EU Clinical Trials Register

Clinical trial results:
A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation

Summary

EudraCT number	2014-001394-13
Trial protocol	DE BE CZ AT PT DK ES SE HU FR HR PL GR IT
Global end of trial date	26 August 2022

Results information

Result version number	v1 (current)
This version publication date	08 September 2023
First version publication date	08 September 2023

Trial information

Trial identification

Sponsor protocol code	C16021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02312258
WHO universal trial number (UTN)	U1111-1160-1702
Other trial identifiers	REec: REec-2015-1414, JapicCTI: JapicCTI-152873, RNEC: 153300410A0048, TCTIN: 1046003327, SNCTP: SNCTP000001745, NRES: 15/NE/0167, HC-CTD: 182602, CRS: MOH_2017-06-15_000529

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the effect of ixazomib maintenance therapy on progression free survival (PFS) compared with placebo, in subjects with newly diagnosed multiple myeloma (NDMM) who have had a major response (complete response [CR], very good partial response [VGPR], or partial response [PR]) to initial therapy and who have not undergone stem-cell transplantation (SCT).

Protection of trial subjects:

Each subject signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	40 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Singapore: 12
Country: Number of subjects enrolled	United Kingdom: 66
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Brazil: 43
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	China: 9
Country: Number of subjects enrolled	Czechia: 69
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 11

Country: Number of subjects enrolled	Greece: 113
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 52
Country: Number of subjects enrolled	Japan: 32
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Serbia: 24
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Turkey: 12
Worldwide total number of subjects	706
EEA total number of subjects	370

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	68
From 65 to 84 years	617
85 years and over	21

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study from 09 April 2015 to 26 August 2022.

Pre-assignment

Screening details:

Participants with newly diagnosed multiple myeloma not treated with stem cell transplantation (SCT) were enrolled and randomised in a 3:2 ratio to receive ixazomib or placebo respectively.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Carer, Data analyst, Investigator, Monitor, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Ixazomib placebo-matching capsule, orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 through 26.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib placebo-matching capsule, was administered orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 through 26.

Arm title	Ixazomib

Arm description:

Ixazomib 3 mg, capsule, orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 to 4 that may have been escalated to 4 mg thereafter up to Cycle 26.

Arm type	Experimental
Investigational medicinal product name	Ixazomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ixazomib 3 mg, capsule, was administered orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 to 4 that may have been escalated to 4 mg thereafter up to Cycle 26.

Number of subjects in period 1	Placebo	Ixazomib
Started	281	425
Completed	0	0
Not completed	281	425
Adverse event, serious fatal	115	181
Withdrawal by Patient	49	76
Lost to follow-up	8	8
Missing	2	1
Reason not Specified	107	159

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Ixazomib placebo-matching capsule, orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 through 26.	
Reporting group title	Ixazomib
Reporting group description:	
Ixazomib 3 mg, capsule, orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 to 4 that may have been escalated to 4 mg thereafter up to Cycle 26.	

Reporting group values	Placebo	Ixazomib	Total
Number of subjects	281	425	706
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	72.8	72.3	
standard deviation	± 6.77	± 6.87	-
Gender categorical			
Units: Subjects			
Male	155	222	377
Female	126	203	329
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	39	63	102
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	5	15	20
White	227	330	557
Unknown or Not Reported	9	15	24
Region of Enrollment			
Units: Subjects			
Australia	11	9	20
China	3	6	9
Japan	15	17	32
Singapore	4	8	12
Korea, Republic Of	10	17	27
Taiwan, Province Of China	3	5	8
Thailand	2	8	10
Austria	2	3	5
Belgium	0	1	1
Czech Republic	31	38	69
Denmark	1	5	6
France	10	6	16
Germany	5	6	11
Greece	50	63	113

Hungary	5	7	12
Israel	5	11	16
Italy	18	34	52
Poland	2	13	15
Portugal	6	10	16
Russia	2	6	8
Serbia	11	13	24
South Africa	2	5	7
Spain	23	25	48
Sweden	3	3	6
Switzerland	1	1	2
Turkey	4	8	12
United Kingdom	20	46	66
Argentina	2	2	4
Brazil	16	27	43
Chile	4	7	11
Colombia	1	2	3
Canada	4	3	7
Mexico	2	4	6
United States	3	6	9
Ethnicity Units: Subjects			
Hispanic or Latino	36	46	82
Not Hispanic or Latino	237	366	603
Unknown or Not Reported	8	13	21

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Ixazomib placebo-matching capsule, orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 through 26.	
Reporting group title	Ixazomib
Reporting group description:	
Ixazomib 3 mg, capsule, orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 to 4 that may have been escalated to 4 mg thereafter up to Cycle 26.	
Subject analysis set title	Ixazomib
Subject analysis set type	Safety analysis
Subject analysis set description:	
test	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[1]

End point description:

PFS is defined as time from date of randomisation to date of first documentation of progressive disease (PD) or death from any cause, as evaluated by an independent review committee (IRC) according to International Myeloma Working Group (IMWG) criteria, or death due to any cause, whichever occurs first. Per IMWG criteria, PD is defined as, increase of 25% of lowest response value in one or more of following criteria: serum M-component (absolute increase ≥0.5 g/ deciliter (dL)); or urine M-component (absolute increase ≥200 mg/24-hour); difference between involved and uninvolved free light chains (FLC) levels (absolute increase >10 mg/dL); or bone marrow plasma cell percentage (absolute plasma cell percentage ≥10%); development of new/ increase in size of existing bone lesions or soft tissue plasmacytoma; or development of hypercalcemia (corrected serum calcium >11.5mg/dL). Intent-to-treat (ITT) Population included all participants who were randomised and had post-randomisation data.

End point type	Primary

End point timeframe:

From randomisation until PD or death (up to 52 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics were planned to be analysed for this endpoint.

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	425		
Units: months				
median (confidence interval 95%)	9.4 (8.51 to 11.47)	17.4 (14.78 to 20.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was measured as the time from the date of randomisation to the date of death. ITT Population included all participants who were randomised and had post-randomisation data.

End point type	Secondary

End point timeframe:

From the date of randomisation every 12 weeks after PD on next-line therapy until death (up to 88 months)

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	425		
Units: months				
median (confidence interval 95%)	69.5 (56.67 to 75.17)	64.8 (54.87 to 74.84)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)

Statistical analysis description:

P-value comparing OS between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), International Staging System (ISS) stage before initial therapy (stage I or II vs stage III), age (<75 versus [vs] >=75 years) at randomisation, and best response to initial therapy (complete response (CR) or very good partial response (VGPR) vs partial response (PR)).

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.473
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.861
upper limit	1.381

Notes:

[2] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Percentage of Participants Who Achieve or Maintain Any Best Response Category During the Treatment Period

End point title	Percentage of Participants Who Achieve or Maintain Any Best Response Category During the Treatment Period

End point description:

Response was assessed according to IMWG criteria based on IRC assessment. Best response included PR, VGPR and CR. PR= >=50% reduction of serum M protein and >=90% or <200 mg reduction urinary

M protein in 24-hour, or >50% decrease in difference between involved and uninvolved FLC levels, or >50% reduction in bone marrow plasma cells, if bone marrow plasma cells >30% and >50% reduction in size of soft tissue plasmacytomas at baseline. VGPR= >90% reduction (<100 mg/24-hour) in serum M-protein + urine M-protein detectable by immunofixation but not on electrophoresis. Complete response= >5% plasma cells in myelogram with absence of paraprotein in serum and urine according to immunofixation. ITT Population included all participants who were randomised and had post-randomisation data. The percentages are rounded off to the single nearest decimal point.

End point type	Secondary
End point timeframe:	
Up to 27 months	

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	425		
Units: percentage of participants				
number (not applicable)				
PR	29	25		
VGPR	37	34		
CR	28	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
End point description:	

TTP is defined as the time from the date of randomisation to the date of first documentation of PD, using IMWG criteria. ITT Population included all participants who were randomised and had post-randomisation data.

End point type	Secondary
End point timeframe:	
From randomisation until PD or death (up to 52 months)	

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	425		
Units: months				
median (confidence interval 95%)	9.6 (8.67 to 11.99)	17.8 (15.67 to 20.63)		

Statistical analyses

Statistical analysis title	Time to Progression (TTP)

Statistical analysis description:

P-value comparing TTP between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.655
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.537
upper limit	0.799

Notes:

[3] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Time to Next Line Therapy (TTNT)

End point title	Time to Next Line Therapy (TTNT)

End point description:

TTNT is defined as the time from the date of randomisation to the date of the first dose of next-line antineoplastic therapy. ITT Population included all participants who were randomised and had post-randomisation data.

End point type	Secondary

End point timeframe:

From randomisation until PD or death (up to 52 months)

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	425		
Units: months				
median (confidence interval 95%)	16.1 (13.54 to 19.35)	22.1 (19.55 to 25.89)		

Statistical analyses

Statistical analysis title	Time to Next Line Therapy (TTNT)

Statistical analysis description:

P-value comparing TTNT between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage

III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.018
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.777
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.631
upper limit	0.957

Notes:

[4] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Duration of Next-line Therapy

End point title	Duration of Next-line Therapy

End point description:

Duration of next-line therapy is defined as the time from the date of the first dose of the line of antineoplastic therapy coming after study treatment to the date of the last dose. ITT Population included all participants who were randomised and had post-randomisation data. Number of subjects analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

From randomisation until PD or death (up to 52 months)

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	215		
Units: months				
median (confidence interval 95%)	14.0 (10.41 to 16.82)	8.7 (7.85 to 10.87)		

Statistical analyses

Statistical analysis title	Duration of Next-line Therapy
Comparison groups	Placebo v Ixazomib

Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.293
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.968
upper limit	1.727

Notes:

[5] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Progression Free Survival 2 (PFS2)

End point title	Progression Free Survival 2 (PFS2)

End point description:

PFS2 is defined as the time from the date of randomisation to objective PD on next-line treatment using IMWG criteria, or death due to any cause, whichever occurred first. ITT Population included all participants who were randomised and had post-randomisation data.

End point type	Secondary

End point timeframe:

From the date of randomisation to every 12 weeks until second PD or death (up to 88 months)

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	425		
Units: months				
median (confidence interval 95%)	50.3 (40.05 to 62.46)	51.3 (44.91 to 63.41)		

Statistical analyses

Statistical analysis title	Progression Free Survival 2 (PFS2)

Statistical analysis description:

P-value comparing PFS2 between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib

Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.893
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.984
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.777
upper limit	1.246

Notes:

[6] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Correlation of MRD Status With PFS and OS

End point title	Correlation of MRD Status With PFS and OS

End point description:

PFS is defined as the time from the date of randomisation to the date of first documentation of PD or death from any cause, as evaluated by an IRC according to IMWG criteria, or death due to any cause, whichever occurred first, assessed for up to 52 months in this endpoint. OS was measured as the time from the date of randomisation to the date of death, assessed for up to 52 months in this endpoint. Participants with various types of known MRD status were pooled together for analysis of overall survival in this outcome measure. ITT Population included all participants who were randomised and had post-randomisation data. Number of subjects analysed is the number of participants with data available for analyses. 'n'=number analysed is the number of participants with data available for analyses for the specified category. The percentages are rounded off to the nearest single decimal point. '9999' indicates that the value was not estimable due to censoring.

End point type	Secondary

End point timeframe:

From randomisation up to 52 months

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	213		
Units: months				
median (confidence interval 95%)				
PFS for Participants with Known MRD+ (n=125,169)	9.3 (7.75 to 11.99)	16.9 (13.47 to 21.29)		
PFS for Participants with Known MRD- (n=26,44)	9999 (23.69 to 9999)	40.5 (26.94 to 9999)		
OS for Participants:Known MRDStatus(n=151,213)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	PFS for Known MRD+ at Study Entry

Statistical analysis description:

P-value comparing PFS between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Ixazomib v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.582
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.425
upper limit	0.796

Notes:

[7] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Statistical analysis title	PFS for Known MRD- at Study Entry

Statistical analysis description:

P-value comparing PFS between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.398
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.537
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.563
upper limit	4.194

Notes:

[8] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Statistical analysis title	OS:MRD-,Known MRD+,Known MRD Status at Study Entry

Statistical analysis description:

P-value comparing OS between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age

(<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Ixazomib v Placebo
Number of subjects included in analysis	364
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.012
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	10.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.194
upper limit	86.649

Notes:

[9] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Percentage of Participants Who Develop a New Primary Malignancy

End point title	Percentage of Participants Who Develop a New Primary Malignancy[10]

End point description:

Safety Population included all participants who received at least 1 dose of ixazomib or placebo. Three placebo participants who erroneously received a single dose of ixazomib were included in the ixazomib arm of the safety population. The percentages are rounded off to the single nearest decimal point.

End point type	Secondary

End point timeframe:

From randomisation until PD or death (up to 52 months)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is applicable only for participants in the safety population.

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	276	426		
Units: percentage of subjects				
number (not applicable)	6.2	5.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to End of Next-line of Therapy

End point title	Time to End of Next-line of Therapy

End point description:

Time to end of the next line of therapy is defined as the time from the date of randomisation to the date of last dose of the next line of antineoplastic therapy following study treatment. ITT Population included

all participants who were randomised and had post-randomisation data. Number of subjects analysed is the number of participants with data available for analysis.

End point type	Secondary
End point timeframe:	
From randomisation until PD or death (up to 52 months)	

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	215		
Units: months				
median (confidence interval 95%)	25.6 (22.70 to 28.48)	23.1 (20.93 to 26.05)		

Statistical analyses

Statistical analysis title	Time to End of Next-line of Therapy
Statistical analysis description:	

P-value comparing Time to End of Next Line Therapy between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.839
upper limit	1.47

Notes:

[11] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Change From Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status
End point description:	

ECOG assesses participant's performance status on 6-point scale:0=fully active/able to carry on all pre-disease activities without restriction;1=restricted in physically strenuous activity, ambulatory/able to carry out light or sedentary work;2=ambulatory (>50% of waking hours),capable of all self-care,unable to carry out any work activities;3=capable of only limited self-care,confined to bed/chair >50% of waking hours;4=completely disabled,cannot carry on any self-care,totally confined to bed/chair;5=dead.

Lower grades indicate improvement.Safety Population=all participants who received atleast 1 dose of ixazomib or placebo.3 placebo participants who erroneously received a single dose of ixazomib were included in ixazomib arm of safety population.Number of participants analysed=number of participants with data available for analysis. '9999'=standard deviation was not estimable for a single participant.'999'=data was not available as no participants were available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 26, progression free survival follow-up (PFSFU)- Visit 37 and progressive disease follow-up (PDFU)- Visit 26 (cycle length=28 days)

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	415		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n=271, 415)	-0.0 (± 0.36)	-0.0 (± 0.42)		
Cycle 3 Day 1 (n=263, 396)	-0.0 (± 0.36)	-0.0 (± 0.42)		
Cycle 4 Day 1 (n=251, 379)	-0.0 (± 0.39)	-0.1 (± 0.42)		
Cycle 5 Day 1 (n=235, 355)	-0.0 (± 0.44)	-0.0 (± 0.44)		
Cycle 6 Day 1 (n=219, 332)	-0.0 (± 0.46)	-0.0 (± 0.43)		
Cycle 7 Day 1 (n=204, 305)	-0.0 (± 0.49)	-0.0 (± 0.42)		
Cycle 8 Day 1 (n=188, 287)	-0.1 (± 0.48)	-0.0 (± 0.42)		
Cycle 9 Day 1 (n=175, 279)	-0.1 (± 0.47)	-0.0 (± 0.45)		
Cycle 10 Day 1 (n=163, 261)	-0.1 (± 0.52)	-0.0 (± 0.47)		
Cycle 11 Day 1 (n=151, 246)	-0.1 (± 0.51)	-0.0 (± 0.43)		
Cycle 12 Day 1 (n=151, 246)	-0.1 (± 0.56)	-0.0 (± 0.43)		
Cycle 13 Day 1 (n=129, 219)	-0.0 (± 0.54)	-0.0 (± 0.46)		
Cycle 14 Day 1 (n=115, 204)	0.0 (± 0.53)	-0.0 (± 0.44)		
Cycle 15 Day 1 (n=104, 185)	-0.0 (± 0.53)	-0.0 (± 0.49)		
Cycle 16 Day 1 (n=96, 177)	-0.0 (± 0.51)	-0.0 (± 0.49)		
Cycle 17 Day 1 (n=84, 164)	-0.0 (± 0.54)	-0.0 (± 0.50)		
Cycle 18 Day 1 (n=74, 159)	0.0 (± 0.51)	-0.0 (± 0.51)		
Cycle 19 Day 1 (n=65, 148)	0.0 (± 0.47)	-0.0 (± 0.49)		
Cycle 20 Day 1 (n=57, 133)	0.0 (± 0.46)	-0.0 (± 0.49)		
Cycle 21 Day 1 (n=52, 122)	0.0 (± 0.48)	-0.0 (± 0.52)		
Cycle 22 Day 1 (n=51, 111)	0.1 (± 0.51)	-0.0 (± 0.52)		
Cycle 23 Day 1 (n=42, 101)	0.0 (± 0.44)	-0.0 (± 0.48)		
Cycle 24 Day 1 (n=41, 91)	0.1 (± 0.54)	-0.0 (± 0.47)		
Cycle 25 Day 1 (n=35, 79)	0.0 (± 0.42)	-0.0 (± 0.47)		
Cycle 26 Day 1 (n=28, 68)	0.0 (± 0.47)	-0.0 (± 0.47)		
PFSFU- Visit 37 (n=0, 1)	999 (± 999)	1.0 (± 9999)		
PDFU- Visit 26 (n=0, 1)	999 (± 999)	1.0 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Conversion From Minimal Residual Disease (MRD) Positive to MRD Negative

End point title	Percentage of Participants With Conversion From Minimal Residual Disease (MRD) Positive to MRD Negative

End point description:

Bone marrow aspirates and blood samples were sent to a central laboratory and were assessed for MRD using flow cytometry. MRD negativity was defined as absence of MRD and MRD positivity was defined as presence of MRD. MRD was assessed by 8-color flow cytometry with the IMWG recommended sensitivity of 10^-5. ITT Population included all participants who were randomised and had post-randomisation data. Number of subjects analysed is the number of participants with data available for analyses. The percentages are rounded off to the nearest single decimal point.

End point type	Secondary

End point timeframe:

Up to 52 months

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	169		
Units: percentage of participants				
number (not applicable)	3	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) as Measured by the Global Health Status

End point title	Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) as Measured by the Global Health Status

End point description:

ECOG assesses participant's performance status on 5-point scale:0=fully active/able to carry on all pre-disease activities without restriction;1=restricted in physically strenuous activity, ambulatory/able to carry out light/sedentary work;2=ambulatory(>50%of waking hours),capable of all self-care,unable to carry out any work activities;3=capable of only limited self-care,confined to bed/chair>50%of waking hours;4=completely disabled,cannot carry on self-care,totally confined to bed/chair;5=dead.Lower grades=improvement.Safety Population=all participants with 1 dose of ixazomib/placebo.3placebo participants who erroneously received single ixazomib dose were included in ixazomib arm of safety.Number of subjects analysed=participants with data available for analysis.'9999'=standard deviation was not estimable for single subject.'999'=data was not available as no participants were available for analyses.'n'=number of participants with data available for analysis for the given time

End point type	Secondary

End point timeframe:

Baseline, Cycles 2 through 26 (cycle length=28 days)

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	407		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 (n=257, 391)	1.7 (± 16.63)	-0.1 (± 16.77)		
Cycle 3 (n=257, 375)	2.1 (± 15.74)	-1.2 (± 17.14)		
Cycle 4 (n=245, 360)	1.5 (± 16.80)	-0.6 (± 16.53)		
Cycle 5 (n=227, 340)	1.8 (± 15.79)	0.6 (± 16.33)		
Cycle 6 (n=213, 307)	1.0 (± 18.33)	-1.5 (± 16.56)		
Cycle 7 (n=202, 292)	3.1 (± 16.32)	-0.7 (± 17.28)		
Cycle 8 (n= 186, 273)	0.9 (± 18.07)	-0.4 (± 17.44)		
Cycle 9 (n=173, 258)	1.4 (± 16.67)	0.1 (± 16.57)		
Cycle 10 (n=163, 245)	2.0 (± 16.38)	-1.6 (± 17.82)		
Cycle 11 (n=152, 233)	3.9 (± 17.37)	0.2 (± 17.75)		
Cycle 12 (n=143, 228)	3.9 (± 14.53)	0.3 (± 16.26)		
Cycle 13 (n=132, 218)	4.2 (± 16.13)	-0.5 (± 16.85)		
Cycle 14 (n=126, 204)	3.1 (± 16.99)	-1.1 (± 17.45)		
Cycle 15 (n=115, 194)	2.2 (± 16.74)	-0.7 (± 17.65)		
Cycle 16 (n=104, 184)	2.5 (± 15.57)	0.5 (± 17.03)		
Cycle 17 (n=100, 182)	2.4 (± 15.09)	-0.2 (± 18.09)		
Cycle 18 (n=91, 182)	0.5 (± 18.40)	1.7 (± 16.87)		
Cycle 19 (n=82, 172)	1.6 (± 18.07)	1.1 (± 17.24)		
Cycle 20 (n=74, 161)	1.1 (± 17.95)	0.4 (± 16.13)		
Cycle 21 (n=72, 153)	1.5 (± 16.39)	1.3 (± 16.19)		
Cycle 22 (n=72, 147)	1.6 (± 15.55)	1.0 (± 17.13)		
Cycle 23 (n=68, 137)	2.1 (± 19.01)	0.9 (± 16.96)		
Cycle 24 (n=64, 132)	-0.3 (± 20.46)	2.3 (± 15.65)		
Cycle 25 (n=56, 125)	0.0 (± 18.80)	0.3 (± 17.52)		
Cycle 26 (n=47, 106)	2.8 (± 17.49)	0.9 (± 17.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in a High-risk Population

End point title	PFS in a High-risk Population

End point description:

High-risk population included but not be limited to participants carrying del17, t(4;14), t(14;16). PFS was defined as the time from the date of randomisation to the date of first documentation of PD or death from any cause. ITT Population included all participants who were randomised and had post-randomisation data. Number of subjects analysed is the number of participants present in the high-risk group.

End point type	Secondary

End point timeframe:

From randomisation until PD or death (up to 52 months)

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	74		
Units: months				
median (confidence interval 95%)	9.6 (5.62 to 13.90)	10.1 (6.01 to 17.02)		

Statistical analyses

Statistical analysis title	PFS in a High-risk Population

Statistical analysis description:

P-value comparing PFS between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib	
Number of subjects included in analysis	122	
Analysis specification	Pre-specified	
Analysis type	superiority[12]	
P-value	= 0.963	
Method	Logrank	
Parameter estimate	Hazard ratio (HR)	
Point estimate	1.011	
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	0.631	
upper limit	1.621	

Notes:

[12] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Percentage of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)[13]

End point description:

An adverse event(AE)=any untoward medical occurrence in participant administered a drug;not necessarily having causal relationship with this treatment.An AE can be any unfavorable,unintended sign(e.g.,clinically significant abnormal laboratory finding),symptom,disease temporally associated with use of drug,whether or not considered related to drug.TEAEs=events occurring post administration of first ixazomib/placebo dose through 30days post last ixazomib/placebo dose.SAE=any untoward medical occurrence resulting in death,was life-threatening,required in-patient hospitalization/prolongation of existing hospitalization,resulted in persistent/significant disability/incapacity,congenital anomaly/birth defect or considered medically significant.Safety Population=all participants receiving 1 ixazomib/placebo dose.3placebo participants who erroneously received single ixazomib dose were included in ixazomib arm of safety population.Percentages were rounded off to nearest single decimal point.

End point type	Secondary

End point timeframe:

First dose of study drug through 30 days after last dose of study drug (up to 88 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is applicable only for participants in the safety population.

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	276	426		
Units: percentage of participants				
number (not applicable)				
SAE	17	24		
TEAE	82	92		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in a High-risk Population

End point title	OS in a High-risk Population

End point description:

High-risk population included but not be limited to participants carrying cytogenetic deletion (del)17, translocation [t](4;14), t(14;16). OS was measured as the time from the date of randomisation to the date of death. ITT Population included all participants who were randomised and had post-randomisation data. Number of subjects analysed is the number of participants present in the high-risk group.

End point type	Secondary

End point timeframe:

From the date of randomisation and every 12 weeks after PD on next-line therapy until death (up to 88 months)

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	74		
Units: months				
median (confidence interval 95%)	48.3 (29.70 to 74.48)	37.3 (26.05 to 47.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Frailty Status and PFS and OS

End point title	Correlation Between Frailty Status and PFS and OS

End point description:

Participant's frailty status is classified as fit, unfit or frail on bases of 4 components: age, Charlson comorbidity scoring system without age weighting, Katz index of independence in activities of daily

living,and Lawton instrumental activities of daily living scale. Sum of 4 frailty scores is total frailty score. Total frailty score of 0=frailty status of fit;of 1 to unfit;and of 2/more to frail. PFS=time from date of randomisation to date of first documentation of PD/death from any cause, evaluated by IRC according to IMWG criteria, or death due to any cause,whichever occurs first. OS=time from date of randomisation to date of death. ITT Population=all participants who were randomised and had post-randomisation data. Number of subjects analysed is number of participants with data available for analysis. 'n'=number of participants with data available for analysis for the specified category. '9999' indicates median, upper, and lower limit of CI were not estimable due to censoring.

End point type	Secondary
End point timeframe:	
From randomisation up to 52 months	

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	172		
Units: months				
median (confidence interval 95%)				
PFS Based on Frailty Status of Fit (n=112, 172)	8.5 (7.39 to 10.41)	18.6 (12.75 to 25.63)		
PFS Based on Frailty Status of Unfit (n=98, 147)	10.6 (7.39 to 14.23)	17.6 (13.17 to 21.78)		
PFS Based on Frailty Status of Frail (n=68, 102)	11.1 (8.44 to 15.67)	15.4 (11.10 to 23.75)		
OS Based on Frailty Status of Fit (n=112, 172)	9999 (9999 to 9999)	9999 (9999 to 9999)		
OS Based on Frailty Status of Unfit (n= 98, 147)	9999 (9999 to 9999)	9999 (39.59 to 9999)		
OS Based on Frailty Status of Frail (n=68, 102)	42.5 (29.93 to 9999)	46.5 (34.30 to 46.52)		

Statistical analyses

Statistical analysis title	PFS Based on Frailty Status of Fit
Statistical analysis description:	

P-value comparing PFS between treatment groups was based on Log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), and age (<75 vs >=75 years) at randomisation.

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.387
upper limit	0.727

Notes:

[14] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), and age (<75 vs >=75 years) at randomisation, comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Statistical analysis title	OS Based on Frailty Status of Frail

Statistical analysis description:

P-value comparing OS between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.63
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.854
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.448
upper limit	1.627

Notes:

[15] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Statistical analysis title	PFS Based on Frailty Status of Frail

Statistical analysis description:

P-value comparing PFS between treatment groups was based on Log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), and age (<75 vs >=75 years) at randomisation.

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.147
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.733
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.481
upper limit	1.117

Notes:

[16] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), and age (<75 vs >=75 years) at randomisation, comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Statistical analysis title	OS Based on Frailty Status of Unfit

Statistical analysis description:

P-value comparing OS between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.124
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	3.601

Notes:

[17] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Statistical analysis title	PFS Based on Frailty Status of Unfit

Statistical analysis description:

P-value comparing PFS between treatment groups was based on Log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), and age (<75 vs >=75 years) at randomisation.

Comparison groups	Placebo v Ixazomib
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.098
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.746
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.526
upper limit	1.058

Notes:

[18] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), and age (<75 vs >=75 years) at randomisation, comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Statistical analysis title	OS Based on Frailty Status of Fit

Statistical analysis description:

P-value comparing OS between treatment groups was based on log-rank test stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR).

Comparison groups	Placebo v Ixazomib

Number of subjects included in analysis	284	
Analysis specification	Pre-specified	
Analysis type	superiority[19]	
P-value	= 0.714	
Method	Logrank	
Parameter estimate	Hazard ratio (HR)	
Point estimate	0.897	
Confidence interval		
level	95 %	
sides	2-sided	
lower limit	0.502	
upper limit	1.602	

Notes:

[19] - Hazard ratio was based on an unadjusted Cox's proportional hazard regression model stratified by initial therapy (proteasome inhibitor-containing or not), ISS stage before initial therapy (stage I or II vs stage III), age (<75 vs >=75 years) at randomisation, and best response to initial therapy (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. A less than 1 hazard ratio was to be considered statistically significant.

Secondary: Pharmacokinetic Parameter: Plasma Concentration of Ixazomib

End point title	Pharmacokinetic Parameter: Plasma Concentration of

End point description:

Plasma concentrations of the complete hydrolysis product of ixazomib citrate (ixazomib) were measured using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) assay. Pharmacokinetic Analysis Population included all participants with at least one pharmacokinetic (PK) sample that was collected and analysed.'n'=number of participants with data available for analysis at the specified time point.

End point type	Secondary

End point timeframe:

Cycle 1 (1 and 4 hours post-dose Day 1, Days 8 and 15 pre-dose); Cycle 2 and 5 (Days 1 and 8 pre-dose) and Cycles 3, 4, 6 to 10 (Day 1 pre-dose) (Cycle length=28 days)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is applicable only for participants in the ixazomib arm group of the pharmacokinetic analysis population.

End point values	Ixazomib			
Subject group type	Reporting group			
Number of subjects analysed	423			
Units: nanogram per millilitre (ng/ml)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 - 1 Hour Post-dose (n=413)	19.353 (± 89.2568)			
Cycle 1 Day 1 - 4 Hours Post-dose (n=403)	12.698 (± 67.8350)			
Cycle 1 Day 8 - Pre-dose (n=409)	1.683 (± 162.3947)			
Cycle 1 Day 15 - Pre-dose (n=411)	2.828 (± 86.7699)			
Cycle 2 Day 1 - Pre-dose (n=410)	1.958 (± 170.8938)			
Cycle 2 Day 8 - Pre-dose (n=394)	3.217 (± 188.6379)			

Cycle 3 Day 1 - Pre-dose (n=391)	2.252 (± 56.2869)		
Cycle 4 Day 1 - Pre-dose (n=372)	2.363 (± 52.9781)		
Cycle 5 Day 1 - Pre-dose (n=348)	2.328 (± 53.0909)		
Cycle 5 Day 8 - Pre-dose (n=257)	4.547 (± 224.4312)		
Cycle 6 Day 1 - Pre-dose (n=320)	2.503 (± 52.9349)		
Cycle 7 Day 1 - Pre-dose (n=298)	2.585 (± 57.9514)		
Cycle 8 Day 1 - Pre-dose (n=281)	2.606 (± 58.5109)		
Cycle 9 Day 1 - Pre-dose (n=269)	2.566 (± 58.1094)		
Cycle 10 Day 1 - Pre-dose (n=250)	2.686 (± 50.2494)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement of PN Events

End point title	Time to Improvement of PN Events

End point description:

PN is defined as the event in the high-level term of peripheral neuropathies NEC according to the MedDRA. A PN event was considered as resolved if its final outcome was resolved with no subsequent PN event of the same preferred term occurring on the improvement date or the day before and after. Time to improvement was defined as the time from the initial onset date (inclusive) to the improvement of event. Safety Population included all subjects who received at least 1 dose of ixazomib or placebo. Number of subjects analysed are the number of participants with events.

End point type	Secondary

End point timeframe:

Up to 52 months

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	83		
Units: days				
median (confidence interval 95%)	81.0 (15.0 to 280.0)	64.0 (29.0 to 393.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Peripheral Neuropathy (PN) Events

End point title	Time to Resolution of Peripheral Neuropathy (PN) Events

End point description:

PN is defined as the event in the high-level term of peripheral neuropathies not elsewhere classified (NEC) according to the medical dictionary for regulatory activities (MedDRA). A PN event was considered as resolved if its final outcome was resolved with no subsequent PN event of the same preferred term occurring on the resolution date or the day before and after. Time to resolution was defined as the time from the initial onset date (inclusive) to the resolution date for resolved events. Safety Population included all subjects who received at least 1 dose of ixazomib or placebo. Number of subjects analysed are the number of participants with events. '9999' indicates that upper limit of confidence interval (CI) was not estimable due to censoring.

End point type	Secondary

End point timeframe:

Up to 52 months

End point values	Placebo	Ixazomib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	83		
Units: days				
median (confidence interval 95%)	196.0 (43.0 to 331.0)	451.0 (98.0 to 9999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
First dose of study drug through 30 days after last dose of study drug (up to 88 months)	
Adverse event reporting additional description:	
Serious and Other Adverse Events: Safety population included all participants who received at least 1 dose of ixazomib or placebo. Three participants assigned to placebo arm each received a single 3 mg dose of ixazomib. These participants were excluded from the placebo arm and included in the ixazomib arm in the safety population.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Ixazomib
Reporting group description:	
Ixazomib 3 mg, capsule, orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 to 4 that may have been escalated to 4 mg thereafter up to Cycle 26.	
Reporting group title	Placebo
Reporting group description:	
Ixazomib placebo-matching capsule, orally, once on Days 1, 8, and 15 of each 28-day cycle from Cycles 1 through 26.	

Serious adverse events	Ixazomib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	101 / 426 (23.71%)	48 / 276 (17.39%)	
number of deaths (all causes)	184	115	
number of deaths resulting from adverse events	11	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	5 / 426 (1.17%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Plasmacytoma			

subjects affected / exposed	2 / 426 (0.47%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Prostate cancer				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Squamous cell carcinoma of skin				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Adenocarcinoma				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Transitional cell cancer of the renal pelvis and ureter				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Basal cell carcinoma				
subjects affected / exposed	3 / 426 (0.70%)	4 / 276 (1.45%)		
occurrences causally related to treatment / all	0 / 5	0 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bladder transitional cell carcinoma				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Carcinoma in situ of skin				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Invasive ductal breast carcinoma				

subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Malignant melanoma		
subjects affected / exposed	2 / 426 (0.47%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal carcinoma		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Non-small cell lung cancer		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastatic malignant melanoma		
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vascular disorders		
Jugular vein thrombosis		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive emergency		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
General disorders and administration site conditions		
Chest pain		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 426 (0.47%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	2 / 426 (0.47%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 426 (0.47%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			

subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Hypoxia		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Interstitial lung disease		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Paraneoplastic pleural effusion		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural effusion		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary embolism		
subjects affected / exposed	2 / 426 (0.47%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Respiratory failure		
subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Dyspnoea		
subjects affected / exposed	0 / 426 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonitis		

subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Injury, poisoning and procedural complications

Fall
subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Tibia fracture
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Subdural haematoma
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Tendon injury
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Soft tissue injury
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Road traffic accident
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Rib fracture
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Pelvic fracture

subjects affected / exposed	0 / 426 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hip fracture		
subjects affected / exposed	3 / 426 (0.70%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis radiation		
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fibula fracture		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Femur fracture		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac disorders		
Cardiac arrest		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Acute myocardial infarction		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial flutter		
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial tachycardia		

subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 426 (0.00%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	2 / 426 (0.47%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 426 (0.47%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 426 (0.00%)	3 / 276 (1.09%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancytopenia		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Eye disorders		
Uveitis		
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cataract		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal disorders		
Inguinal hernia		
subjects affected / exposed	3 / 426 (0.70%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal haemorrhage		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Large intestine polyp		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal pain		

subjects affected / exposed	2 / 426 (0.47%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal pain upper				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ascites				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Chilaiditi's syndrome				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Diarrhoea				
subjects affected / exposed	2 / 426 (0.47%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	2 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dyspepsia				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastric disorder				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Rectal prolapse				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Melaena				

subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 426 (0.70%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 426 (1.17%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcapsular renal haematoma			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar spinal stenosis		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscular weakness		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal chest pain		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoarthritis		
subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pain in extremity		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Back pain		
subjects affected / exposed	0 / 426 (0.00%)	2 / 276 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal pain		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Neck pain		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteolysis		

subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pathological fracture				
subjects affected / exposed	3 / 426 (0.70%)	2 / 276 (0.72%)		
occurrences causally related to treatment / all	0 / 3	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Trismus				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Infections and infestations				
Varicella				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cellulitis				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bronchitis				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bronchiolitis				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal wall abscess				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory tract infection				

subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia viral				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Pneumonia				
subjects affected / exposed	16 / 426 (3.76%)	2 / 276 (0.72%)		
occurrences causally related to treatment / all	4 / 17	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lower respiratory tract infection				
subjects affected / exposed	5 / 426 (1.17%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	1 / 5	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Influenza				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Infection				
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Herpes zoster				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Rhinovirus infection				
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sepsis				

subjects affected / exposed	3 / 426 (0.70%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0
Septic shock		
subjects affected / exposed	4 / 426 (0.94%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 4	0 / 1
Upper respiratory tract infection		
subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection		
subjects affected / exposed	6 / 426 (1.41%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolism and nutrition disorders		
Dehydration		
subjects affected / exposed	2 / 426 (0.47%)	0 / 276 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperkalaemia		
subjects affected / exposed	0 / 426 (0.00%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypercalcaemia		
subjects affected / exposed	1 / 426 (0.23%)	1 / 276 (0.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hyponatraemia		

subjects affected / exposed	1 / 426 (0.23%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ixazomib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	340 / 426 (79.81%)	188 / 276 (68.12%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 426 (6.10%)	16 / 276 (5.80%)	
occurrences (all)	32	22	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	66 / 426 (15.49%)	25 / 276 (9.06%)	
occurrences (all)	91	30	
Headache			
subjects affected / exposed	23 / 426 (5.40%)	11 / 276 (3.99%)	
occurrences (all)	33	14	
Dizziness			
subjects affected / exposed	27 / 426 (6.34%)	16 / 276 (5.80%)	
occurrences (all)	34	17	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 426 (7.28%)	19 / 276 (6.88%)	
occurrences (all)	42	26	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	49 / 426 (11.50%)	28 / 276 (10.14%)	
occurrences (all)	59	32	
Pyrexia			
subjects affected / exposed	44 / 426 (10.33%)	13 / 276 (4.71%)	
occurrences (all)	60	15	
Asthenia			

subjects affected / exposed	25 / 426 (5.87%)	17 / 276 (6.16%)	
occurrences (all)	33	21	
Oedema peripheral			
subjects affected / exposed	37 / 426 (8.69%)	16 / 276 (5.80%)	
occurrences (all)	48	20	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	36 / 426 (8.45%)	21 / 276 (7.61%)	
occurrences (all)	50	26	
Diarrhoea			
subjects affected / exposed	102 / 426 (23.94%)	35 / 276 (12.68%)	
occurrences (all)	209	43	
Dyspepsia			
subjects affected / exposed	24 / 426 (5.63%)	7 / 276 (2.54%)	
occurrences (all)	26	8	
Nausea			
subjects affected / exposed	119 / 426 (27.93%)	23 / 276 (8.33%)	
occurrences (all)	202	32	
Vomiting			
subjects affected / exposed	102 / 426 (23.94%)	11 / 276 (3.99%)	
occurrences (all)	187	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 426 (7.28%)	19 / 276 (6.88%)	
occurrences (all)	38	22	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	24 / 426 (5.63%)	12 / 276 (4.35%)	
occurrences (all)	31	14	
Rash maculo-papular			
subjects affected / exposed	36 / 426 (8.45%)	2 / 276 (0.72%)	
occurrences (all)	47	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	26 / 426 (6.10%)	12 / 276 (4.35%)	
occurrences (all)	27	12	

Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	25 / 426 (5.87%)	13 / 276 (4.71%)	
occurrences (all)	30	14	
Myalgia			
subjects affected / exposed	22 / 426 (5.16%)	8 / 276 (2.90%)	
occurrences (all)	26	8	
Back pain			
subjects affected / exposed	62 / 426 (14.55%)	33 / 276 (11.96%)	
occurrences (all)	67	40	
Arthralgia			
subjects affected / exposed	61 / 426 (14.32%)	30 / 276 (10.87%)	
occurrences (all)	78	37	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	36 / 426 (8.45%)	18 / 276 (6.52%)	
occurrences (all)	50	27	
Upper respiratory tract infection			
subjects affected / exposed	69 / 426 (16.20%)	32 / 276 (11.59%)	
occurrences (all)	104	44	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	36 / 426 (8.45%)	13 / 276 (4.71%)	
occurrences (all)	48	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2018	The following major changes were implemented based on Amendment 5: 1. Reduced the number of participants be enrolled from 761 to 700. 2. Modified the statistical to change the timing of the first interim analysis (IA), allocate statistical power to a subgroup analysis, and updated the PFS assumptions and type I error allocation. 3. Modified the statistical design to adopt an adaptive design to test OS at the second IA. 5. Moved the details of analysis of the secondary endpoint, duration of the next line of therapy, to correct section. 6. Described how adjustment for potential effects of subsequent therapy used after study discontinuation may be analysed. 7. Changed the duration of the study to accommodate other changes to the statistical design. 8. Listed 2 secondary objectives in the Protocol Summary that were accidentally not yet listed there: "To determine the effect of ixazomib maintenance therapy on duration of next-line therapy"; and "To assess the correlation between MRD status (detected using 8-color flow cytometry) and PFS and OS, using bone marrow aspirates." 9. Update details about storage of study drug.
23 September 2020	The following major changes were implemented based on Amendment 7: 1. Discontinued a number of efficacy response assessments, including central laboratory assessments of efficacy for protocol purposes and IRC evaluations, and clarified safety laboratory evaluation. 2. Updated the estimated study duration. 3. Updated language about the management of clinical events in participants receiving ixazomib. 4. Required all participants to reconsent. 5. Added flexibility in study conduct in unavoidable circumstances (e.g., the coronavirus disease-2019 [COVID-19] pandemic). 6. Updated the procedures for SAE reporting. 7. Added information about alternative monitoring approaches, such as remote source data verification, in the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic.
15 November 2021	The following major changes were implemented based on Amendment 9: 1. Changed the legal entity name of the sponsor. 2. Clarified language regarding procedures for reporting product complaints or medication errors and for study conduct regarding the coronavirus disease 2019 (COVID-19) pandemic. 3. Clarified local laboratory assessment recordings.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported