Clinical trial results:
A Randomized, Open-label Phase 3 Study of Carfilzomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Transplant-ineligible Patients With Newly Diagnosed Multiple Myeloma

Summary

EudraCT number	2012-005283-97
Trial protocol	BE CZ AT DE HU GB IT NL FR GR PL ES BG
Global end of trial date	04 November 2016

Results information

Result version number	v1 (current)
This version publication date	15 November 2017
First version publication date	15 November 2017

Trial information

Trial identification

Sponsor protocol code	2012-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01818752
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	04 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the progression-free survival of transplant ineligible patients newly diagnosed with multiple myeloma who were treated with carfilzomib, melphalan and prednisone (CMP) or with Velcade® (bortezomib), melphalan and prednisone (VMP).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	22 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Bulgaria: 40
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Czech Republic: 97
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Spain: 53
Country: Number of subjects enrolled	France: 37
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Greece: 23
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Italy: 37

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 83
Country: Number of subjects enrolled	Romania: 46
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	Ukraine: 65
Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	China: 102
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Korea, Republic of: 79
Country: Number of subjects enrolled	New Zealand: 11
Country: Number of subjects enrolled	Singapore: 10
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Mexico: 5
Worldwide total number of subjects	955
EEA total number of subjects	520

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)	51
From 65 to 84 years	884
85 years and over	20

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 183 centers in Argentina, Australia, Austria, Belgium, Bulgaria, Canada, China, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Poland, Romania, Russia, Singapore, South Korea, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, and United States.

Pre-assignment

Screening details:

Eligible participants were randomized in a 1:1 ratio. Randomization was stratified by International Staging System (ISS) stage (stage 1 versus stages 2 or 3), choice of route of bortezomib administration (intravenous [IV] versus subcutaneous [SC]), region (North America, Europe, Asia Pacific, or other), and age (< 75 years versus ≥ 75 years).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bortezomib, Melphalan, Prednisone

Arm description:

Participants received bortezomib in combination with melphalan and prednisone for nine 42-day cycles. Bortezomib was administered either IV or subcutaneously at 1.3 mg/m² during cycles 1 to 4 on days 1, 4, 8, 11, 22, 25, 29, and 32 followed by 1.3 mg/m² during cycles 5 to 9 on days 1, 8, 22, and 29. On days 1 to 4 of each cycle, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².

Arm type	Active comparator
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	Alkeran
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Melphalan 9 mg/m² was taken orally on days 1 to 4 of all cycles.

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

Dosage and administration details:

Prednisone 60 mg/m² was taken orally on days 1 to 4 of all cycles.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade®
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bortezomib 1.3 mg/m² was administered as a bolus IV injection or as a subcutaneous injection (per investigator's choice, dose modification, or regulatory approval) on days 1, 4, 8, 11, 22, 25, 29, and 32 of cycles 1 to 4, and on days 1, 8, 22, and 29 of cycles 5 to 9.

Arm title	Carfilzomib, Melphalan, Prednisone

Arm description:

Participants received carfilzomib administered in combination with melphalan and prednisone for nine 42-day cycles. Carfilzomib was administered as an intravenous (IV) infusion on days 1, 2, 8, 9, 22, 23, 29, and 30 of each 42-day cycle. The carfilzomib dose was at 20 mg/m² on cycle 1, days 1 and 2 followed by 36 mg/m² thereafter. On days 1 to 4, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	PR-171
Other name	Krypolis®
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Carfilzomib was administered over 30 minutes on days 1, 2, 8, 9, 22, 23, 29, and 30 for nine 42-day cycles. Carfilzomib 20 mg/m² IV was administered on days 1 and 2 of cycle 1, followed by escalation to 36 mg/m² IV starting on day 8 of cycle 1.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	Alkeran
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Melphalan 9 mg/m² was taken orally on days 1 to 4 of all cycles.

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

Dosage and administration details:

Prednisone 60 mg/m² was taken orally on days 1 to 4 of all cycles.

Number of subjects in period 1	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone
Started	477	478
Received Treatment	470	474
Completed	291	284
Not completed	186	194
Consent withdrawn by subject	15	14
Physician decision	8	8
Adverse event, non-fatal	62	74
Death	15	19
Other	7	9
Non-compliance	16	18
Randomized but not Dosed	7	4
Lost to follow-up	1	-

Disease Progression	55	48

Baseline characteristics

Reporting groups	
Reporting group title	Bortezomib, Melphalan, Prednisone
Reporting group description:	
Participants received bortezomib in combination with melphalan and prednisone for nine 42-day cycles. Bortezomib was administered either IV or subcutaneously at 1.3 mg/m² during cycles 1 to 4 on days 1, 4, 8, 11, 22, 25, 29, and 32 followed by 1.3 mg/m² during cycles 5 to 9 on days 1, 8, 22, and 29. On days 1 to 4 of each cycle, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².	
Reporting group title	Carfilzomib, Melphalan, Prednisone
Reporting group description:	
Participants received carfilzomib administered in combination with melphalan and prednisone for nine 42-day cycles. Carfilzomib was administered as an intravenous (IV) infusion on days 1, 2, 8, 9, 22, 23, 29, and 30 of each 42-day cycle. The carfilzomib dose was at 20 mg/m² on cycle 1, days 1 and 2 followed by 36 mg/m² thereafter. On days 1 to 4, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².	

Reporting group values	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone	Total
Number of subjects	477	478	955
Age categorical Units: Subjects			
Adults (18-64 years)	35	16	51
From 65-84 years	430	454	884
85 years and over	12	8	20
Age Continuous Units: years			
arithmetic mean	71.5	72.0	
standard deviation	± 6.5	± 5.7	-
Gender, Male/Female Units: Subjects			
Female	238	235	473
Male	239	243	482
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	2	1	3
Asian	121	123	244
Black or African American	0	3	3
White	339	329	668
Other	3	1	4
Multiple	0	2	2
Not Reported	12	19	31
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	18	33
Not Hispanic or Latino	443	427	870
Unknown or Not Reported	19	33	52
Stratification Factor: International Staging System (ISS) Stage			
The International Staging System (ISS) for myeloma was published by the International Myeloma			

Working Group: • Stage I: β2-microglobulin (β2M) < 3.5 mg/L, albumin >= 3.5 g/dL • Stage II: β2M < 3.5 mg/L and albumin < 3.5 g/dL; or β2M 3.5 mg/L - 5.5 mg/L irrespective of the serum albumin • Stage III: β2M ≥ 5.5 mg/L			
Units: Subjects			
Stage I	99	95	194
Stage II or III	378	383	761
Stratification Factor: Route of Bortezomib Administration			
The route of bortezomib administration (IV versus SC) was made per investigator's choice, dose modification, or regulatory approval. The investigator selected the route for all participants prior to randomization to treatment group in order to minimize any evaluation bias because of imbalances in potential prognostic factors that might have impacted the investigator’s choice of a particular route.			
Units: Subjects			
Intravenous	123	123	246
Subcutaneous	354	355	709
Stratification Factor: Region of Enrollment			
Units: Subjects			
Asia Pacific	141	140	281
North America	12	8	20
Europe	317	320	637
Other	7	10	17
Stratification Factor: Age			
Units: Subjects			
< 75 years	329	327	656
≥ 75 years	148	151	299
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a participants disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. 0 = Fully Active; 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, no self-care, confined to bed or chair; 5 = Dead.			
Units: Subjects			
0 (Fully active)	125	129	254
1 (Restrictive but ambulatory)	250	260	510
2 (Ambulatory but unable to work)	101	89	190
Missing	1	0	1

End points

End points reporting groups

Reporting group title	Bortezomib, Melphalan, Prednisone

Reporting group description:

Participants received bortezomib in combination with melphalan and prednisone for nine 42-day cycles. Bortezomib was administered either IV or subcutaneously at 1.3 mg/m² during cycles 1 to 4 on days 1, 4, 8, 11, 22, 25, 29, and 32 followed by 1.3 mg/m² during cycles 5 to 9 on days 1, 8, 22, and 29. On days 1 to 4 of each cycle, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².

Reporting group title	Carfilzomib, Melphalan, Prednisone

Reporting group description:

Participants received carfilzomib administered in combination with melphalan and prednisone for nine 42-day cycles. Carfilzomib was administered as an intravenous (IV) infusion on days 1, 2, 8, 9, 22, 23, 29, and 30 of each 42-day cycle. The carfilzomib dose was at 20 mg/m² on cycle 1, days 1 and 2 followed by 36 mg/m² thereafter. On days 1 to 4, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Progression-free survival was defined as the time from randomization to the earlier of documented disease progression or death due to any cause. PFS was analyzed using Kaplan-Meier methods. The duration of PFS was censored for participants with no baseline and/or post-baseline disease assessments, who started a new anti-cancer therapy before documentation of disease progression or death, death or disease progression after missed disease assessment of 100 consecutive days or longer, or who were alive without documentation of disease progression before the data cutoff date, including lost to follow-up prior to disease progression. Participants were evaluated for disease response and progression according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC), determined centrally using a validated computer algorithm in a blinded manner.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 15 July 2016; median follow-up time for PFS was 21.6.and 22.2 months in the bortezomib and carfilzomib arms respectively.

End point values	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	478		
Units: months				
median (confidence interval 95%)	22.1 (20.8 to 24.4)	22.3 (20.9 to 26.7)		

Statistical analyses

Statistical analysis title	Analysis of Progression-free Survival

Statistical analysis description:

The inferential test associated with the primary analysis of PFS was assessed against an overall 1-sided

significance level of α=0.025.
The hazard ratio (Carfilzomib/Bortezomib) was estimated using a Cox proportional hazards model stratified by ISS stage, choice of route of bortezomib administration, region and age.

Comparison groups	Bortezomib, Melphalan, Prednisone v Carfilzomib, Melphalan, Prednisone
Number of subjects included in analysis	955
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.159 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.906
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.746
upper limit	1.101

Notes:

[1] - Log-rank p-value (1-sided) stratified by ISS stage, choice of route of bortezomib administration, region and age. The p-value boundary for PFS analysis was 0.02141.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) was defined as the time from randomization to the date of death (whatever the cause). Participants who were alive or lost to follow-up as of the data analysis cut-off date were censored on the date the patient was last known to be alive. Median overall survival was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 15 July 2016; median follow-up time for OS was 22.2 and 22.5 months in the bortezomib and carfilzomib arms respectively.

End point values	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	478		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (31.5 to 99999)		

Statistical analyses

Statistical analysis title	Analysis of Overall Survival

Statistical analysis description:

Based on the pre-specified multiplicity adjustment method, secondary endpoints were to be tested only if the results of the primary endpoint were significant. The p-values for all secondary endpoints are descriptive only.
The hazard ratio (Carfilzomib/Bortezomib) was estimated using a Cox proportional hazards model stratified by ISS stage, choice of route of bortezomib administration, region and age.

Comparison groups	Bortezomib, Melphalan, Prednisone v Carfilzomib, Melphalan, Prednisone
Number of subjects included in analysis	955
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8934 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.211
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.896
upper limit	1.637

Notes:

[2] - Log-rank p-value (1-sided) stratified by ISS stage, choice of route of bortezomib administration, region and age.

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Disease response was evaluated according to the IMWG-URC using a validated computer algorithm. Overall response was defined as the percentage of participants with a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR). sCR: As for CR, normal serum free light chain (SFLC) ratio and no clonal cells in bone marrow (BM). CR: No immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and < 5% plasma cells in BM biopsy; VGPR: Serum and urine M-protein detectable by immunofixation but not electrophoresis or ≥ 90% reduction in serum M-protein with urine M-protein <100 mg/24 hours. A ≥ 50% reduction in the size of soft tissue plasmacytomas if present at baseline. PR: ≥ 50% reduction of serum M-protein and reduction in urine M-protein by ≥ 90% or to < 200 mg/24 hours. A ≥ 50% reduction in the size of soft tissue plasmacytomas if present at baseline.

End point type	Secondary

End point timeframe:

Disease response was assessed every 3 weeks during the first 54 weeks and every 6 weeks thereafter until PD or the data cut-off date of 15 July 2016; median follow-up time was 21.6.and 22.2 months in the bortezomib and carfilzomib arms respectively.

End point values	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	478		
Units: percentage of participants				
number (confidence interval 95%)	78.8 (74.9 to 82.4)	84.3 (80.7 to 87.5)		

Statistical analyses

Statistical analysis title	Analysi of Overall Response Rate

Statistical analysis description:

Based on the pre-specified multiplicity adjustment method, secondary endpoints were to be tested only

if the results of the primary endpoint were significant. The p-values for all secondary endpoints are descriptive only.
Odds ratio (Carfilzomib/Bortezomib) was estimated using the Mantel-Haenszel method stratified by ISS stage, choice of route of bortezomib administration, region and age.

Comparison groups	Bortezomib, Melphalan, Prednisone v Carfilzomib, Melphalan, Prednisone
Number of subjects included in analysis	955
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0218 [3]
Method	Stratified Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.973

Notes:

[3] - Cochran-Mantel-Haenszel Chi-square test stratified by ISS stage, choice of route of bortezomib administration, region and age.

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

Complete response rate was defined as the percentage of participants in each treatment group who achieved a sCR or CR per the IMWG-URC as their best response. sCR: As for CR, normal serum free light chain (SFLC) ratio and no clonal cells in bone marrow (BM). CR: No immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and < 5% plasma cells in BM biopsy.

End point type	Secondary

End point timeframe:

Disease response was assessed every 3 weeks during the first 54 weeks and every 6 weeks thereafter until PD or the data cut-off date of 15 July 2016; median follow-up time was 21.6.and 22.2 months in the bortezomib and carfilzomib arms respectively.

End point values	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	478		
Units: percentage of participants				
number (confidence interval 95%)	23.1 (19.4 to 27.1)	25.9 (22.1 to 30.1)		

Statistical analyses

Statistical analysis title	Analysis of Complete Response rate

Statistical analysis description:

Based on the pre-specified multiplicity adjustment method, secondary endpoints were to be tested only if the results of the primary endpoint were significant. The p-values for all secondary endpoints are descriptive only.

Odds ratio (Carfilzomib/Bortezomib) was estimated using the Mantel-Haenszel method stratified by ISS stage, choice of route of bortezomib administration, region and age.

Comparison groups	Bortezomib, Melphalan, Prednisone v Carfilzomib, Melphalan, Prednisone
Number of subjects included in analysis	955
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1388 [4]
Method	Stratified Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.179
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.875
upper limit	1.589

Notes:

[4] - Cochran-Mantel-Haenszel Chi-square test stratified by ISS stage, choice of route of bortezomib administration, region and age.

Secondary: Percentage of Participants With ≥ Grade 2 Peripheral Neuropathy

End point title	Percentage of Participants With ≥ Grade 2 Peripheral Neuropathy

End point description:

Neuropathy events were defined as Grade 2 or higher peripheral neuropathy as specified by peripheral neuropathy Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query, narrow (scope) (SMQN) terms. Peripheral neuropathy was assessed by neurologic exam and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03: Grade 1: Asymptomatic; Grade 2: Moderate symptoms, limiting instrumental activities of daily living (ADL) Grade 3: Severe symptoms; limiting self-care ADL; Grade 4: Life-threatening consequences, urgent intervention indicated; Grade 5: Death.
The safety population included all randomized participants who received at least 1 dose of any study treatment (i.e., carfilzomib, bortezomib, melphalan, or prednisone).

End point type	Secondary

End point timeframe:

From the first dose of any study drug up to 30 days after the last dose of any study drug as of the data cut-off date of 15 July 2016; median duration of treatment was 52 weeks in both treatment groups.

End point values	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	470	474		
Units: percentage of participants				
number (confidence interval 95%)	35.1 (30.8 to 39.6)	2.5 (1.3 to 4.4)		

Statistical analyses

Statistical analysis title	Analysis of Neuropathy Events

Statistical analysis description:

Based on the pre-specified multiplicity adjustment method, secondary endpoints were to be tested only if the results of the primary endpoint were significant. The p-values for all secondary endpoints are descriptive only.
Unstratified odds ratio (Carfilzomib/Bortezomib) was estimated.

Comparison groups	Bortezomib, Melphalan, Prednisone v Carfilzomib, Melphalan, Prednisone
Number of subjects included in analysis	944
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Pearson Chi-Square test
Parameter estimate	Odds ratio (OR)
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.088

Notes:

[5] - Based on the pre-specified multiplicity adjustment method, secondary endpoints were to be tested only if the results of the primary endpoint were significant. The p-values for all secondary endpoints are descriptive only.

Secondary: European Organisation for Research and Treatment of Cancer Quality of Life Core Module (EORTC QLQ-C30) Global Health Status/Quality of Life (QOL) Scores

End point title	European Organisation for Research and Treatment of Cancer Quality of Life Core Module (EORTC QLQ-C30) Global Health Status/Quality of Life (QOL) Scores

End point description:

The EORTC QLQ-C30 is a validated self-rating questionnaire including 30 items used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Global Health Status/QOL scale was scored between 0 and 100, with higher scores indicating better Global Health Status/QOL.

End point type	Secondary

End point timeframe:

Baseline, weeks 6, 12, 18, 24, 30, 36, 42 and 48

End point values	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	478		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 425, 425)	53.3 (± 21.9)	53.9 (± 22.5)		
Week 6 (n = 412, 407)	56.2 (± 19.5)	61.1 (± 19.6)		
Week 12 (n = 376, 389)	55.3 (± 19.8)	62.4 (± 17.7)		
Week 18 (n = 341, 369)	55.7 (± 18.8)	63.2 (± 17.4)		
Week 24 (n = 320, 345)	57.3 (± 17.6)	63.3 (± 17.1)		
Week 30 (n = 298, 317)	61.6 (± 17.8)	63.0 (± 17.8)		

Week 36 (n = 285, 308)	61.9 (± 17.5)	64.0 (± 18.1)		
Week 42 (n = 275, 288)	63.3 (± 17.7)	65.0 (± 18.1)		
Week 48 (n = 261, 265)	62.9 (± 18.4)	65.1 (± 17.1)		

Statistical analyses

Statistical analysis title	Analysis of QLQ-C30 Global Health Status/QoL

Statistical analysis description:

Treatment groups were compared using a linear mixed model for repeated measures (MMRM). The model included the fixed, categorical effects of treatment (all baseline responses were modeled with a dummy treatment), the randomization stratification factors – ISS stage, choice of route of bortezomib administration, region, age, and random effects of subject intercept and coefficient on time.

Comparison groups	Bortezomib, Melphalan, Prednisone v Carfilzomib, Melphalan, Prednisone
Number of subjects included in analysis	955
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Least squares mean difference
Point estimate	4.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.48
upper limit	6.51
Variability estimate	Standard error of the mean
Dispersion value	0.773

Notes:

[6] - Based on the pre-specified multiplicity adjustment method, secondary endpoints were to be tested only if the results of the primary endpoint were significant. The p-values for all secondary endpoints are descriptive only.

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

Adverse events (AEs)were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03, where GRADE 1 = Mild; GRADE 2 = Moderate; GRADE 3 = Severe; GRADE 4 = Life-threatening; GRADE 5 = Fatal. A serious adverse event is an adverse event that met 1 or more of the following criteria: • Death • Life-threatening • Required inpatient hospitalization or prolongation of an existing hospitalization • Resulted in persistent or significant disability/incapacity • Congenital anomaly/birth defect • Important medical event that jeopardized the participant and may have required medical or surgical intervention to prevent 1 of the outcomes listed above. Treatment-related adverse events are adverse events considered related to at least 1 investigational product by the investigator, including those with unknown relationship.

End point type	Secondary

End point timeframe:

From the first dose of study medication until 30 days after the last dose; the median duration of treatment was 11.99 months for Bortezomib, Melphalan, and Prednisone and 12.04 months for the Carfilzomib, Melphalan, and Prednisone group.

End point values	Bortezomib, Melphalan, Prednisone	Carfilzomib, Melphalan, Prednisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	470	474		
Units: participants				
All adverse events	454	460		
AEs ≥ grade 3	358	354		
Serious adverse events	198	235		
Leading to discontinuation of study drug	71	83		
Fatal adverse events	20	30		
Treatment-related adverse events (TRAEs)	431	408		
TRAEs ≥ grade 3	285	268		
Treatment-related serious adverse events	102	136		
TRAE leading to discontinuation of study drug	50	54		
Treatment-related fatal adverse events	5	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study medication until 30 days after the last dose; the median duration of treatment was 11.99 months for Bortezomib, Melphalan, and Prednisone and 12.04 months for the Carfilzomib, Melphalan, and Prednisone group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Carfilzomib, Melphalan, Prednisone

Reporting group description:

Participants received carfilzomib administered in combination with melphalan and prednisone for nine 42-day cycles. Carfilzomib was administered as an intravenous (IV) infusion on days 1, 2, 8, 9, 22, 23, 29, and 30 of each 42-day cycle. The carfilzomib dose was at 20 mg/m² on cycle 1, days 1 and 2 followed by 36 mg/m² thereafter. On days 1 to 4, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².

Reporting group title	Bortezomib, Melphalan, Prednisone

Reporting group description:

Participants received bortezomib in combination with melphalan and prednisone for nine 42-day cycles. Bortezomib was administered either IV or subcutaneously at 1.3 mg/m² during cycles 1 to 4 on days 1, 4, 8, 11, 22, 25, 29, and 32 followed by 1.3 mg/m² during cycles 5 to 9 on days 1, 8, 22, and 29. On days 1 to 4 of each cycle, melphalan was administered at 9 mg/m² and prednisone was administered at 60 mg/m².

Serious adverse events	Carfilzomib, Melphalan, Prednisone	Bortezomib, Melphalan, Prednisone	
Total subjects affected by serious adverse events			
subjects affected / exposed	235 / 474 (49.58%)	198 / 470 (42.13%)	
number of deaths (all causes)	106	92	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage I			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (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 skin			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Circulatory collapse			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
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	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	8 / 474 (1.69%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	4 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 474 (0.63%)	7 / 470 (1.49%)	
occurrences causally related to treatment / all	2 / 3	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypovolaemic shock			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
Aortic aneurysm repair			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone operation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebroplasty			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asthenia			
subjects affected / exposed	4 / 474 (0.84%)	6 / 470 (1.28%)	
occurrences causally related to treatment / all	3 / 4	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Disease progression			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 474 (0.42%)	5 / 470 (1.06%)	
occurrences causally related to treatment / all	1 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site pain			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
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	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	16 / 474 (3.38%)	8 / 470 (1.70%)	
occurrences causally related to treatment / all	13 / 27	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Immobile			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	9 / 474 (1.90%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	4 / 11	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (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	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal haematoma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	2 / 474 (0.42%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 474 (1.48%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	2 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	6 / 474 (1.27%)	4 / 470 (0.85%)	
occurrences causally related to treatment / all	4 / 6	2 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract congestion			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
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	3 / 474 (0.63%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Illusion			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 474 (0.42%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood uric acid increased			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 474 (0.42%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine output decreased			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	4 / 474 (0.84%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 474 (0.42%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat illness			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			

subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 474 (0.21%)	4 / 470 (0.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoconiosis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injury cervical			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			

subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 474 (0.84%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			

subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	7 / 474 (1.48%)	4 / 470 (0.85%)	
occurrences causally related to treatment / all	5 / 7	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac amyloidosis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	22 / 474 (4.64%)	7 / 470 (1.49%)	
occurrences causally related to treatment / all	21 / 26	4 / 7	
deaths causally related to treatment / all	3 / 4	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	8 / 474 (1.69%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	8 / 10	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive cardiomegaly			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			

subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (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	3 / 474 (0.63%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic nervous system imbalance			

subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic neuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Headache			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			

subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 474 (0.00%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 474 (0.84%)	5 / 470 (1.06%)	
occurrences causally related to treatment / all	2 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	11 / 474 (2.32%)	6 / 470 (1.28%)	
occurrences causally related to treatment / all	9 / 15	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	4 / 474 (0.84%)	5 / 470 (1.06%)	
occurrences causally related to treatment / all	4 / 5	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 474 (0.84%)	4 / 470 (0.85%)	
occurrences causally related to treatment / all	3 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 474 (1.05%)	11 / 470 (2.34%)	
occurrences causally related to treatment / all	5 / 5	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Diplopia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 474 (0.63%)	7 / 470 (1.49%)	
occurrences causally related to treatment / all	3 / 3	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	0 / 474 (0.00%)	5 / 470 (1.06%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 474 (0.00%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 474 (0.42%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 474 (0.63%)	6 / 470 (1.28%)	
occurrences causally related to treatment / all	1 / 3	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 474 (0.00%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	19 / 474 (4.01%)	10 / 470 (2.13%)	
occurrences causally related to treatment / all	15 / 25	2 / 13	
deaths causally related to treatment / all	2 / 3	0 / 0	
Chronic kidney disease			
subjects affected / exposed	3 / 474 (0.63%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	14 / 474 (2.95%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	5 / 17	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Renal impairment			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal injury			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ureterolithiasis			

subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	3 / 474 (0.63%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 474 (1.27%)	4 / 470 (0.85%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	3 / 474 (0.63%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Polyarthritis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 474 (0.21%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	8 / 474 (1.69%)	4 / 470 (0.85%)	
occurrences causally related to treatment / all	1 / 8	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			

subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	3 / 474 (0.63%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Legionella infection			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	5 / 474 (1.05%)	5 / 470 (1.06%)	
occurrences causally related to treatment / all	5 / 6	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	46 / 474 (9.70%)	31 / 470 (6.60%)	
occurrences causally related to treatment / all	25 / 60	15 / 38	
deaths causally related to treatment / all	1 / 1	2 / 4	
Postoperative wound infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas bronchitis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			

subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	8 / 474 (1.69%)	7 / 470 (1.49%)	
occurrences causally related to treatment / all	3 / 9	4 / 10	
deaths causally related to treatment / all	0 / 4	2 / 4	
Sepsis syndrome			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	2 / 474 (0.42%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 474 (0.42%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 474 (0.63%)	4 / 470 (0.85%)	
occurrences causally related to treatment / all	2 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	5 / 474 (1.05%)	3 / 470 (0.64%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 474 (0.00%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	1 / 474 (0.21%)	5 / 470 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 474 (0.42%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperproteinaemia			
subjects affected / exposed	0 / 474 (0.00%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 474 (0.21%)	1 / 470 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 474 (0.21%)	2 / 470 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tetany			
subjects affected / exposed	1 / 474 (0.21%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	3 / 474 (0.63%)	0 / 470 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Carfilzomib, Melphalan, Prednisone	Bortezomib, Melphalan, Prednisone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	437 / 474 (92.19%)	437 / 470 (92.98%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	29 / 474 (6.12%)	16 / 470 (3.40%)	
occurrences (all)	49	17	
Blood creatinine increased			
subjects affected / exposed	35 / 474 (7.38%)	22 / 470 (4.68%)	
occurrences (all)	84	54	
Neutrophil count decreased			
subjects affected / exposed	57 / 474 (12.03%)	71 / 470 (15.11%)	
occurrences (all)	333	444	
Platelet count decreased			
subjects affected / exposed	53 / 474 (11.18%)	62 / 470 (13.19%)	
occurrences (all)	282	431	

Weight decreased			
subjects affected / exposed	15 / 474 (3.16%)	28 / 470 (5.96%)	
occurrences (all)	17	38	
White blood cell count decreased			
subjects affected / exposed	54 / 474 (11.39%)	58 / 470 (12.34%)	
occurrences (all)	397	559	
Vascular disorders			
Hypertension			
subjects affected / exposed	101 / 474 (21.31%)	33 / 470 (7.02%)	
occurrences (all)	220	75	
Hypotension			
subjects affected / exposed	16 / 474 (3.38%)	37 / 470 (7.87%)	
occurrences (all)	17	49	
Nervous system disorders			
Dizziness			
subjects affected / exposed	45 / 474 (9.49%)	39 / 470 (8.30%)	
occurrences (all)	62	48	
Headache			
subjects affected / exposed	44 / 474 (9.28%)	23 / 470 (4.89%)	
occurrences (all)	68	31	
Hypoaesthesia			
subjects affected / exposed	14 / 474 (2.95%)	25 / 470 (5.32%)	
occurrences (all)	16	39	
Neuralgia			
subjects affected / exposed	2 / 474 (0.42%)	45 / 470 (9.57%)	
occurrences (all)	2	77	
Neuropathy peripheral			
subjects affected / exposed	30 / 474 (6.33%)	152 / 470 (32.34%)	
occurrences (all)	43	305	
Paraesthesia			
subjects affected / exposed	20 / 474 (4.22%)	31 / 470 (6.60%)	
occurrences (all)	22	58	
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 474 (1.69%)	64 / 470 (13.62%)	
occurrences (all)	9	137	
Polyneuropathy			

subjects affected / exposed	5 / 474 (1.05%)	36 / 470 (7.66%)	
occurrences (all)	5	91	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	169 / 474 (35.65%)	143 / 470 (30.43%)	
occurrences (all)	528	433	
Leukopenia			
subjects affected / exposed	33 / 474 (6.96%)	38 / 470 (8.09%)	
occurrences (all)	115	256	
Neutropenia			
subjects affected / exposed	120 / 474 (25.32%)	121 / 470 (25.74%)	
occurrences (all)	438	462	
Thrombocytopenia			
subjects affected / exposed	83 / 474 (17.51%)	91 / 470 (19.36%)	
occurrences (all)	415	357	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	68 / 474 (14.35%)	65 / 470 (13.83%)	
occurrences (all)	108	98	
Chest pain			
subjects affected / exposed	24 / 474 (5.06%)	11 / 470 (2.34%)	
occurrences (all)	30	14	
Chills			
subjects affected / exposed	42 / 474 (8.86%)	14 / 470 (2.98%)	
occurrences (all)	76	15	
Fatigue			
subjects affected / exposed	79 / 474 (16.67%)	85 / 470 (18.09%)	
occurrences (all)	139	162	
Oedema peripheral			
subjects affected / exposed	84 / 474 (17.72%)	54 / 470 (11.49%)	
occurrences (all)	128	68	
Pyrexia			
subjects affected / exposed	169 / 474 (35.65%)	79 / 470 (16.81%)	
occurrences (all)	377	144	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	11 / 474 (2.32%)	26 / 470 (5.53%)	
occurrences (all)	13	48	
Abdominal pain			
subjects affected / exposed	12 / 474 (2.53%)	27 / 470 (5.74%)	
occurrences (all)	22	34	
Abdominal pain upper			
subjects affected / exposed	22 / 474 (4.64%)	32 / 470 (6.81%)	
occurrences (all)	26	50	
Constipation			
subjects affected / exposed	65 / 474 (13.71%)	114 / 470 (24.26%)	
occurrences (all)	96	178	
Diarrhoea			
subjects affected / exposed	97 / 474 (20.46%)	132 / 470 (28.09%)	
occurrences (all)	145	296	
Nausea			
subjects affected / exposed	167 / 474 (35.23%)	133 / 470 (28.30%)	
occurrences (all)	332	234	
Vomiting			
subjects affected / exposed	116 / 474 (24.47%)	89 / 470 (18.94%)	
occurrences (all)	263	140	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	62 / 474 (13.08%)	62 / 470 (13.19%)	
occurrences (all)	87	73	
Dyspnoea			
subjects affected / exposed	72 / 474 (15.19%)	34 / 470 (7.23%)	
occurrences (all)	111	40	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	39 / 474 (8.23%)	22 / 470 (4.68%)	
occurrences (all)	53	30	
Rash			
subjects affected / exposed	26 / 474 (5.49%)	47 / 470 (10.00%)	
occurrences (all)	36	57	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	49 / 474 (10.34%)	66 / 470 (14.04%)	
occurrences (all)	59	72	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	32 / 474 (6.75%)	32 / 470 (6.81%)	
occurrences (all)	41	46	
Back pain			
subjects affected / exposed	53 / 474 (11.18%)	56 / 470 (11.91%)	
occurrences (all)	72	66	
Bone pain			
subjects affected / exposed	29 / 474 (6.12%)	27 / 470 (5.74%)	
occurrences (all)	38	42	
Pain in extremity			
subjects affected / exposed	30 / 474 (6.33%)	45 / 470 (9.57%)	
occurrences (all)	42	65	
Infections and infestations			
Bronchitis			
subjects affected / exposed	40 / 474 (8.44%)	39 / 470 (8.30%)	
occurrences (all)	49	48	
Nasopharyngitis			
subjects affected / exposed	31 / 474 (6.54%)	33 / 470 (7.02%)	
occurrences (all)	40	48	
Pneumonia			
subjects affected / exposed	31 / 474 (6.54%)	26 / 470 (5.53%)	
occurrences (all)	51	36	
Upper respiratory tract infection			
subjects affected / exposed	50 / 474 (10.55%)	51 / 470 (10.85%)	
occurrences (all)	73	63	
Urinary tract infection			
subjects affected / exposed	30 / 474 (6.33%)	26 / 470 (5.53%)	
occurrences (all)	45	36	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	67 / 474 (14.14%)	88 / 470 (18.72%)	
occurrences (all)	93	112	

Hyperglycaemia			
subjects affected / exposed	29 / 474 (6.12%)	37 / 470 (7.87%)	
occurrences (all)	73	102	
Hyperuricaemia			
subjects affected / exposed	30 / 474 (6.33%)	22 / 470 (4.68%)	
occurrences (all)	50	38	
Hypocalcaemia			
subjects affected / exposed	48 / 474 (10.13%)	41 / 470 (8.72%)	
occurrences (all)	86	68	
Hypokalaemia			
subjects affected / exposed	54 / 474 (11.39%)	63 / 470 (13.40%)	
occurrences (all)	77	122	
Hyponatraemia			
subjects affected / exposed	17 / 474 (3.59%)	24 / 470 (5.11%)	
occurrences (all)	31	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2013	Major changes included: •increased the time required for contraception in women of childbearing potential and men •excluded subjects with acute diffuse infiltrative pulmonary disease or pericardial disease •excluded subjects with hypersensitivity to melphalan or excipients of Alkeran •removed cytogenetics from the disease response assessments •removed proteomic analysis from the biomarker analyses •clarified the timing of bone marrow samples •clarified methods for whole genome sequencing or whole exome sequencing
30 September 2013	Major changes included: •allowed bone marrow biopsy sample or bone marrow aspirate slides for study entry, to be taken within 30 days before randomization, and for establishment of complete response •clarified that carfilzomib will be infused over 30 5 minutes, followed by a post-infusion flush within 30 minutes •clarified the disease response categories for IMWG-URC •specified that inferential analyses were not planned for duration of response
21 November 2013	•Amendment identical to Amendment 2 with the exception that the following was removed from the clarification to IMWG-URC: "All response categories (CR, sCR, VGPR, PR) and disease progression require 2 consecutive assessments from samples collected 4 hours apart before the institution of any new therapy". (This statement was removed).
02 May 2014	Major changes included: •included MRD and PFS2 as exploratory objectives and endpoints •allowed screening bone marrow biopsy or bone marrow aspirate slides to be taken within 45 days before randomization •clarified that intravenous hydration post-carfilzomib infusion was not mandatory in cycle 1 •excluded plasmapheresis as a concomitant procedure during screening through active follow-up •clarified that FISH analysis was only conducted in countries that met tissue transportation requirements to a laboratory acceptable to the sponsor
02 November 2015	Major changes included: •revised testing procedures and multiplicity adjustment method for secondary endpoints •clarified that IRC-assessed PFS was a supportive analysis •updated the guidelines for carfilzomib- and melphalan-related nonhematologic toxicities •aligned risk and discomfort language •included an additional analysis method for MRD assessment •changed OS testing from noninferiority testing to superiority testing •removed FACT/GOG-NTx score from the definition of the neuropathy event endpoint and added it as an exploratory endpoint

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported