs after the First Dose of Study Drug by SOC and PT
4) Frequency count of Study Drug-related Grade 3 or higher TEAEs after the First Dose of Study Drug by SOC and PT
5) Frequency count of TEAEs after the First Dose of Study Drug by SOC and PT by Grade
6) Frequency count of Study Drug-related TEAEs after the First Dose of Study Drug by SOC and PT by Grade
7) Frequency count of TEAEs Resulting in Discontinuation of Treatment after the First Dose of Study Drug by SOC and PT
8) Frequency count of Serious TEAEs after the First Dose of Study Drug by SOC and PT
9) Frequency count of Non-serious TEAEs after the First Dose of Study Drug by SOC and PT
10) Frequency count of TEAEs that Result in Death after the First Dose of Study Drug by SOC and PT

Note for calculation of incidence rate:

Same as 7.1.3

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 6.2.2.

10 REVISION HISTORY

This document is a translation of the 4th Japanese version.