Clinical trial results:
A Phase 3, Multicenter, Randomized, Double Blind Study of Bortezomib and Dexamethasone in Combination with Either Venetoclax or Placebo in Subjects with Relapsed or Refractory Multiple Myeloma Who are Sensitive or Naïve to Proteasome Inhibitors

Summary

EudraCT number	2015-004411-20
Trial protocol	IE DE HU IT
Global end of trial date	15 August 2022

Results information

Result version number	v1 (current)
This version publication date	30 July 2023
First version publication date	30 July 2023

Trial information

Trial identification

Sponsor protocol code	M14-031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02755597
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.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	15 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase 3, multicenter, randomized, double blind, placebo-controlled study evaluating the efficacy and safety of venetoclax plus bortezomib and dexamethasone in participants with relapsed or refractory multiple myeloma who are considered sensitive or naïve to proteasome inhibitors and received 1 to 3 prior lines of therapy for multiple myeloma.

Protection of trial subjects:

The Investigator or his/her representative was to explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement was to be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	11 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 31
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Australia: 60
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Japan: 31
Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	United States: 6

Worldwide total number of subjects	291
EEA total number of subjects	49

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)	131
From 65 to 84 years	157
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult male and female subjects with relapsed or refractory multiple myeloma who were sensitive or naïve to proteasome inhibitors, had received 1 to 3 prior lines of therapy for multiple myeloma, and who met all inclusion criteria and none of the exclusion criteria were eligible for enrollment into the study.

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	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Venetoclax + Bortezomib and Dexamethasone

Arm description:

Cycles 1-8: Venetoclax 800 mg orally every day (QD) on Days 1 - 21 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 4, 8 & 11 and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 & 12; Cycles 9 and beyond: Venetoclax 800 mg orally every day (QD) on Days 1 - 35 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 8, 15 and 22 and dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 and 23

Arm type	Experimental
Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	ABT-199, VENCLEXTA, VENCLYXTO
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants self-administered venetoclax tablets by mouth QD in combination with bortezomib. Venetoclax was to be given before other agents administered on the same day, if applicable. Each venetoclax dose was to be taken all at one time with approximately 240 mL of water within 30 minutes after completion of breakfast or the subject's first meal of the day. Tablets were to be swallowed whole and must not have been broken, chewed, or crushed. On days that pre-dose PK sampling was required, dosing occurred at the clinic to facilitate PK sampling.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Injection , Intravenous use

Dosage and administration details:

Bortezomib (subcutaneous injection [preferred] or IV) was given following administration of venetoclax or placebo in Cycles 1 -8 on Days 1, 4, 8 and 11, and for Cycles 9 and beyond, on Days 1, 8, 15 and 22 and was to be administered per the prescribing information. The route of administration was to stay the same during the study.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone was to be given orally, administered per the prescribing information, the day of bortezomib dosing and the following day, given the protocol-defined dosing window (bortezomib dosing window is ± 1 day) is maintained. If bortezomib was interrupted or a dose is skipped, dexamethasone was to be administered as scheduled per protocol (unless dexamethasone was interrupted due to toxicity).

Arm title	Placebo + Bortezomib and Dexamethasone

Arm description:

Cycles 1-8: Placebo (to match venetoclax 100 mg tablet) 800 mg orally every day (QD) on Days 1 - 21 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 4, 8 & 11 and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 & 12; Cycles 9 and beyond: Placebo (to match venetoclax 100 mg tablet) 800 mg orally every day (QD) on Days 1 - 35 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 8, 15 and 22 and dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 & 23

Arm type	Placebo
Investigational medicinal product name	Placebo for venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants self-administered placebo tablets by mouth QD in combination with bortezomib. Placebo was to be given before other agents administered on the same day, if applicable. Each placebo dose was to be taken all at one time with approximately 240 mL of water within 30 minutes after completion of breakfast or the subject's first meal of the day. Tablets were to be swallowed whole and must not have been broken, chewed, or crushed. On days that pre-dose PK sampling was required, dosing occurred at the clinic to facilitate PK sampling.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Injection , Intravenous use

Dosage and administration details:

Bortezomib (subcutaneous injection [preferred] or IV) was given following administration of venetoclax or placebo in Cycles 1 -8 on Days 1, 4, 8 and 11, and for Cycles 9 and beyond, on Days 1, 8, 15 and 22 and was to be administered per the prescribing information. The route of administration was to stay the same during the study.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone was to be given orally, administered per the prescribing information, the day of bortezomib dosing and the following day, given the protocol-defined dosing window (bortezomib dosing window is ± 1 day) is maintained. If bortezomib was interrupted or a dose is skipped, dexamethasone was to be administered as scheduled per protocol (unless dexamethasone was interrupted due to toxicity).

Number of subjects in period 1	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone
Started	194	97
Completed	0	0
Not completed	194	97
Study terminated by Sponsor	67	47
Death	78	36
Other, not specified	20	3
Withdrew consent	27	11
Lost to follow-up	1	-
Subject missing reason for study discontinuation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Venetoclax + Bortezomib and Dexamethasone
Reporting group description:	
Cycles 1-8: Venetoclax 800 mg orally every day (QD) on Days 1 - 21 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 4, 8 & 11 and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 & 12; Cycles 9 and beyond: Venetoclax 800 mg orally every day (QD) on Days 1 - 35 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 8, 15 and 22 and dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 and 23	

Reporting group title	Placebo + Bortezomib and Dexamethasone
Reporting group description:	
Cycles 1-8: Placebo (to match venetoclax 100 mg tablet) 800 mg orally every day (QD) on Days 1 - 21 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 4, 8 & 11 and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 & 12; Cycles 9 and beyond: Placebo (to match venetoclax 100 mg tablet) 800 mg orally every day (QD) on Days 1 - 35 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 8, 15 and 22 and dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 & 23	

Reporting group values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone	Total
Number of subjects	194	97	291
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.9	65.9	
standard deviation	± 9.41	± 7.81	-
Gender categorical Units: Subjects			
Female	97	42	139
Male	97	55	152
Ethnicity Units: Subjects			
Hispanic or Latino	25	7	32
Not Hispanic or Latino	169	90	259
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	59	28	87
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	3	12
White	124	66	190
More than one race	2	0	2
Unknown or Not Reported	0	0	0
Number of prior lines of multiple myeloma therapy Units: Subjects			
1 line	91	44	135

2-3 lines	103	53	156
Prior exposure to proteasome inhibitors (PI) Units: Subjects			
Refractory	0	2	2
Sensitive	131	66	197
Naïve	61	28	89
Unknown	2	0	2
MISSING	0	1	1
Prior exposure to an immunomodulatory drug (IMID) Units: Subjects			
Refractory	64	36	100
Sensitive	67	29	96
Naïve	63	30	93
Unknown	0	1	1
MISSING	0	1	1
Prior exposure to an anti-CD38 monoclonal antibody Units: Subjects			
Refractory	5	1	6
Sensitive	0	0	0
Naïve	185	95	280
Unknown	0	0	0
MISSING	4	1	5
Multiple myeloma International Staging System(ISS) stage			
The International Staging System for multiple myeloma: Stage I: Serum β2 microglobulin (Sβ2M), < 3.5 mg/L; serum albumin ≥3.5 g/dL Stage II: Sβ2M < 3.5 mg/L; serum albumin < 3.5 g/dL; or Sβ2M 3.5 to 5.5 mg/L, irrespective of serum albumin Stage III: Sβ2M > 5.5 mg/L			
Units: Subjects			
Stage I	81	48	129
Stage II	69	32	101
Stage III	39	13	52
Not evaluable	5	3	8
MISSING	0	1	1
Chromosomal abnormality (CA) risk by fluorescent in situ hybridization (FISH)			
A 4 mL bone marrow aspirate sample was collected for baseline assessment of chromosomal abnormalities, including t(11;14), t(4;14), t(14;16), del 17p, 5+, 9+, 15+			
Units: Subjects			
High	31	18	49
Standard	141	72	213
Unknown	9	4	13
MISSING	13	3	16
Prior stem cell transplant Units: Subjects			
Autologous	114	57	171
Allogeneic	2	0	2
Syngeneic	0	0	0
MISSING	78	40	118

Time since diagnosis Units: days median full range (min-max)	 1263.5 62.0 to 8356.0	 1461.0 195.0 to 4906.0	 -
Number of prior lines of therapy Units: number of prior lines of therapy median full range (min-max)	 1.0 1.0 to 3.0	 2.0 1.0 to 3.0	 -

End points

End points reporting groups

Reporting group title	Venetoclax + Bortezomib and Dexamethasone

Reporting group description:

Cycles 1-8: Venetoclax 800 mg orally every day (QD) on Days 1 - 21 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 4, 8 & 11 and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 & 12; Cycles 9 and beyond: Venetoclax 800 mg orally every day (QD) on Days 1 - 35 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 8, 15 and 22 and dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 and 23

Reporting group title	Placebo + Bortezomib and Dexamethasone

Reporting group description:

Cycles 1-8: Placebo (to match venetoclax 100 mg tablet) 800 mg orally every day (QD) on Days 1 - 21 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 4, 8 & 11 and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 & 12; Cycles 9 and beyond: Placebo (to match venetoclax 100 mg tablet) 800 mg orally every day (QD) on Days 1 - 35 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 8, 15 and 22 and dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 & 23

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS is defined as the number of days from the date the participant was randomized to the date of the first documented progressive disease (PD) as determined by an Independent Review Committee (IRC) or death due to any cause, whichever occurs first. PFS was analyzed by Kaplan-Meier methodology.

End point type	Primary

End point timeframe:

Median duration of follow-up was 28.6 months for the venetoclax group and 28.6 months for the placebo group

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194[1]	97[2]		
Units: months				
median (confidence interval 95%)	23.2 (15.3 to 27.5)	11.5 (9.6 to 15.0)		

Notes:

[1] - All randomized participants, analyzed by treatment group assignment given at time of randomization
[2] - All randomized participants, analyzed by treatment group assignment given at time of randomization

Statistical analyses

Statistical analysis title	Venetoclax vs Placebo

Statistical analysis description:

Stratified Analysis; Stratification factors: Prior exposure to proteasome inhibitors (naïve versus

sensitive), and number of prior lines of therapy (1 versus 2 or 3)

Comparison groups	Venetoclax + Bortezomib and Dexamethasone v Placebo + Bortezomib and Dexamethasone
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.656
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.471
upper limit	0.913

Notes:

[3] - Hazard ratio was estimated by Cox proportional hazards model

Secondary: Very Good Partial Response (VGPR) or Better Response Rate

End point title	Very Good Partial Response (VGPR) or Better Response Rate

End point description:

The percentage of participants with documented best overall response of Very Good Partial Response (VGPR) or better (VGPR, Complete response [CR], or Stringent complete response [sCR]) per 2016 standard International Myeloma Working Group (IMWG) criteria as determined by an Independent Review Committee (IRC) was computed.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 1, Day 1, and on Day 1 of every cycle thereafter; median time on follow-up was 28.6 months for the venetoclax group and 28.6 months for the placebo group

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194[4]	97[5]		
Units: percentage of participants				
number (confidence interval 95%)	60.3 (53.1 to 67.2)	38.1 (28.5 to 48.6)		

Notes:

[4] - All randomized participants, analyzed by treatment group assignment given at time of randomization

[5] - All randomized participants, analyzed by treatment group assignment given at time of randomization

Statistical analyses

Statistical analysis title	Venetoclax vs Placebo

Statistical analysis description:

Stratified Analysis; Stratification factors: Prior exposure to proteasome inhibitors (naïve versus

sensitive), and number of prior lines of therapy (1 versus 2 or 3)

Comparison groups	Venetoclax + Bortezomib and Dexamethasone v Placebo + Bortezomib and Dexamethasone
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Secondary: Progression-Free Survival (PFS) in Participants With High B-cell Lymphoma 2 (BCL-2) Expression

End point title	Progression-Free Survival (PFS) in Participants With High B-cell Lymphoma 2 (BCL-2) Expression

End point description:

PFS is defined as the number of days from the date the participant was randomized to the date of the first documented progressive disease (PD) per investigator assessment or death due to any cause, whichever occurs first. PFS was analyzed by Kaplan-Meier methodology.

BCL-2 expression was determined through central laboratory testing by immunohistochemistry (IHC) and based on a pre-specified scoring algorithm. High clinical score of 2+: ≥50% of tumor cells with moderate or higher cytoplasmic staining but < 50% of tumor cells with strong staining intensity; high clinical score of 3+: ≥50% of tumor cells with strong cytoplasmic staining.

End point type	Secondary

End point timeframe:

Median duration of follow-up was 28.6 months for the venetoclax group and 28.6 months for the placebo group

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[6]	47[7]		
Units: months				
median (confidence interval 95%)	23.8 (19.5 to 34.7)	11.4 (9.1 to 15.0)		

Notes:

[6] - Randomized subjects analyzed by Tx group assignment at randomization, with high BCL-2 expression
[7] - Randomized subjects analyzed by Tx group assignment at randomization, with high BCL-2 expression

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR is defined as the number of days from the participant's date of first documented response (partial response [PR] or better) to the date of first documented progressive disease (PD) as determined by an Independent Review Committee (IRC) or death due to multiple myeloma, whichever occurs first. DOR was analyzed by Kaplan-Meier methodology.

In the table below, 999 and 99999 indicates not estimable/calculable due to low number of participants with events.

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 1, Day 1, and on Day 1 of every cycle thereafter; median time on follow-up was 28.6 months for the venetoclax group and 28.6 months for the placebo group

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158[8]	67[9]		
Units: months				
median (confidence interval 95%)	999 (22.8 to 99999)	12.8 (10.6 to 15.5)		

Notes:

[8] - All randomized participants, analyzed by treatment group assignment given at time of randomization
[9] - All randomized participants, analyzed by treatment group assignment given at time of randomization

Statistical analyses

Statistical analysis title	Venetoclax vs Placebo

Statistical analysis description:

Stratified Analysis; Stratification factors: Prior exposure to proteasome inhibitors (naïve versus sensitive), and number of prior lines of therapy (1 versus 2 or 3)

Comparison groups	Venetoclax + Bortezomib and Dexamethasone v Placebo + Bortezomib and Dexamethasone
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.508
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.343
upper limit	0.753

Notes:

[10] - Hazard ratio was estimated by Cox proportional hazards model

Secondary: Mean Change From Baseline in Brief Pain Inventory - Short Form (BPI-SF) Worst Pain

End point title	Mean Change From Baseline in Brief Pain Inventory - Short Form (BPI-SF) Worst Pain

End point description:

The BPI-SF is a pain-specific measure developed to assess patient-reported severity (or intensity) of pain (4 items) and the impact of pain on daily functioning (7 items) in patients with cancer pain. The four pain severity items assess pain at its "worst in last 24 hours," "least in last 24 hours," "average," and "now" (current pain). For these items, participants are asked to rate their pain on an 11-point numeric rating scale with anchors of 0 (no pain) and 10 (pain as bad as you can imagine). The Worst Pain scores range from 0 to 10, with higher scores indicating severe pain. Negative changes from baseline indicate improvement.

99999 in the table below indicates not calculable/estimable due to n=1 subject

End point type	Secondary

End point timeframe:

Baseline; Cycle 3 (Cycles 1 - 8 are 21 days, Cycles 9 and beyond are 35 days) through Cycle 47, collected on Day 1 of every other cycle and at the Treatment Completion Visit (TCV) while participant is on treatment

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184[11]	92[12]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 3, Day 1 (n= 162, 79)	-0.6 (± 2.59)	-0.5 (± 2.46)		
Cycle 5, Day 1 (n= 140, 70)	0.0 (± 2.65)	-0.2 (± 3.15)		
Cycle 7, Day 1 (n= 126, 70)	-0.1 (± 2.56)	0.2 (± 2.98)		
Cycle 9, Day 1 (n= 113, 65)	-0.2 (± 3.11)	0.0 (± 2.88)		
Cycle 11, Day 1 (n= 98, 55)	-0.4 (± 2.57)	0.1 (± 3.45)		
Cycle 13, Day 1 (n= 82, 43)	-0.2 (± 2.71)	-0.1 (± 3.22)		
Cycle 15, Day 1 (n= 76, 31)	-0.2 (± 2.92)	-0.0 (± 3.08)		
Cycle 17, Day 1 (n= 66, 27)	-0.3 (± 2.54)	-0.1 (± 2.06)		
Cycle 19, Day 1 (n= 67, 22)	-0.1 (± 2.59)	-0.2 (± 1.95)		
Cycle 21, Day 1 (n= 59, 18)	-0.1 (± 2.39)	-0.3 (± 2.89)		
Cycle 23, Day 1 (n= 55, 17)	-0.0 (± 3.20)	-0.2 (± 2.61)		
Cycle 25, Day 1 (n= 47, 13)	0.4 (± 2.65)	0.2 (± 3.00)		
Cycle 27, Day 1 (n= 37, 14)	0.2 (± 2.53)	0.1 (± 1.92)		
Cycle 29, Day 1 (n= 40, 15)	-0.2 (± 2.83)	0.3 (± 2.15)		
Cycle 31, Day 1 (n= 39, 9)	0.0 (± 3.11)	0.6 (± 1.33)		
Cycle 33, Day 1 (n= 37, 7)	-0.2 (± 2.88)	0.4 (± 1.40)		
Cycle 35, Day 1 (n= 34, 6)	0.1 (± 2.77)	-0.2 (± 1.33)		
Cycle 37, Day 1 (n= 31, 4)	0.4 (± 2.78)	1.5 (± 2.65)		
Cycle 39, Day 1 (n= 26, 3)	0.1 (± 2.70)	-0.3 (± 1.15)		
Cycle 41, Day 1 (n= 21, 3)	0.1 (± 3.00)	0.3 (± 1.15)		
Cycle 43, Day 1 (n= 17, 2)	-0.1 (± 3.07)	0.5 (± 0.71)		
Cycle 45, Day 1 (n= 9, 2)	-0.7 (± 3.64)	1.0 (± 0.00)		
Cycle 47, Day 1 (n= 4, 1)	-2.8 (± 3.77)	1.0 (± 99999)		
Final visit (n= 175, 87)	0.3 (± 3.28)	0.4 (± 3.55)		

Notes:

[11] - Randomized subjects, analyzed by Tx assignment at randomization, with baseline + post-baseline data

[12] - Randomized subjects, analyzed by Tx assignment at randomization, with baseline + post-baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Physical Functioning Scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point title	Mean Change From Baseline in Physical Functioning Scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point description:

The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). For the Physical Functioning scale, participants rate five items on a four-point scale, with 1 as "not at all" and 4 as "very much." The Physical Functioning Scale scores range from 0 to 100 and were calculated per the EORTC QLQ-C30 Scoring Manual (3rd edition), version 3.0. A high scale score represents high/healthy level of functioning. Positive changes from baseline indicate improvement.

99999 in the table below indicates not calculable/estimable due to n=1 subject

End point type	Secondary

End point timeframe:

Baseline; Cycle 3 (Cycles 1 - 8 are 21 days, Cycles 9 and beyond are 35 days) through Cycle 47, collected on Day 1 of every other cycle and at the Treatment Completion Visit (TCV) while participant is on treatment

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184[13]	92[14]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 3, Day 1 (n= 161, 79)	-5.0 (± 18.22)	-4.6 (± 19.50)		
Cycle 5, Day 1 (n= 140, 70)	-3.9 (± 18.38)	-7.8 (± 21.50)		
Cycle 7, Day 1 (n= 126, 70)	-6.1 (± 20.19)	-8.6 (± 19.76)		
Cycle 9, Day 1 (n= 114, 65)	-3.5 (± 19.54)	-8.0 (± 20.01)		
Cycle 11, Day 1 (n= 99, 55)	-1.5 (± 15.92)	-7.5 (± 18.46)		
Cycle 13, Day 1 (n= 83, 43)	-3.2 (± 16.57)	-8.8 (± 22.85)		
Cycle 15, Day 1 (n= 77, 31)	-2.3 (± 18.72)	-7.3 (± 22.27)		
Cycle 17, Day 1 (n= 67, 27)	-1.8 (± 16.23)	-8.6 (± 19.90)		
Cycle 19, Day 1 (n= 68, 22)	-2.5 (± 19.30)	-7.0 (± 19.35)		
Cycle 21, Day 1 (n= 59, 18)	-1.5 (± 17.81)	-8.5 (± 20.43)		
Cycle 23, Day 1 (n= 55, 17)	-3.4 (± 20.32)	-7.5 (± 20.53)		

Cycle 25, Day 1 (n= 48, 13)	-3.8 (± 17.28)	0.5 (± 23.95)		
Cycle 27, Day 1 (n= 38, 14)	-8.6 (± 21.69)	-3.3 (± 18.44)		
Cycle 29, Day 1 (n= 40, 15)	-8.7 (± 21.25)	-4.0 (± 19.81)		
Cycle 31, Day 1 (n= 40, 9)	-2.8 (± 17.98)	2.2 (± 18.56)		
Cycle 33, Day 1 (n= 38, 7)	-4.0 (± 22.76)	-4.8 (± 23.64)		
Cycle 35, Day 1 (n= 35, 6)	-7.0 (± 16.64)	4.4 (± 18.70)		
Cycle 37, Day 1 (n= 31, 4)	-7.5 (± 22.49)	15.0 (± 14.78)		
Cycle 39, Day 1 (n= 27, 3)	-10.1 (± 18.80)	8.9 (± 10.18)		
Cycle 41, Day 1 (n= 22, 3)	-13.0 (± 25.65)	13.3 (± 23.09)		
Cycle 43, Day 1 (n= 17, 2)	-7.8 (± 23.12)	13.3 (± 18.86)		
Cycle 45, Day 1 (n= 10, 2)	-1.3 (± 10.33)	13.3 (± 18.86)		
Cycle 47, Day 1 (n= 4, 1)	0.0 (± 14.40)	0.0 (± 99999)		
Final visit (n= 175, 87)	-11.8 (± 22.85)	-10.0 (± 21.52)		

Notes:

[13] - Randomized subjects, analyzed by Tx assignment at randomization, with baseline + post-baseline data
[14] - Randomized subjects, analyzed by Tx assignment at randomization, with baseline + post-baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Global Health Status/Quality of Life Scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point title	Mean Change From Baseline in Global Health Status/Quality of Life Scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

End point description:

The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). For the Global Health Status/Quality of Life scale, participants rate two items on a seven point scale, with 1 as "very poor" and 7 as "excellent." The Global Health Status/Quality of Life scale ranges from 0 to 100 and was calculated per the EORTC QLQ-C30 Scoring Manual (3rd edition), version 3.0. A high score for the global health status/QoL represents a high QoL. Positive changes from baseline indicate improvement.

99999 in the table below indicates not calculable/estimable due to n=1 subject

End point type	Secondary

End point timeframe:

Baseline; Cycle 3 (Cycles 1 - 8 are 21 days, Cycles 9 and beyond are 35 days) through Cycle 47, collected on Day 1 of every other cycle and at the Treatment Completion Visit (TCV) while participant is on treatment

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184[15]	92[16]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 3, Day 1 (n= 161, 79)	-1.9 (± 22.75)	-2.2 (± 22.63)		
Cycle 5, Day 1 (n= 140, 70)	-5.1 (± 26.74)	-2.5 (± 23.54)		
Cycle 7, Day 1 (n= 126, 70)	-8.3 (± 26.76)	-6.7 (± 24.56)		
Cycle 9, Day 1 (n= 114, 65)	-6.9 (± 26.33)	-6.7 (± 24.22)		
Cycle 11, Day 1 (n= 99, 55)	-0.5 (± 25.58)	-5.2 (± 25.38)		
Cycle 13, Day 1 (n= 83, 43)	-1.0 (± 25.05)	-1.7 (± 22.24)		
Cycle 15, Day 1 (n= 77, 31)	-4.9 (± 26.09)	0.5 (± 23.56)		
Cycle 17, Day 1 (n= 67, 27)	-5.1 (± 24.91)	-7.7 (± 21.55)		
Cycle 19, Day 1 (n= 68, 22)	-1.3 (± 19.51)	0.8 (± 26.09)		
Cycle 21, Day 1 (n= 59, 18)	-6.6 (± 26.16)	-5.6 (± 20.01)		
Cycle 23, Day 1 (n= 55, 17)	-2.9 (± 23.20)	-1.0 (± 22.99)		
Cycle 25, Day 1 (n= 48, 13)	-4.7 (± 26.29)	-4.5 (± 24.68)		
Cycle 27, Day 1 (n= 38, 14)	-9.0 (± 24.46)	4.2 (± 26.70)		
Cycle 29, Day 1 (n= 40, 15)	-6.9 (± 24.67)	-1.1 (± 26.33)		
Cycle 31, Day 1 (n= 40, 9)	-4.8 (± 26.48)	5.6 (± 35.36)		
Cycle 33, Day 1 (n= 38, 7)	-7.7 (± 27.22)	-7.1 (± 22.79)		
Cycle 35, Day 1 (n= 35, 6)	-3.8 (± 24.03)	4.2 (± 29.23)		
Cycle 37, Day 1 (n= 31, 4)	-13.7 (± 29.86)	10.4 (± 12.50)		
Cycle 39, Day 1 (n= 27, 3)	-9.3 (± 28.05)	0.0 (± 0.00)		
Cycle 41, Day 1 (n= 22, 3)	-11.0 (± 30.47)	8.3 (± 8.33)		
Cycle 43, Day 1 (n= 17, 2)	2.0 (± 28.95)	-8.3 (± 23.57)		
Cycle 45, Day 1 (n= 10, 2)	-1.7 (± 33.75)	4.2 (± 5.89)		
Cycle 47, Day 1 (n= 4, 1)	10.4 (± 22.95)	-8.3 (± 99999)		
Final visit (n= 175, 87)	-8.1 (± 26.40)	-6.7 (± 28.50)		

Notes:

[15] - Randomized subjects, analyzed by Tx assignment at randomization, with baseline + post-baseline data

[16] - Randomized subjects, analyzed by Tx assignment at randomization, with baseline + post-baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Patient Reported Outcomes Measurement Information System [PROMIS] Cancer Fatigue Short Form [SF] Score

End point title	Mean Change From Baseline in Patient Reported Outcomes Measurement Information System [PROMIS] Cancer Fatigue Short Form [SF] Score

End point description:

PROMIS Cancer Fatigue SF is a seven item questionnaire that assesses the impact and experience of fatigue over the past 7 days. All questions employ the following five response options: 1 = Not at all, 2 = A little bit, 3 = Somewhat, 4 = Quite a bit, and 5 = Very much. The total raw score is the sum of the responses to each question and is converted to a T-score. The T-score re-scales the total raw score to a standardized score with a mean of 50 and a standard deviation of 10. The [PROMIS] Cancer Fatigue Short Form [SF] 7a T-Scores range from 29.4 to 83.2, with higher scores indicating more fatigue.

Negative changes from baseline indicate improvement.

In the table below, 99999 indicates not calculable/estimable due to low numbers of participants with events.

End point type	Secondary

End point timeframe:

Baseline; Cycle 3 (Cycles 1 - 8 are 21 days, Cycles 9 and beyond are 35 days) through Cycle 47, collected on Day 1 of every other cycle and at the Treatment Completion Visit (TCV) while participant is on treatment

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185[17]	92[18]		
Units: T-score				
arithmetic mean (standard deviation)				
Cycle 3, Day 1 (n= 163, 79)	2.2 (± 9.54)	1.8 (± 8.12)		
Cycle 5, Day 1 (n= 141, 70)	3.3 (± 9.25)	2.4 (± 10.34)		
Cycle 7, Day 1 (n= 126, 70)	3.2 (± 9.28)	2.6 (± 9.70)		
Cycle 9, Day 1 (n= 114, 65)	2.3 (± 8.90)	2.6 (± 8.67)		
Cycle 11, Day 1 (n= 99, 55)	0.6 (± 8.54)	3.1 (± 8.98)		
Cycle 13, Day 1 (n= 83, 43)	1.8 (± 8.03)	2.3 (± 6.97)		
Cycle 15, Day 1 (n= 77, 31)	1.5 (± 8.84)	2.1 (± 7.66)		
Cycle 17, Day 1 (n= 67, 27)	1.2 (± 8.11)	2.6 (± 8.05)		
Cycle 19, Day 1 (n= 68, 22)	0.7 (± 8.52)	0.9 (± 9.32)		
Cycle 21, Day 1 (n= 59, 18)	1.6 (± 8.58)	1.2 (± 7.66)		
Cycle 23, Day 1 (n= 55, 17)	2.0 (± 8.08)	1.5 (± 8.83)		
Cycle 25, Day 1 (n= 48, 13)	2.0 (± 8.59)	-0.1 (± 8.73)		
Cycle 27, Day 1 (n= 38, 14)	3.4 (± 8.19)	-0.1 (± 9.59)		
Cycle 29, Day 1 (n= 40, 15)	3.9 (± 8.07)	0.8 (± 8.51)		
Cycle 31, Day 1 (n= 40, 9)	2.8 (± 8.43)	-0.3 (± 9.15)		
Cycle 33, Day 1 (n= 38, 7)	2.0 (± 8.93)	3.7 (± 9.17)		
Cycle 35, Day 1 (n= 35, 6)	3.4 (± 9.27)	1.1 (± 7.22)		
Cycle 37, Day 1 (n= 31, 4)	4.1 (± 9.72)	-3.0 (± 11.72)		
Cycle 39, Day 1 (n= 27, 3)	3.6 (± 8.12)	4.1 (± 2.82)		
Cycle 41, Day 1 (n= 22, 3)	3.3 (± 8.69)	-0.7 (± 6.90)		
Cycle 43, Day 1 (n= 17, 2)	5.3 (± 9.28)	4.4 (± 1.91)		
Cycle 45, Day 1 (n= 10, 2)	-0.3 (± 7.99)	1.8 (± 0.28)		
Cycle 47, Day 1 (n= 4, 1)	-2.5 (± 6.30)	0.0 (± 99999)		
Final visit (n= 176, 87)	5.0 (± 10.95)	2.9 (± 9.96)		

Notes:

[17] - Randomized subjects, analyzed by Tx assignment at randomization, with baseline + post-baseline data

[18] - Randomized subjects, analyzed by Tx assignment at randomization, with baseline + post-baseline data

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the number of days from the date of randomization to the date of death due to any cause. All events of death were to be included, regardless of whether the event occurred while the participant was still taking study drug or after the participant discontinued study drug. If a participant is not known to have died, OS was censored at the date of last contact. The distribution of OS was estimated using Kaplan-Meier methodology.

In the table below, 999 and 99999 indicate not calculable/estimable due to low numbers of participants with events.

End point type	Secondary

End point timeframe:

Median duration of follow-up was 45.6 months for the venetoclax group and 45.6 months for the placebo group

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194[19]	97[20]		
Units: months				
median (confidence interval 95%)	999 (44.4 to 99999)	999 (44.0 to 99999)		

Notes:

[19] - All randomized participants, analyzed by treatment group assignment given at time of randomization

[20] - All randomized participants, analyzed by treatment group assignment given at time of randomization

Statistical analyses

Statistical analysis title	Venetoclax vs Placebo

Statistical analysis description:

Stratified Analysis; Stratification factors: Prior exposure to proteasome inhibitors (naïve versus sensitive), and number of prior lines of therapy (1 versus 2 or 3)

Comparison groups	Venetoclax + Bortezomib and Dexamethasone v Placebo + Bortezomib and Dexamethasone
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.385 [21]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.191

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.802
upper limit	1.77

Notes:

[21] - Hazard ratio was estimated by Cox proportional hazards model

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP is defined as the number of days from the date of randomization to the date of first documented progressive disease (PD) as determined by an Independent Review Committee (IRC) or death due to multiple myeloma, whichever occurs first. TTP was analyzed by Kaplan-Meier methodology.

In the table below, 99999 indicates not calculable/estimable due to low numbers of participants with events.

End point type	Secondary

End point timeframe:

Median time on follow-up was 28.6 months for the venetoclax group and 28.6 months for the placebo group

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194[22]	97[23]		
Units: months				
median (confidence interval 95%)	25.4 (20.6 to 99999)	12.2 (9.9 to 15.0)		

Notes:

[22] - All randomized participants, analyzed by treatment group assignment given at time of randomization

[23] - All randomized participants, analyzed by treatment group assignment given at time of randomization

Statistical analyses

Statistical analysis title	Venetoclax vs Placebo

Statistical analysis description:

Stratified Analysis; Stratification factors: Prior exposure to proteasome inhibitors (naïve versus sensitive), and number of prior lines of therapy (1 versus 2 or 3)

Comparison groups	Venetoclax + Bortezomib and Dexamethasone v Placebo + Bortezomib and Dexamethasone

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [24]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.571
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.405
upper limit	0.805

Notes:

[24] - Hazard ratio was estimated by Cox proportional hazards model

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Overall response rate is defined as the percentage of participants with documented best overall response of Partial Response (PR) or better (PR, Very good partial response [VGPR], Complete response [CR], or Stringent complete response [sCR]) per International Myeloma Working Group (IMWG) criteria as determined by an Independent Review Committee (IRC).

End point type	Secondary

End point timeframe:

Response was assessed at Cycle 1, Day 1, and on Day 1 of every cycle thereafter; median time on follow-up was 28.6 months for the venetoclax group and 28.6 months for the placebo group

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194[25]	97[26]		
Units: percentage of participants				
number (confidence interval 95%)	81.4 (75.2 to 86.7)	69.1 (58.9 to 78.1)		

Notes:

[25] - All randomized participants, analyzed by treatment group assignment given at time of randomization

[26] - All randomized participants, analyzed by treatment group assignment given at time of randomization

Statistical analyses

Statistical analysis title	Venetoclax vs Placebo

Statistical analysis description:

Stratified Analysis; Stratification factors: Prior exposure to proteasome inhibitors (naïve versus sensitive), and number of prior lines of therapy (1 versus 2 or 3)

Comparison groups	Venetoclax + Bortezomib and Dexamethasone v Placebo + Bortezomib and Dexamethasone

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Cochran-Mantel-Haenszel

Secondary: Minimal Residual Disease (MRD) Negativity Rate

End point title	Minimal Residual Disease (MRD) Negativity Rate

End point description:

MRD negativity rate is defined as the percentage of participants who have negative MRD by bone marrow aspirate at any time point after randomization and before progression or starting subsequent therapy. MRD negativity was defined at 10^−5 threshold (less than one residual myeloma cell per 10^5 total nucleated cells) as measured by centralized testing of bone marrow aspirate by Next Generation Sequencing (NGS). MRD positive participants include those of which all tested samples were found to be MRD positive or indeterminate. Participants with missing or unevaluable MRD status were considered as MRD positive.

End point type	Secondary

End point timeframe:

Assessed at Screening; to confirm a stringent Complete Response (sCR) or Complete Response (CR); at 6 months and 12 months post-confirmed CR/sCR

End point values	Venetoclax + Bortezomib and Dexamethasone	Placebo + Bortezomib and Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	194[27]	97[28]		
Units: percentage of participants				
number (confidence interval 95%)	15.5 (10.7 to 21.3)	2.1 (0.3 to 7.3)		

Notes:

[27] - All randomized participants, analyzed by treatment group assignment given at time of randomization

[28] - All randomized participants, analyzed by treatment group assignment given at time of randomization

Statistical analyses

Statistical analysis title	Venetoclax vs Placebo

Statistical analysis description:

Stratified Analysis; Stratification factors: Prior exposure to proteasome inhibitors (naïve versus sensitive), and number of prior lines of therapy (1 versus 2 or 3)

Comparison groups	Venetoclax + Bortezomib and Dexamethasone v Placebo + Bortezomib and Dexamethasone

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality is reported from enrollment to the end of the study; median time on follow-up was 48.4 months for the venetoclax group and 47.2 months for the placebo group.

Adverse event reporting additional description:

TEAEs and SAEs were collected from first dose of study drug until 30 days after last dose of study drug; mean time on venetoclax was 582.2 days and mean time on placebo was 431.3 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo + Bortezomib and Dexamethasone

Reporting group description:

Cycles 1-8: Placebo (to match venetoclax 100 mg tablet) 800 mg orally every day (QD) on Days 1 - 21 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 4, 8 & 11 and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 & 12; Cycles 9 and beyond: Placebo (to match venetoclax 100 mg tablet) 800 mg orally every day (QD) on Days 1 - 35 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 8, 15 and 22 and dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 & 23

Reporting group title	Venetoclax + Bortezomib and Dexamethasone

Reporting group description:

Cycles 1-8: Venetoclax 800 mg orally every day (QD) on Days 1 - 21 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 4, 8 & 11 and dexamethasone 20 mg orally on Days 1, 2, 4, 5, 8, 9, 11 & 12; Cycles 9 and beyond: Venetoclax 800 mg orally every day (QD) on Days 1 - 35 plus bortezomib 1.3 mg/m^2 subcutaneously or IV on Days 1, 8, 15 and 22 and dexamethasone 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 and 23

Serious adverse events	Placebo + Bortezomib and Dexamethasone	Venetoclax + Bortezomib and Dexamethasone	
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 96 (55.21%)	115 / 193 (59.59%)	
number of deaths (all causes)	36	80	
number of deaths resulting from adverse events	1	15	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF LUNG			

subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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 METASTATIC			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROENDOCRINE TUMOUR			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTEATOMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST CANCER			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR PAIN			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MEDIASTINAL NEOPLASM			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	2 / 96 (2.08%)	5 / 193 (2.59%)	
occurrences causally related to treatment / all	2 / 2	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
ASTHENIA			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	1 / 96 (1.04%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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	1 / 96 (1.04%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
ENDOMETRIOSIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
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 / 96 (2.08%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			

subjects affected / exposed	0 / 96 (0.00%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY CONGESTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			

subjects affected / exposed	0 / 96 (0.00%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS DISORDER			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY HYPERTENSION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
INFLUENZA A VIRUS TEST POSITIVE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

JOINT DISLOCATION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	1 / 96 (1.04%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	3 / 96 (3.13%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	0 / 96 (0.00%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANKLE FRACTURE			
subjects affected / exposed	2 / 96 (2.08%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FOREARM FRACTURE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOFT TISSUE INJURY			

subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE FRACTURES			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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 FAILURE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA UNSTABLE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 96 (0.00%)	4 / 193 (2.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIOMYOPATHY			

subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC CARDIOMYOPATHY			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
AUTONOMIC NEUROPATHY			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLIC STROKE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
BRAIN OEDEMA			

subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 96 (0.00%)	4 / 193 (2.07%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 96 (1.04%)	4 / 193 (2.07%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 96 (0.00%)	6 / 193 (3.11%)	
occurrences causally related to treatment / all	0 / 0	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOPENIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CATARACT			
subjects affected / exposed	3 / 96 (3.13%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
GLAUCOMA			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
DYSPEPSIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 96 (1.04%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CROHN'S DISEASE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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 / 96 (2.08%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	2 / 96 (2.08%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCARCERATED INGUINAL HERNIA			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE POLYP			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 96 (0.00%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			

subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PSEUDO-OBSTRUCTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILIARY COLIC			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DRUG ERUPTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL IMPAIRMENT			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE KIDNEY INJURY			
subjects affected / exposed	3 / 96 (3.13%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLLAKIURIA			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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			
SPINAL PAIN			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SACRAL PAIN			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	1 / 96 (1.04%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA MUSCLE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHONDROCALCINOSIS PYROPHOSPHATE			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

BONE LESION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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	2 / 96 (2.08%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VERTEBRAL WEDGING			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (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			
CELLULITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS BACTERIAL			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATYPICAL PNEUMONIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BILIARY SEPSIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 PNEUMONIA			
subjects affected / exposed	1 / 96 (1.04%)	6 / 193 (3.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 3	
ENDOCARDITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	4 / 96 (4.17%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS B REACTIVATION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 96 (0.00%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			

subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPHILUS INFECTION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LISTERIOSIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 96 (5.21%)	4 / 193 (2.07%)	
occurrences causally related to treatment / all	4 / 7	2 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
MEDICAL DEVICE SITE INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METAPNEUMOVIRUS INFECTION			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ADENOVIRAL			

subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAINFLUENZAE VIRUS INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIODONTITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	14 / 96 (14.58%)	35 / 193 (18.13%)	
occurrences causally related to treatment / all	6 / 19	26 / 53	
deaths causally related to treatment / all	0 / 0	2 / 3	
NECROTISING FASCIITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA BACTERIAL			

subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA INFLUENZAL			
subjects affected / exposed	0 / 96 (0.00%)	4 / 193 (2.07%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	1 / 96 (1.04%)	0 / 193 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
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	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHINOVIRUS INFECTION			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	0 / 96 (0.00%)	6 / 193 (3.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 4	
SEPTIC SHOCK			
subjects affected / exposed	1 / 96 (1.04%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
STREPTOCOCCAL BACTERAEMIA			

subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONSILLITIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 96 (1.04%)	3 / 193 (1.55%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 96 (2.08%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	0 / 96 (0.00%)	2 / 193 (1.04%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERVOLAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			

subjects affected / exposed	1 / 96 (1.04%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METABOLIC ACIDOSIS			
subjects affected / exposed	0 / 96 (0.00%)	1 / 193 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Bortezomib and Dexamethasone	Venetoclax + Bortezomib and Dexamethasone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 96 (98.96%)	191 / 193 (98.96%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	15 / 96 (15.63%)	20 / 193 (10.36%)	
occurrences (all)	18	23	
HYPOTENSION			
subjects affected / exposed	4 / 96 (4.17%)	23 / 193 (11.92%)	
occurrences (all)	5	25	
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	5 / 96 (5.21%)	13 / 193 (6.74%)	
occurrences (all)	6	15	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	2 / 96 (2.08%)	30 / 193 (15.54%)	
occurrences (all)	2	39	
FATIGUE			
subjects affected / exposed	31 / 96 (32.29%)	63 / 193 (32.64%)	
occurrences (all)	43	90	
INJECTION SITE REACTION			
subjects affected / exposed	5 / 96 (5.21%)	5 / 193 (2.59%)	
occurrences (all)	5	6	
MALAISE			

subjects affected / exposed	2 / 96 (2.08%)	10 / 193 (5.18%)	
occurrences (all)	3	10	
OEDEMA PERIPHERAL			
subjects affected / exposed	20 / 96 (20.83%)	38 / 193 (19.69%)	
occurrences (all)	25	57	
PAIN			
subjects affected / exposed	5 / 96 (5.21%)	4 / 193 (2.07%)	
occurrences (all)	5	4	
PYREXIA			
subjects affected / exposed	11 / 96 (11.46%)	31 / 193 (16.06%)	
occurrences (all)	13	40	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	7 / 96 (7.29%)	10 / 193 (5.18%)	
occurrences (all)	10	20	
Immune system disorders			
HYPOGAMMAGLOBULINAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	11 / 193 (5.70%)	
occurrences (all)	0	13	
Respiratory, thoracic and mediastinal disorders			
RHINORRHOEA			
subjects affected / exposed	5 / 96 (5.21%)	6 / 193 (3.11%)	
occurrences (all)	6	8	
PRODUCTIVE COUGH			
subjects affected / exposed	4 / 96 (4.17%)	14 / 193 (7.25%)	
occurrences (all)	5	25	
OROPHARYNGEAL PAIN			
subjects affected / exposed	5 / 96 (5.21%)	18 / 193 (9.33%)	
occurrences (all)	8	23	
EPISTAXIS			
subjects affected / exposed	7 / 96 (7.29%)	8 / 193 (4.15%)	
occurrences (all)	10	8	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	6 / 96 (6.25%)	7 / 193 (3.63%)	
occurrences (all)	8	7	
DYSPNOEA			

subjects affected / exposed	15 / 96 (15.63%)	22 / 193 (11.40%)	
occurrences (all)	21	33	
COUGH			
subjects affected / exposed	20 / 96 (20.83%)	44 / 193 (22.80%)	
occurrences (all)	27	65	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	29 / 96 (30.21%)	56 / 193 (29.02%)	
occurrences (all)	33	73	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	9 / 96 (9.38%)	15 / 193 (7.77%)	
occurrences (all)	13	22	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	5 / 96 (5.21%)	17 / 193 (8.81%)	
occurrences (all)	7	23	
BLOOD CREATININE INCREASED			
subjects affected / exposed	2 / 96 (2.08%)	14 / 193 (7.25%)	
occurrences (all)	5	18	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	3 / 96 (3.13%)	13 / 193 (6.74%)	
occurrences (all)	5	15	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 96 (1.04%)	21 / 193 (10.88%)	
occurrences (all)	1	54	
PLATELET COUNT DECREASED			
subjects affected / exposed	15 / 96 (15.63%)	33 / 193 (17.10%)	
occurrences (all)	50	78	
WEIGHT DECREASED			
subjects affected / exposed	2 / 96 (2.08%)	11 / 193 (5.70%)	
occurrences (all)	3	15	
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	6 / 96 (6.25%)	12 / 193 (6.22%)	
occurrences (all)	7	13	

FALL			
subjects affected / exposed	8 / 96 (8.33%)	22 / 193 (11.40%)	
occurrences (all)	11	25	
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	6 / 96 (6.25%)	5 / 193 (2.59%)	
occurrences (all)	6	6	
Nervous system disorders			
HYPOAESTHESIA			
subjects affected / exposed	8 / 96 (8.33%)	14 / 193 (7.25%)	
occurrences (all)	12	16	
DYSGEUSIA			
subjects affected / exposed	5 / 96 (5.21%)	16 / 193 (8.29%)	
occurrences (all)	5	18	
DIZZINESS			
subjects affected / exposed	10 / 96 (10.42%)	34 / 193 (17.62%)	
occurrences (all)	11	44	
HEADACHE			
subjects affected / exposed	16 / 96 (16.67%)	31 / 193 (16.06%)	
occurrences (all)	19	50	
PARAESTHESIA			
subjects affected / exposed	5 / 96 (5.21%)	18 / 193 (9.33%)	
occurrences (all)	6	24	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	27 / 96 (28.13%)	59 / 193 (30.57%)	
occurrences (all)	35	84	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	24 / 96 (25.00%)	36 / 193 (18.65%)	
occurrences (all)	36	60	
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	9 / 96 (9.38%)	54 / 193 (27.98%)	
occurrences (all)	16	183	
LYMPHOPENIA			
subjects affected / exposed	0 / 96 (0.00%)	19 / 193 (9.84%)	
occurrences (all)	0	54	
ANAEMIA			

subjects affected / exposed	23 / 96 (23.96%)	48 / 193 (24.87%)	
occurrences (all)	31	73	
THROMBOCYTOPENIA			
subjects affected / exposed	34 / 96 (35.42%)	53 / 193 (27.46%)	
occurrences (all)	78	120	
Eye disorders			
VISION BLURRED			
subjects affected / exposed	5 / 96 (5.21%)	8 / 193 (4.15%)	
occurrences (all)	5	9	
CATARACT			
subjects affected / exposed	11 / 96 (11.46%)	24 / 193 (12.44%)	
occurrences (all)	17	33	
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	1 / 96 (1.04%)	10 / 193 (5.18%)	
occurrences (all)	1	12	
ABDOMINAL DISTENSION			
subjects affected / exposed	3 / 96 (3.13%)	15 / 193 (7.77%)	
occurrences (all)	3	17	
ABDOMINAL PAIN			
subjects affected / exposed	8 / 96 (8.33%)	23 / 193 (11.92%)	
occurrences (all)	10	38	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	7 / 96 (7.29%)	20 / 193 (10.36%)	
occurrences (all)	9	26	
CONSTIPATION			
subjects affected / exposed	29 / 96 (30.21%)	68 / 193 (35.23%)	
occurrences (all)	35	89	
DIARRHOEA			
subjects affected / exposed	46 / 96 (47.92%)	114 / 193 (59.07%)	
occurrences (all)	79	282	
DYSPEPSIA			
subjects affected / exposed	9 / 96 (9.38%)	24 / 193 (12.44%)	
occurrences (all)	10	28	
FLATULENCE			

subjects affected / exposed	2 / 96 (2.08%)	12 / 193 (6.22%)	
occurrences (all)	2	13	
GASTRITIS			
subjects affected / exposed	3 / 96 (3.13%)	10 / 193 (5.18%)	
occurrences (all)	4	16	
NAUSEA			
subjects affected / exposed	22 / 96 (22.92%)	73 / 193 (37.82%)	
occurrences (all)	28	112	
STOMATITIS			
subjects affected / exposed	5 / 96 (5.21%)	8 / 193 (4.15%)	
occurrences (all)	5	9	
VOMITING			
subjects affected / exposed	17 / 96 (17.71%)	38 / 193 (19.69%)	
occurrences (all)	27	62	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	4 / 96 (4.17%)	25 / 193 (12.95%)	
occurrences (all)	5	27	
URTICARIA			
subjects affected / exposed	6 / 96 (6.25%)	2 / 193 (1.04%)	
occurrences (all)	6	2	
PRURITUS			
subjects affected / exposed	8 / 96 (8.33%)	33 / 193 (17.10%)	
occurrences (all)	11	47	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	12 / 96 (12.50%)	27 / 193 (13.99%)	
occurrences (all)	13	37	
MUSCULAR WEAKNESS			
subjects affected / exposed	10 / 96 (10.42%)	17 / 193 (8.81%)	
occurrences (all)	10	19	
MUSCLE SPASMS			
subjects affected / exposed	8 / 96 (8.33%)	17 / 193 (8.81%)	
occurrences (all)	8	22	
BONE PAIN			

subjects affected / exposed	5 / 96 (5.21%)	15 / 193 (7.77%)	
occurrences (all)	5	20	
BACK PAIN			
subjects affected / exposed	17 / 96 (17.71%)	43 / 193 (22.28%)	
occurrences (all)	23	48	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	6 / 96 (6.25%)	9 / 193 (4.66%)	
occurrences (all)	6	12	
PAIN IN EXTREMITY			
subjects affected / exposed	14 / 96 (14.58%)	25 / 193 (12.95%)	
occurrences (all)	15	32	
MYALGIA			
subjects affected / exposed	4 / 96 (4.17%)	13 / 193 (6.74%)	
occurrences (all)	4	13	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	3 / 96 (3.13%)	10 / 193 (5.18%)	
occurrences (all)	4	11	
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 96 (4.17%)	15 / 193 (7.77%)	
occurrences (all)	4	16	
BRONCHITIS			
subjects affected / exposed	15 / 96 (15.63%)	30 / 193 (15.54%)	
occurrences (all)	20	45	
CONJUNCTIVITIS			
subjects affected / exposed	7 / 96 (7.29%)	22 / 193 (11.40%)	
occurrences (all)	8	26	
INFLUENZA			
subjects affected / exposed	4 / 96 (4.17%)	28 / 193 (14.51%)	
occurrences (all)	11	38	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 96 (4.17%)	15 / 193 (7.77%)	
occurrences (all)	4	19	
NASOPHARYNGITIS			

subjects affected / exposed	8 / 96 (8.33%)	35 / 193 (18.13%)	
occurrences (all)	15	92	
PNEUMONIA			
subjects affected / exposed	3 / 96 (3.13%)	14 / 193 (7.25%)	
occurrences (all)	3	18	
SINUSITIS			
subjects affected / exposed	0 / 96 (0.00%)	10 / 193 (5.18%)	
occurrences (all)	0	14	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	25 / 96 (26.04%)	55 / 193 (28.50%)	
occurrences (all)	46	149	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	13 / 96 (13.54%)	42 / 193 (21.76%)	
occurrences (all)	14	60	
HYPERGLYCAEMIA			
subjects affected / exposed	8 / 96 (8.33%)	20 / 193 (10.36%)	
occurrences (all)	12	29	
HYPOCALCAEMIA			
subjects affected / exposed	0 / 96 (0.00%)	16 / 193 (8.29%)	
occurrences (all)	0	21	
HYPOKALAEMIA			
subjects affected / exposed	8 / 96 (8.33%)	32 / 193 (16.58%)	
occurrences (all)	12	49	
HYPOMAGNESAEMIA			
subjects affected / exposed	4 / 96 (4.17%)	12 / 193 (6.22%)	
occurrences (all)	11	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2017	Amendment 1 ●Updated number of subjects enrolled from approximately 240 to approximately 280 ●Clarified that procedures that are completed as standard of care within 7 days of consent may be considered for screening ●Updated Overall Study Design and Plan: Description –Treatment to reflect window for visits, language for dosing diaries and study-treatment dosing compliance ●Clarified that the requirement of the consumption of water (subjects are to drink 1 –2 liters of water daily) for 3 days prior to first dose of treatment is a daily requirement, to reduce risk of TLS ●Added additional birth control methods and revised male contraceptive requirement ●Removed "oligo-secretory" condition from Exclusion Criterion 3 ●Clarified the radiotherapy and corticosteroid exclusionary requirement in Exclusion Criterion 8 ●Clarified requirement of antiviral pretreatment ●Provided window for completion of baseline Patient-Reported Outcome (PRO) assessments and limited timeframe for completion of all subsequent PROs ●Clarified that survival and post treatment information will be collected beginning on date of progression ●Removed requirement of date and time of blood sample collection recorded on the eCRF ●Added screening requirement of plasmacytoma evaluation for clarification ●Clarified that dose capping and rounding of bortezomib is acceptable; removed 2 hour dosing window of bortezomib ●Allowed delays of up to 7 days in the initiation of a cycle due to toxicity or scheduling issues ● Revised Dose Reductions and Treatment Guidelines for Toxicity Related to Bortezomib table to include detailed instructions for grade 1 with pain or grade 2 toxicities ●Added that laboratory reference ranges must be entered into EDC ●Revised Appendix K, Tumor Lysis Syndrome Classification-- remove footnote pertaining to ULN and ages below 18 and clarified corrected serum calcium equation
15 December 2017	Amendment 2 ●Targeted number of PFS events was increased from 110 to approximately 136 to gather more data on PFS to ensure more reliable assessment of treatment effect ●Targeted number of PFS events for efficacy interim analysis was increased from 83 to approximately 109 to ensure more robust assessment of treatment effect at the interim analyses ●Restored Exclusion Criterion 11--"Male subject who is considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug" ●Clarified the definition of minimum increase in the size of plasmacytoma required for determination of progressive disease ●Clarified dexamethasone dosing when bortezomib dosing schedule is modified ●Ensured accurate measurement of the disease response endpoints ●Revised text to align with updated IMWG recommendations for MRD evaluations

09 March 2018	Amendment 3 ●Removed interim analysis per Sponsor discretion ●Added "Start of new anti-cancer therapy prior to PD/death" as an additional scenario for censoring scenario for time to event analysis ●Updated Appendix G –Schedule of Assessments –Follow-up for clarity
09 January 2019	Amendment 4 ●Updated Patient-Reported Outcome (PRO) Assessments to re-name ePROs performed out of protocol window as Unscheduled ●Updated management of venetoclax in cases of vomiting according to new venetoclax guidance ●Included the possibility of a generic bortezomib ● Changed the number of overall survival events at the final OS analysis and number of interim analyses for OS; and updated the power calculations for OS after these changes, reducing to 116 from 170 to allow earlier final OS analysis. One additional OS interim analysis based on 75% of total targeted OS events was introduced to assess treatment effect on OS before the final OS analysis. ●Updated P-gp inhibitor examples according to new venetoclax guidance
15 March 2019	Amendment 5 ●Updated Section 3.3, Nonclinical Pharmacology and Clinical Data and Section 3.5, Benefits and Risks and included recent data from the primary endpoint analysis from this study (Study M14-031, Bellini Study) where a higher proportion of deaths possibly related to infections was observed in the venetoclax arm ●Updated to include antibiotic prophylaxis, infection management, and pneumococcal and influenza vaccine guidance for subjects receiving venetoclax in combination with a proteasome inhibitor based on this study (Study M14-031, Bellini Study) where a higher proportion of deaths possibly related to infections was observed in the venetoclax arm ●Updated to allow more frequent collection of the secondary endpoint of Overall Survival
24 September 2019	Amendment 6 ●Updated Section 3.3, Nonclinical Pharmacology and Clinical Data, removing information from the protocol that is referenced in the most current version of the Investigator's Brochure ●Revised antibiotic prophylaxis and pneumococcal and influenza vaccine guidance in order to align with IDMC recommendations, added additional infection management strategies ●Clarified allowable corticosteroid use while on study treatment ●Allowed for collection of more detailed data on deaths that occur in the non-treatment emergent setting to further evaluate the cause of death of subjects in the progression or survival follow up period
20 April 2020	Amendment 7 ●Revised pneumococcal and influenza vaccine guidance in order to align with IDMC recommendations ●Clarified the study drug nomenclature ●Updated the information in the protocol for clarity and alignment based on the results of the primary progression free survival analysis

16 December 2020	Amendment 8 ●Noted that COVID-19 related risks are not expected to differ substantially between study subjects and broader population of subjects receiving treatment for multiple myeloma ●Provided COVID-19 pandemic-related protocol modifications ●Noted that final OS analysis is planned for when about 116 OS events occur. All objectives specified in protocol will be completed with the final OS analysis and therefore 1) maintaining study blind is not required 2) all data considered for analysis per protocol can be considered mature ●Provided treatment flexibility with bortezomib and dexamethasone dosing per investigator decision once subjects are unblinded ●Simplified study-related procedures for subjects in Arm 2 (Placebo + Bd) at time of unblinding, as these measures may no longer be applicable to them ●Noted that once subjects are unblinded and final OS analysis is complete, IDMC supervision will be complete; AbbVie will continue to monitor subjects' safety ●Provided updated end of study guidance ●Clarified that after unblinding, subjects who are benefiting from study treatment can continue in the study as, due to the partial clinical hold, they are not able to be rolled over into an extension study ●Clarified that imaging scans are no longer required to be sent to an independent central imaging vendor because 1) the planned primary progression free survival analysis was completed at the first interim analysis; 2) the primary progression free survival/response data is considered mature with no further changes expected ●Clarified that since objectives specified in the protocol will be completed with the final OS analysis and, from a statistics/scientific perspective, keeping the study blinded following the final OS analysis is not needed, the study can be unblinded once final OS analysis is complete ●Defined Last Subject Last Visit at the time the number of OS events required for the final OS analysis is reached

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported